Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 05-10844

54. **TÍTULO** COMPOSICION Y ACTIVIDAD ANTIVIRAL DE DERIVADOS DE PIPERAZINA AZABICICLOACETILCO. SUBSTITUIDO.

51. **CLASIFICACIÓN INTERNACIONAL** A61K31/496; A61K31/497 A61K31/506 A61P37/00

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

DOMICILIO PRINCETON, NEW JERSEY, Estados Unidos de América.

74. **APODERADO** Hector Gomez Mejia.

22. **BOGOTÁ, D. C.,** 08/02/2005.

(FORMA P-10)

PETITORIO

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Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05010044 00000000 Folios: 1103
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 07-Mar20-2005

1 SOLICITUD DE:

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

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **BRISTOL – MYERS SQUIBB COMPANY** Dirección: P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: HECTOR GOMEZ MEJIA Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 22720 TP 19436
4 INVENTOR (ES) (72)	Nombre: Tao Wang, Zhongxing Zhang, Nicholas A. Meanwell, John F. Kadow, Zhiwei Yin, Qiufen May Xue, Alicia Regueiro-Ren, John D. Matiskella, Yasutsugu Ueda Dirección: 1312 Town Brooke, Middletown, CT 06457, US; 14 Marlieshamheath Lane, Madison, CT 06443, US; 15 Valli Drive, East Hampton, CT 06424, US; 9 Quarry Run, Wallingford, CT 06492, US; 234 Sherman Avenue, Apt. 80, Meriden, CT 06450, US; 75 Barrington Way, Glastonbury, CT 06033, US; 69 Greenview Terrace, Middletown, CT 06457, US; 130 High Hill Road, Wallingford, CT 06492, US; 46 Olde Orchard Road, Clinton, CT 06413, Estados Unidos de América (Respectivamente) Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

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Titulo (54): COMPOSICION Y ACTIVIDAD ANTIVIRAL DE DERIVADOS DE PIPERAZINA AZAINDOLOXOACETICO SUBSTITUIDO

7 Clasificación Internacional (51) A61K31/496 ; A61K31/497 ; A61K31/506

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $443.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
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- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros - Tarjeta de Propietarios

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente.

NOMBRE: HECTOR GOMEZ MEJIA

FIRMA:

C.C. 2720 de Bogotá T.P. 1936 del C.S.J.

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

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

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Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 567
FECHA : ENERO 4 DE 2005

***** 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	28028770	04/01/2005	134,400.00
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	28028771	04/01/2005	9,585,000.00

***** 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	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/US2003/024415 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

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

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

APODERADO HECTOR GOMEZ MEJIA

TITULO COMPOSICION Y ACTIVIDAD ANTIVIRAL DE DERIVADOS DE PIPERAZINA AZAINDOLOXOACETICO SUBSTITUIDO CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD BOLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) TAO WANG, ZHONGXING ZHANG, NICHOLAS A. MEANWELL, JOHN F. KADOW, ZHIWEI YIN,

OTROS QIUFEN MAY XUE, ALICIA REGUEIRO-REN, JOHN D. MATISKELLA, YASUTSUGU UEDA

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

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

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(54) Title: COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED AZAINDOLEOXOACETIC PIPERAZINE DERIVATIVES

(57) Abstract: This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the invention is concerned with azaindoleoxoacetyl piperazine derivatives. These compounds possess unique antiviral activity, whether used alone or in combination with other antivirals, antiinfectives, immunomodulators or HIV entry inhibitors. More particularly, the present invention relates to the treatment of HIV and AIDS.

WO 2004/014380 A1

COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED AZAINDOLEOXOACETIC PIPERAZINE DERIVATIVES

REFERENCE TO RELATED APPLICATIONS

This Continuation in Part application claims the benefit of USSN 10/214,982 filed August 7, 2002.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the invention is concerned with azaindole piperazine diamide derivatives that possess unique antiviral activity. More particularly, the present invention relates to compounds useful for the treatment of HIV and AIDS.

Background Art

HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 42 million people infected worldwide at the end of 2002. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2002, ~5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nine nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations(zidovudine or AZT (or Retrovir®), didanosine (or Videx®), stavudine (or Zerit®), lamivudine (or 3TC or Epivir®), zalcitabine (or DDC or Hivid®), abacavir succinate (or Ziagen®), Tenofovir disoproxil fumarate salt (or Viread®),

Combivir® (contains -3TC plus AZT), Trizivir® (contains abacavir, lamivudine, and zidovudine); three non-nucleoside reverse transcriptase inhibitors: nevirapine (or Viramune®), delavirdine (or Rescriptor®) and efavirenz (or Sustiva®), and eight peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra®(lopinavir and Ritonavir), and Atazanavir (Reyataz®). Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present (Larder and Kemp; Gulick; Kuritzkes; Morris-Jones *et al*; Schinazi *et al*; Vacca and Condra; Flexner; Berkhout and Ren *et al*; (Ref. 6-14)). Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options.

Currently marketed HIV-1 drugs are dominated by either nucleoside reverse transcriptase inhibitors or peptidomimetic protease inhibitors. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have recently gained an increasingly important role in the therapy of HIV infections (Pedersen & Pedersen, Ref 15). At least 30 different classes of NNRTI have been described in the literature (De Clercq, Ref. 16) and several NNRTIs have been evaluated in clinical trials. Dipyridodiazepinone (nevirapine), benzoxazinone (efavirenz) and bis(heteroaryl) piperazine derivatives (delavirdine) have been approved for clinical use. However, the major drawback to the development and application of NNRTIs is the propensity for rapid emergence of drug resistant strains, both in tissue cell culture and in treated

individuals, particularly those subject to monotherapy. As a consequence, there is considerable interest in the identification of NNRTIs less prone to the development of resistance (Pedersen & Pedersen, Ref 15).

Several indole derivatives including indole-3-sulfones, piperazino indoles, pyrazino indoles, and 5H-indolo[3,2-b][1,5]benzothiazepine derivatives have been reported as HIV-1 reverse transciptase inhibitors (Greenlee et al, Ref. 1; Williams et al, Ref. 2; Romero et al, Ref. 3; Font et al, Ref. 17; Romero et al, Ref. 18; Young et al, Ref. 19; Genin et al, Ref. 20; Silvestri et al, Ref. 21). Indole 2-carboxamides have also been described as inhibitors of cell adhesion and HIV infection (Boschelli et al, US 5,424,329, Ref. 4). Finally, 3-substituted indole natural products (Semicochliodinol A and B, didemethylasterriquinone and isocochliodinol) were disclosed as inhibitors of HIV-1 protease (Fredenhagen et al, Ref. 22). Other indole derivatives exhibiting antiviral activity useful for treating HIV are disclosed in PCT WO 00/76521 (Ref. 93). Also, indole derivatives are disclosed in PCT WO 00/71535 (Ref. 94).

Structurally related aza-indole amide derivatives have been disclosed previously (Kato et al, Ref. 23; Levacher et al, Ref. 24; Dompe Spa, WO-09504742, Ref. 5(a); SmithKline Beecham PLC, WO-09611929, Ref. 5(b); Schering Corp., US-05023265, Ref. 5(c)). However, these structures differ from those claimed herein in that they are aza-indole mono-amide rather than unsymmetrical aza-indole piperazine diamide derivatives, and there is no mention of the use of these compounds for treating viral infections, particularly HIV. Other azaindoles have been also disclosed by Wang et al, Ref. 95. Indole and azaindole piperazine containing derivatives have been disclosed in four different PCT and issued U.S. patent applications (Reference 93-95, 106). Nothing in these references can be construed to disclose or suggest the novel compounds of this invention and their use to inhibit HIV infection.

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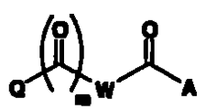
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SUMMARY DESCRIPTION OF THE INVENTION

The present invention comprises compounds of Formula I, or pharmaceutically acceptable salts thereof, which are effective antiviral agents, particularly as inhibitors of HIV.

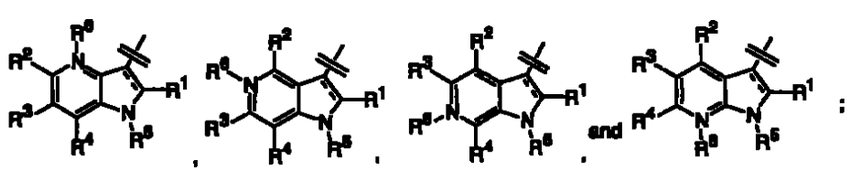
A first embodiment of a first aspect of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,



I

wherein:

Q is selected from the group consisting of:



R^1, R^2, R^3, and R^4, are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, $COOR^{56}$, XR^{57}, $C(O)R^7$, $C(O)NR^{55}R^{56}$, B, D, and E with the proviso that at least one of R^1-R^4 is selected from B or E;

wherein - - represents a carbon-carbon bond or does not exist;

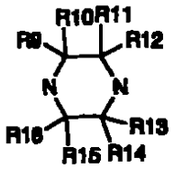
m is 1 or 2;

R^5 is hydrogen or $(CH_2)_nCH_3$, $-C(O)(CH_2)_nCH_3$, $-C(O)O(CH_2)_nCH_3$, $-C(O)(CH_2)_nN(CH_3)_2$ wherein n is 0-5;

R^6 is O or does not exist;

A is selected from the group consisting of C_{1-6}alkoxy, aryl and heteroaryl; in which said aryl is phenyl or napthyl; said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, benzoimidazolyl and benzothiazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different members selected from the group consisting of amino, nitro, cyano, hydroxy, C_{1-6}alkoxy, $-C(O)NH_2$, C_{1-6}alkyl, $-NHC(O)CH_3$, halogen and trifluoromethyl;

-W- is



;

B is selected from the group consisting of $-C(=NR^{46})(R^{47})$, $C(O)NR^{40}R^{41}$, aryl, heteroaryl, heteroalicyclic, $S(O)_2R^8$, $C(O)R^7$, XR^{8a}, (C_{1-6})alkyl$NR^{40}R^{41}$, (C_{1-6})alkyl$COOR^{8b}$; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group F; wherein aryl is napthyl or substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;

q is 0, 1, or 2;

D is selected from the group consisting of (C_{1-6})alkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are optionally substituted with one to three same or

different halogens or from one to three same or different substituents selected from the group consisting of $C(O)NR^{55}R^{56}$, hydroxy, cyano and XR^{57};

E is selected from the group consisting of (C_{1-6})alkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, $-C(O)NR_{56}R_{57}$, $C(O)R_{57}$, $SO_2(C_{1-6})$alkyl and SO_2Ph; wherein heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, (C_{1-6})thioalkoxy, cyano, halogen, nitro, $-C(O)R^{57}$, benzyl, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}C(O)-(C_{3-6})$cycloalkyl, $-NR^{42}C(O)$-aryl, $-NR^{42}C(O)$-heteroaryl, $-NR^{42}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$alkyl, $-NR^{42}S(O)_2-(C_{3-6})$cycloalkyl, $-NR^{42}S(O)2$-aryl, $-NR^{42}S(O)_2$-heteroaryl, $-NR^{42}S(O)2$-heteroalicyclic, $S(O)_2(C_{1-6})$alkyl, $S(O)_2$aryl, $-S(O)2\ NR^{42}R^{43}$, $NR^{42}R^{43}$, (C_{1-6})alkyl$C(O)NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$, $NHC(O)NR^{42}R^{43}$, $OC(O)NR^{42}R^{43}$, $NHC(O)OR^{54}$, (C_{1-6})alkyl$NR^{42}R^{43}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, and aryloxy, are optionally substituted with one to nine same or different halogens or from one to five same or different substituents selected from the group G; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

G is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, cyano, halogen, nitro, $-C(O)R^{57}$, benzyl, $-NR^{48}C(O)-(C_{1-6})$alkyl, $-NR^{48}C(O)-(C_{3-6})$cycloalkyl, $-NR^{48}C(O)$-aryl, $-NR^{48}C(O)$-heteroaryl, $-NR^{48}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{48}S(O)_2-(C_{1-6})$alkyl, $-NR^{48}S(O)_2-$

(C_{3-6})cycloalkyl, -NR^{48}S(O)2-aryl, -$NR^{48}S(O)_2$-heteroaryl, -NR^{48}S(O)2-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide, $NR^{48}R^{49}$, (C_{1-6})alkyl C(O)$NR^{48}R^{49}$, C(O)$NR^{48}R^{49}$, NHC(O)$NR^{48}R^{49}$, OC(O)$NR^{48}R^{49}$, NHC(O)OR^{54}, (C_{1-6})alkyl$NR^{48}R^{49}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein

aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^7 is selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or with from one to three same or different substituents selected from the group F;

wherein for R^7, R^8, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^8 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

R^{8a} is a member selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein each member is independently optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

R^{8b} is selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, are each independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; wherein said (C_{1-6})alkyl is optionally substituted with one to three same or different halogens;

X is selected from the group consisting of NH or NCH_3, O, and S;

R^{40} and R^{41} are independently selected from the group consisting of (a) hydrogen; (b) (C_{1-6})alkyl or (C_{3-7})cycloalkyl substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F; and (c) (C_{1-6})alkoxy, aryl, heteroaryl or heteroalicyclic; or R^{40} and R^{41} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F; wherein for R^{40} and R^{41} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine; provided when B is $C(O)NR^{40}R^{41}$, at least one of R^{40} and R^{41} is not selected from groups (a) or (b);

R^{42} and R^{43} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, allyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl and heteroalicyclic; or R^{42} and R^{43} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G; wherein for R^{42} and R^{43} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R_a and R_b are each independently H, (C_{1-6})alkyl or phenyl;

R^{46} is selected from the group consisting of H, OR^{57}, and $NR^{55}R^{56}$;

R^{47} is selected from the group consisting of H, amino, halogen, phenyl, and (C_{1-6})alkyl;

R^{48} and R^{49} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl;

R^{50} is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, and benzyl; wherein each of said (C_{1-6})alkyl, (C_{3-7})cycloalkyl and benzyl are optionally substituted with one to three same or different halogen, amino, OH, CN or NO_2;

R^{54} is selected from the group consisting of hydrogen and (C_{1-6})alkyl;

$R^{54'}$ is (C_{1-6})alkyl;

R^{55} and R^{56} are independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; and

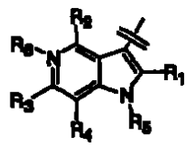
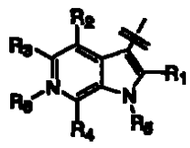
R^{57} is selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl.

A preferred embodiment are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^1 is hydrogen;

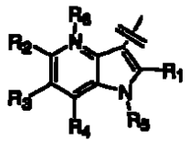
Q is either:

(a)  or  ;

wherein R^2 is selected from the group consisting of hydrogen, halogen, hydroxy, -O(C_{1-6})alkyl, cyano, nitro and XR^{57};

wherein R^3 is selected from the group consisting of hydrogen, halogen, hydroxy, -O(C_{1-6})alkyl, cyano, -$COOR^{56}$, nitro, XR^{57}; phenyl optionally substituted with one to three same or different halogens or one of methoxy, hydroxy or XR^{57}; furyl, oxazolyl, or pyrazolyl, independently optionally substituted with halogen, methoxy, (C_{1-3})alkyl or XR^{57}; or

(b) Q is:

 ;

wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, hydroxy, -O(C_{1-6})alkyl, cyano, nitro , -$COOR^{56}$, XR^{57}, -C(O) $NR^{55}R^{56}$; phenyl optionally substituted with one to three same or different halogens or one of methoxy, hydroxy or XR^{57}; furyl, oxalzolyl or pyrazolyl, independently optionally substituted with (C_{1-3})alkyl, halogen, methoxy or XR^{57};

and for both (a) and (b):

m is 2;

R^5 is hydrogen;

R^6 does not exist;

A is selected from the group consisting of C_{1-6}alkoxy, aryl and heteroaryl; wherein said aryl is phenyl; heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl and isoxazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different members selected from the group consisting of amino, cyano, hydroxy C_{1-6}alkoxy, C_{1-6}alkyl, -NHC(O)CH_3, halogen and trifluoromethyl;

- - represents a carbon-carbon bond;

X is NH or NCH_3;

R^{57} is H or (C_{1-3})alkyl; and

R^{55} and R^{56} are independently H or (C_{1-6})alkyl.

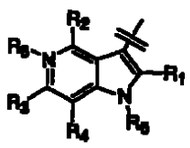
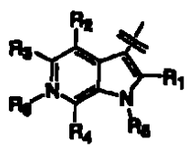
Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, hydroxy, or halogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} ,and R^{16} are each independently hydrogen or methyl with the proviso that only one is methyl;

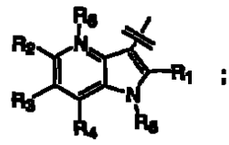
Q is either:

(a)  or  ;

and then R^2 is selected from the group consisting of hydrogen, halogen and methoxy; and

R_3 is hydrogen; or

(b) Q is:



;

and R^2 is halogen or hydrogen and R^3 is hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B;

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl, heteroaryl, oxazoline, pyrazinone and methylene dioxy or ethylene dioxy fused to a benzene or pyridine; wherein said heteroaryl or phenyl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl and heteroaryl; wherein said phenyl is substituted and heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, (C_{1-6})thioalkoxy, cyano, halogen, -$C(O)R^{57}$, benzyl, -$NR^{42}C(O)$-(C_{1-6})alkyl, -$NR^{42}C(O)$-(C_{3-6})cycloalkyl, -$NR^{42}C(O)$-aryl, -$NR^{42}C(O)$-heteroaryl, -$NR^{42}C(O)$-heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, -$NR^{42}S(O)_2$-(C_{1-6})alkyl, -$NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ and $COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G;

G is selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, halogen, -$NR^{48}C(O)$-(C_{1-6})alkyl, -$NR^{48}C(O)$-(C_3)cycloalkyl, 4, 5, or 6 membered ring cyclic N-lactam, -$NR^{48}S(O)_2$-(C_{1-6})alkyl, $NR^{48}R^{49}$, (C_{1-6})alkyl $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ and (C_{1-6})alkyl$NR^{48}R^{49}$;

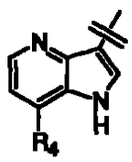
R^{40} is hydrogen; and

R^{41} is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl and heteroaryl; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, or heteroaryl are substituted with one to three same or different halogens or one to two same or different substituents selected from the group consisting of methyl, (C_{1-3})alkoxy, heteroaryl and aryl; wherein said aryl or heteroaryl are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, -$NR^{42}C(O)$-(C_{1-6})alkyl, $NR^{42}R^{43}$ and $C(O)NR^{42}R^{43}$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

Q is



;

A is Phenyl, 2-pyridyl, or 3-pyridyl;

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$ or heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

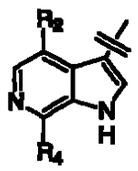
wherein:

B is heteroaryl, wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

Q is



;

R^2 is selected from the group consisting of hydrogen, halogen, and methoxy;

R^4 is B;

B is selected from the group consisting of -C(O)$NR^{40}R^{41}$ or heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A is phenyl, 2-pyridyl, or 3-pyridyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is -C(O)$NR^{40}R^{41}$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl, wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl (C_{1-6})alkoxy, hydroxy, heteroaryl, heteroalicyclic, methoxy, $-S(C_{1-3})$alkyl, halogen, $-C(O)R^{57}$, $C(O)NR^{42}R^{43}$, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}C(O)-(C_{3-6})$cycloalkyl, $-NR^{42}C(O)$-aryl, $-NR^{42}C(O)$-heteroaryl, $-NR^{42}C(O)$-heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$alkyl, $-NR^{42}S(O)_2-(C_{3-6})$cycloalkyl, $-NR^{42}S(O)2$-aryl, $-NR^{42}S(O)_2$-heteroaryl, $-NR^{42}S(O)2$-heteroalicyclic, $NR^{42}R^{43}$, $NR^{55}(C_{1-3})$alkyl$NR^{55}R^{56}$ and $COOR^{54}$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

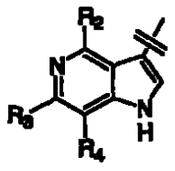
wherein:

A is phenyl, 2-pyridyl, or 3-pyridyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

Q is



;

R^2 is selected from the group consisting of hydrogen and methoxy;

R^3 is hydrogen; and

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$ and heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is fluoro.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is methoxy.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole,

azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, -thiazole, pyrrole, piperazine, pyrrolidine and N-pyrrolidone.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is –C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -methoxy, -NHC(C_1-C_6 alkyl) and -N(C_1-C_6 alkyl)$_2$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -NHC(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -heteroaryl and a 4, 5, or 6 membered cyclic N-lactam.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is –C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -methoxy, -NHC(C_1-C_6 alkyl) and -N(C_1-C_6 alkyl)$_2$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -COOC_1-C_6 alkyl, -NHC(O)-(C_1-$_6$alkyl), -NHS(O)$_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, -thiazole, pyrrole, piperazine, pyrrolidine and N-pyrrolidone.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is –C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -methoxy, -NHC(C_1-C_6 alkyl) and -N(C_1-C_6 alkyl)$_2$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is thienyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is thienyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, amino, -NHC(O)-(C_1-C_6 alkyl), -C(O)-NH_2, C(O)NHMe, $C(O)NMe_2$ and -$NR^{55}R^{56}$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substitment selected from the group F consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A compound of claim 3 is depicted in Table 2.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A compound of claim 3 is depicted in Table 2-1.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A compound of claim 3 is depicted in Table 3.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A compound of claim 3 is depicted in Table 4.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A compound of claim 3 is depicted in Table 5.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

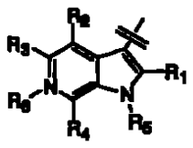
wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; wherein said phenyl or heteroaryl is independently optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, or halogen;

- - represents a carbon-carbon bond;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} are each independently hydrogen or methyl, with the proviso that only zero, one, or two is methyl;

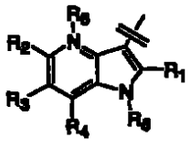
Q is either:

(a)  ;

R^2 is selected from the group consisting of hydrogen, halogen, and methoxy; and

R_3 is hydrogen; or

(b) Q is:

 ;

R^2 and R^3 are hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B;

B is heteroaryl selected from the group consisting of triazole, pyrazole, oxazole, pyrazine, pyrimidine and oxadiazole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

F is selected from the group consisting of (C_{1-6})alkyl, heteroaryl, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}R^{43}$ and $C(O)NR^{42}R^{43}$;

R^5 is hydrogen;

R^6 does not exist; and

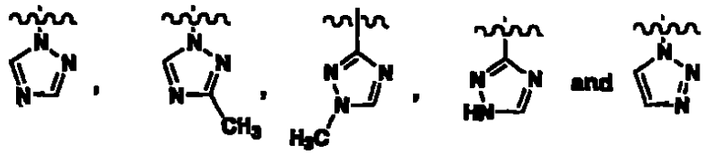
R^{42} and R^{43} are independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; or R^{42} and R^{43} taken together with the nitrogen to which they are attached form a heteroalicyclic selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, tetrahydrofuran, tetrahydropyran, azepine and morpholine.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is H, Cl , F, or methoxy; and

R^4 is selected from the group consisting of



Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is methoxy or fluoro; and

one of R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, or R^{16} is methyl and the others are hydrogen.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is methoxy; and

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} are each hydrogen.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

one of R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, or R^{16} is (R)-methyl and the others are hydrogen.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

one of R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, or R^{16} is (S)-methyl and the others are hydrogen.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is methoxy, hydrogen, chloro, or fluoro; and

R^4 is oxadiazole.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is methoxy, hydrogen, chloro or fluoro; and

R^4 is oxadiazole substituted with a single fluoro, chloro, amino or methyl group.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

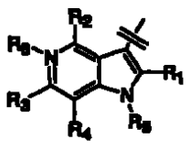
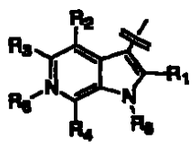
wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein said heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, hydroxy, or halogen;

R^9, R^{10}, R^{11}, R^{12}, R^{15}, and R^{16} are each hydrogen;

R^{13} and R^{14} are each independently hydrogen or methyl with the proviso that only one is methyl;

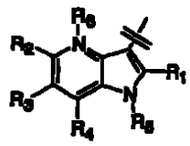
Q is either:

(a)  or  ;

R^2 is selected from the group consisting of hydrogen, halogen and methoxy; and

R_3 is hydrogen; or

(b) Q is:

 ;

and R^2 is halogen or hydrogen and R^3 is hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B; and

B is selected from the group consisting of -C(O)$NR^{40}R^{41}$, substituted phenyl, heteroaryl, oxazoline, pyrazinone, methylene dioxy or ethylene dioxy fused to a

benzene or pyridine; wherein said heteroaryl or phenyl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl and heteroaryl; wherein said phenyl is substituted and heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, (C_{1-6})thioalkoxy, cyano, halogen, $-C(O)R^{57}$, benzyl, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}C(O)-(C_{3-6})$cycloalkyl, $-NR^{42}C(O)$-aryl, $-NR^{42}C(O)$-heteroaryl, $-NR^{42}C(O)$-heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$alkyl, $-NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ and $COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G;

G is selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, halogen, $-NR^{48}C(O)-(C_{1-6})$alkyl, $-NR^{48}C(O)-(C_3)$cycloalkyl, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{48}S(O)_2-(C_{1-6})$alkyl, $NR^{48}R^{49}$, (C_{1-6})alkyl $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ and (C_{1-6})alkyl$NR^{48}R^{49}$;

R^{40} is hydrogen;

R^{41} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, or heteroaryl; wherein said (C_{1-6})alkyl,

(C_{3-7})cycloalkyl, phenyl, or heteroaryl are substituted with one to three same or different halogens or one to two same or different methyl, (C_{1-3})alkoxy, heteroaryl or aryl; wherein said aryl or heteroaryl are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, -$NR^{42}C(O)$-(C_{1-6})alkyl, $NR^{42}R^{43}$ and $C(O)NR^{42}R^{43}$.

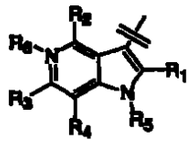
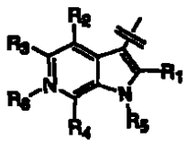
Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, hydroxy, or halogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} ,and R^{16} are each independently hydrogen or methyl with the proviso that only one is methyl;

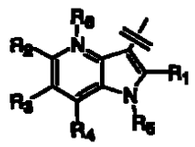
Q is either:

(a)  or  ;

wherein R^2 is selected from the group consisting of hydrogen, halogen and methoxy; and

R_3 is hydrogen; or

(b) Q is:



wherein R^2 is halogen or hydrogen; and R^3 is hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B;

B is selected from the group consisting of -C(O)$NR^{40}R^{41}$, substituted phenyl, heteroaryl, oxazoline, pyrazinone, methylene dioxy or ethylene dioxy fused to a benzene or pyridine; wherein said heteroaryl or phenyl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is selected from the group consisting of pyrazinone and methylene dioxy or ethylene dioxy fused to a benzene ring; wherein said group is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -NHC(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -heteroaryl and a 4, 5, or 6 membered cyclic N-lactam.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

B is selected from the group consisting of oxadiazole, triazole, pyrazole, pyrazine and pyrimidine; wherein said group is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -NHS(O)$_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -NHC(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -heteroaryl, a 4, 5, or 6 membered cyclic N-lactam and (C_{1-6})alkyl$NR^{48}R^{49}$.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

heteroaryl in B is selected from the group consisting of pyrazine and pyrimidine.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

heteroaryl in B is selected from the group consisting of pyrazine and pyrimidine.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

wherein R^9, R^{10}, R^{15} and R^{16} are each hydrogen; and R^{11}, R^{12}, R^{13}, and R^{14} are each independently hydrogen or methyl with the proviso that up to one can be methyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

one of R^{11}, R^{12}, R^{13}, and R^{14} is methyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

the carbon atom of the piperazine ring to which the methyl group of R^{11}, R^{12}, R^{13}, and R^{14} is attached has an (R) configuration.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^{11}, R^{12}, R^{13}, and R^{14} are each hydrogen; and R^{9}, R^{10}, R^{15} and R^{16} are each independently hydrogen or methyl with the proviso that up to one can be methyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

one of R^{9}, R^{10}, R^{15} and R^{16} is methyl.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

the carbon atom of the piperazine ring to which the methyl group of R^9, R^{10}, R^{15} and R^{16} is attached has an (R) configuration.

Another preferred embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,

wherein:

R^1 is hydrogen;

m is 2;

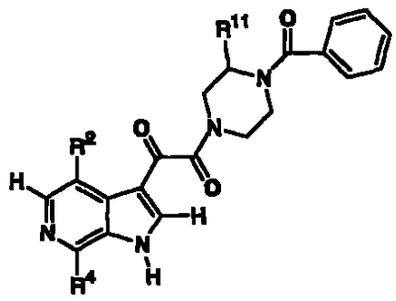
R^5 is hydrogen;

R^6 does not exist;

A is selected from the group consisting of C_{1-6}alkoxy, aryl and heteroaryl; wherein aryl is phenyl; heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl and isoxazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different amino, cyano, hydroxy C_{1-6}alkoxy, C_{1-6}alkyl, $-NHC(O)CH_3$, halogen and trifluoromethyl; and

- - represents a carbon-carbon bond.

A most preferred embodiment is a compound of Formula Ia, including pharmaceutically acceptable salts thereof,

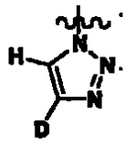


Ia

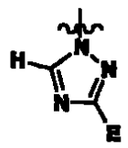
wherein:

R^2 is methoxy, fluoro or chloro.

R^4 is selected from the group consisting of either:



which is a 1,2,3 triazole directly attached via the nitrogen atom of position 1 of the triazole wherein said 1,2,3 triazole is substituted with D at position 4
or R^4 is:



which is a 1,2,4 triazole attached via the nitrogen atom of position 1 of the triazole wherein said 1,2,4 triazole is substituted with E at position 3.

D is selected from hydrogen or C_1-C_3 alkyl.

E is selected from the group consisting hydrogen, (C_1-C_3)alkyl, $O(C_1-C_3)$alkyl or CH_2OCH_3.

R^{11} is either hydrogen or methyl in which the configuration to which the methyl is attached is (R) with the proviso that when R^4 is 1,2,3 triazole, then R^{11} is hydrogen.

Another embodiment of the invention is a pharmaceutical formulation comprising an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier. When used for treating HIV infection, said formulation can optionally additionally contain an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: an AIDS antiviral agent; an antiinfective agent; an immunomodulator; and HIV entry inhibitors.

A third embodiment of the invention is a method for treating mammals infected with a virus, such as HIV, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, a pharmaceutically acceptable carrier, optionally in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

Since the compounds of the present invention, may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present invention includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formula I in addition to the mixtures thereof.

DEFINITIONS

The term "C_{1-6} alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

"Halogen" refers to chlorine, bromine, iodine or fluorine.

An "aryl" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and $-NR^xR^y$, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl,

carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl. diazinyl, pyrazine, triazinyltriazine, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $-NR^xR^y$, wherein R^x and R^y are as defined above.

As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$, wherein R^x and R^y are as defined above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually

selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, cycloheptane, cycloheptatriene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalo- methanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an –OH group.

An "alkoxy" group refers to both an –O-alkyl and an –O-cycloalkyl group as defined herein.

An "aryloxy" group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

A "heteroaryloxy" group refers to a heteroaryl-O- group with heteroaryl as defined herein.

A "heteroalicycloxy" group refers to a heteroalicyclic-O- group with heteroalicyclic as defined herein.

A "thiohydroxy" group refers to an –SH group.

A "thioalkoxy" group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an –S-aryl and an –S-heteroaryl group, as defined herein.

A "thioheteroaryloxy" group refers to a heteroaryl-S- group with heteroaryl as defined herein.

A "thioheteroalicycloxy" group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

A "carbonyl" group refers to a –C(=O)-R" group, where R" is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An "aldehyde" group refers to a carbonyl group where R" is hydrogen.

A "thiocarbonyl" group refers to a –C(=S)-R" group, with R" as defined herein.

A "Keto" group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heterosaliacyclic group.

A "trihalomethanecarbonyl" group refers to a $Z_3CC(=O)$- group with said Z being a halogen.

A "C-carboxy" group refers to a –C(=O)O-R" groups, with R" as defined herein.

An "O-carboxy" group refers to a R"C(-O)O-group, with R" as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R" is hydrogen.

A "trihalomethyl" group refers to a $-CZ_3$, group wherein Z is a halogen group as defined herein.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$- groups with Z as defined above.

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^X$- group with Z and R^X as defined herein.

A "sulfinyl" group refers to a –S(=O)-R" group, with R" as defined herein and, in addition, as a bond only; i.e., -S(O)-.

A "sulfonyl" group refers to a $-S(=O)_2R$" group with R" as defined herein and, in addition as a bond only; i.e., $-S(O)_2-$.

A "S-sulfonamido" group refers to a $-S(=O)_2NR^XR^Y$, with R^X and R^Y as defined herein.

A "N-Sulfonamido" group refers to a $R"S(=O)_2NR_x$- group with R_x as defined herein.

A "O-carbamyl" group refers to a $-OC(=O)NR^xR^y$ as defined herein.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y as defined herein.

A "O-thiocarbamyl" group refers to a $-OC(=S)NR^xR^y$ group with R^x and R^y as defined herein.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$- group with R^x and R^y as defined herein.

An "amino" group refers to an $-NH_2$ group.

A "C-amido" group refers to a $-C(=O)NR^xR^y$ group with R^x and R^y as defined herein.

A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y as defined herein.

A "N-amido" group refers to a $R^xC(=O)NR^y$- group, with R^x and R^y as defined herein.

A cyclic 4, 5, or six membered ring N-lactam refers to rings of 4, 5 or 6 atoms containing a single amide group as two of the ring atoms which is linked to the parent molecule at the amide nitrogen.

An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group with R^x and R^y as defined herein and R^{y2} defined the same as R^x and R^y.

A "guanidino" group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y and R^{y2} as defined herein.

A "guanyl" group refers to a $R^xR^yNC(=N)-$ group, with R^x and R^Y as defined herein.

A "cyano" group refers to a –CN group.

A "silyl" group refers to a $-Si(R'')_3$, with R'' as defined herein.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x as defined herein.

A "hydrazino" group refers to a $-NR^xNR^yR^{y2}$ group with R^x, R^y and R^{y2} as defined herein.

Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

It is known in the art that nitogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present invention are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

Physiologically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this invention. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without

limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)- aminomethane), or with bases such as piperidine or morpholine.

In the method of the present invention, the term "antiviral effective amount" means the total amount of each active component of the method that is sufficient to show a meaningful patient benefit, i.e., healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing or ameliorating diseases associated with HIV infection.

The present invention is also directed to combinations of the compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following table.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)
Amprenivir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir

Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene	Syntex	Sight threatening
Ganciclovir		CMV peripheral CMV retinitis

Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266) (-)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, STOCRINE	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)

GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection

Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boehringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)

Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (Viread®)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
Combivir®	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
abacavir succinate (or Ziagen®)	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
REYATAZ® (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDs, protease inhibitor
FUZEON (or T-20)	Roche / Trimeris	HIV infection AIDs, viral Fusion inhibitor

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IMMUNOMODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT

HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldesalukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE	Ciba-Geigy Corp.	Kaposi's sarcoma
Muramyl-Tripeptide Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic

rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP

Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia .
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting

Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

Additionally, the compounds of the invention herein may be used in combination with another class of agents for treating AIDS which are called HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194.

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is indinavir, which is the *sulfate* salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC;

(3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The preparative procedures and anti-HIV-1 activity of the novel azaindole piperazine diamide analogs of Formula I are summarized below in Schemes 1-64.

Abbreviations

The following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, are used throughout the description of the invention and the examples. Some of the abbreviations used are as follows:

h	=	hour(s)
rt	=	room temperature
mol	=	mole(s)
mmol	=	millimole(s)
g	=	gram(s)
mg	=	milligram(s)
mL	=	milliliter(s)
TFA	=	Trifluoroacetic Acid
DCE	=	1,2-Dichloroethane
CH_2Cl_2	=	Dichloromethane
TPAP	=	tetrapropylammonium perruthenate

	THF	=	Tetrahydofuran
	DEPBT	=	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
	DMAP	=	4-dimethylaminopyridine
	P-EDC	=	Polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	EDC	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	DMF	=	*N,N*-dimethylformamide
	Hunig's Base	=	*N,N*-Diisopropylethylamine
	mCPBA	=	*meta*-Chloroperbenzoic Acid
	azaindole	=	1*H*-Pyrrolo-pyridine
	4-azaindole	=	1*H*-pyrrolo[3,2-*b*]pyridine
	5-azaindole	=	1*H*-Pyrrolo[3,2-*c*]pyridine
	6-azaindole	=	1*H*-pyrrolo[2,3-*c*]pyridine
	7-azaindole	=	1*H*-Pyrrolo[2,3-*b*]pyridine
	PMB	=	4-Methoxybenzyl
	DDQ	=	2, 3-Dichloro-5, 6-dicyano-1, 4-benzoquinone
	OTf	=	Trifluoromethanesulfonoxy
	NMM	=	4-Methylmorpholine
	PIP-COPh	=	1-Benzoylpiperazine
	NaHMDS	=	Sodium hexamethyldisilazide
	EDAC	=	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
	TMS	=	Trimethylsilyl
	DCM	=	Dichloromethane
	DCE	=	Dichloroethane

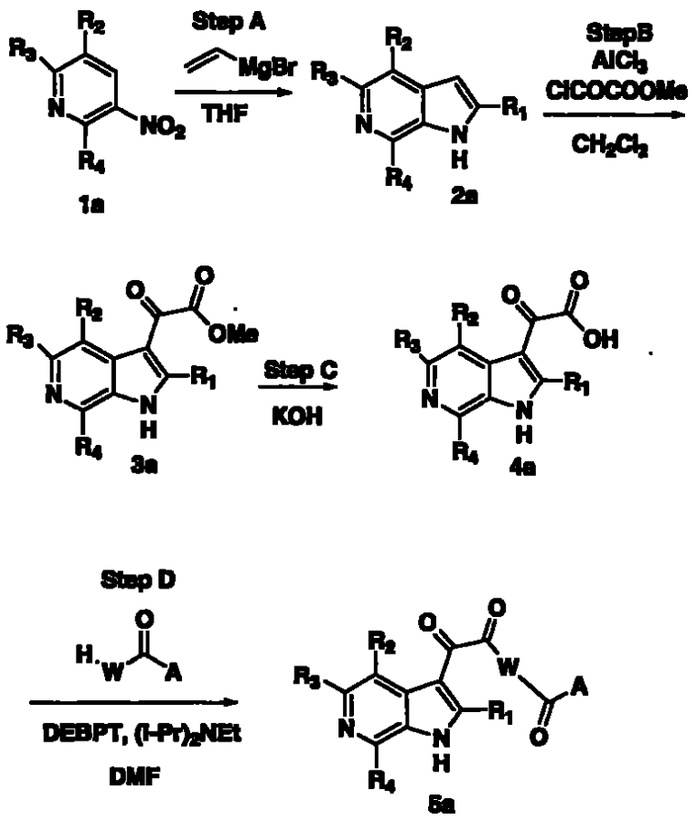
MeOH	=	Methanol
THF	=	Tetrahrdrofuran
EtOAc	=	Ethyl Acetate
LDA	=	Lithium diisopropylamide
TMP-Li	=	2,2,6,6-tetramethylpiperidinyl lithium
DME	=	Dimethoxyethane
DIBALH	=	Diisobutylaluminum hydride
HOBT	=	1-hydroxybenzotriazole
CBZ	=	Benzyloxycarbonyl
PCC	=	Pyridinium chlorochromate
Me	=	Methyl
Ph	=	Phenyl

Chemistry

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formula I include pharmaceutically acceptable salts thereof.

General procedures to construct substituted azaindole piperazine diamides of Formula I and intermediates useful for their synthesis are described in the following Schemes, 1-81.

Scheme 1



Step A in Scheme 1 depicts the synthesis of an aza indole intermediate, 2a, via the well known Bartoli reaction in which vinyl magnesium bromide reacts with an aryl or heteroaryl nitro group, such as in 1, to form a five-membered nitrogen containing ring as shown. Some references for the above transformation include: Bartoli et al. a) *Tetrahedron Lett.* **1989**, *30*, 2129. b) *J. Chem. Soc. Perkin Trans. 1* **1991**, 2757. c) *J. Chem. Soc. Perkin Trans. II* **1991**, 657. d) SynLett (1999), 1594. In the preferred procedure, a solution of vinyl Magnesium bromide in THF (typically 1.0M but from 0.25 to 3.0M) is added dropwise to a solution of the nitro pyridine in THF at -78° under an inert atmosphere of either nitrogen or Argon. After addition is completed, the reaction temperature is allowed to warm to -20° and then is stirred for approximately 12h before quenching with 20% aq ammonium chloride solution. The reaction is extracted with ethyl acetate and then worked up in a typical manner using a drying agent such as anhydrous magnesium sulfate or sodium sulfate. Products are

generally purified using chromatography over Silica gel. Best results are generally achieved using freshly prepared vinyl Magnesium bromide. In some cases, vinyl Magnesium chloride may be substituted for vinyl Magnesium bromide.

Substituted azaindoles may be prepared by methods described in the literature or may be available from commercial sources. Thus there are many methods for carrying out step A in the literature and the specific examples are too numerous to even list. Alternative syntheses of aza indoles and general methods for carrying out step A include, but are not limited to, those described in the following references (a-k below): a) Prokopov, A. A.; Yakhontov, L. N. *Khim.-Farm. Zh.* **1994**, *28(7)*, 30-51; b) Lablache-Combier, A. **Heteroaromatics.** Photoinduced Electron Transfer **1988**, Pt. C, 134-312; c) Saify, Zafar Said. *Pak. J. Pharmacol.* **1986**, *2(2)*, 43-6; d) Bisagni, E. *Jerusalem Symp. Quantum Chem. Biochem.* **1972**, *4*, 439-45; e) Yakhontov, L. N. *Usp. Khim.* **1968**, *37(7)*, 1258-87; f) Willette, R. E. *Advan. Heterocycl. Chem.* **1968**, *9*, 27-105; g) Mahadevan, I.; Rasmussen, M. *Tetrahedron* **1993**, *49(33)*, 7337-52; h) Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29(2)*, 359-67; i) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64(26)*, 9430-9443; j) Spivey, A.C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39(48)*, 8919-8922; k) Advances in Heterocyclic Chemistry (Academic press) **1991**, *Vol. 52*, pg 235-236 and references therein.

Step B. Intermediate 3a can be prepared by reaction of aza-indole, intermediate 2a, with an excess of ClCOCOOMe in the presence of $AlCl_3$ (aluminum chloride) (Sycheva et al, Ref. 26, Sycheva, T.V.; Rubtsov, N.M.; Sheinker, Yu.N.; Yakhontov, L.N. Some reactions of 5-cyano-6-chloro-7-azaindoles and lactam-lactim tautomerism in 5-cyano-6-hydroxy-7-azaindolines. *Khim. Geterotsikl. Soedin.*, **1987**, 100-106). Typically an inert solvent such as CH_2Cl_2 is used but others such as THF, Et_2O, DCE, dioxane, benzene, or toluene may find applicability either alone or in mixtures. Other oxalate esters such as ethyl or benzyl mono esters of oxalic acid could also suffice for either method shown above. More lipophilic esters ease isolation during aqueous extractions. Phenolic or substituted phenolic (such as pentafluorophenol) esters enable direct coupling of the HW(C=O)A group, such as a piperazine, in Step D without activation. Lewis acid catalysts, such as tin

tetrachloride, titanium IV chloride, and aluminum chloride are employed in Step B with aluminum chloride being most preferred. Alternatively, the azaindole is treated with a Grignard reagent such as MeMgI (methyl magnesium iodide), methyl magnesium bromide or ethyl magnesium bromide and a zinc halide, such as $ZnCl_2$ (zinc chloride) or zinc bromide, followed by the addition of an oxalyl chloride mono ester, such as ClCOCOOMe (methyl chlorooxoacetate) or another ester as above, to afford the aza-indole glyoxyl ester (Shadrina et al, Ref. 25). Oxalic acid esters such as methyl oxalate, ethyl oxalate or as above are used. Aprotic solvents such as CH_2Cl_2, Et_2O, benzene, toluene, DCE, or the like may be used alone or in combination for this sequence. In addition to the oxalyl chloride mono esters, oxalyl chloride itself may be reacted with the azaindole and then further reacted with an appropriate amine, such as a piperazine derivative (See Scheme 52, for example).

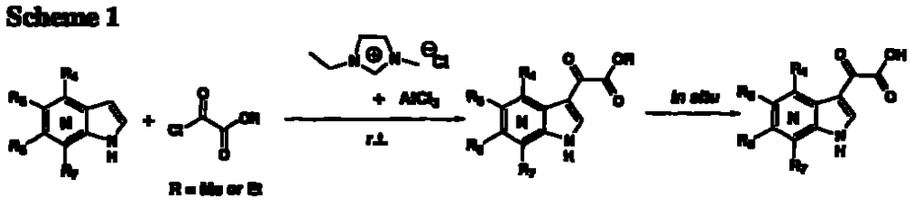
Step C. Hydrolysis of the methyl ester, (intermediate 3a, Scheme 1) affords a potassium salt of intermediate 4a, which is coupled with mono-benzoylated piperazine derivatives as shown in Step D of Scheme 1. Some typical conditions employ methanolic or ethanolic sodium hydroxide followed by careful acidification with aqueous hydrochloric acid of varying molarity but 1M HCl is preferred. The acidification is not utilized in many cases as described above for the preferred conditions. Lithium hydroxide or potassium hydroxide could also be employed and varying amounts of water could be added to the alcohols. Propanols or butanols could also be used as solvents. Elevated temperatures up to the boiling points of the solvents may be utilized if ambient temperatures do not suffice. Alternatively, the hydrolysis may be carried out in a non polar solvent such as CH_2Cl_2 or THF in the presence of Triton B. Temperatures of –78 °C to the boiling point of the solvent may be employed but -10 °C is preferred. Other conditions for ester hydrolysis are listed in reference 41 and both this reference and many of the conditions for ester hydrolysis are well known to chemists of average skill in the art.

Alternative procedures for step B and C:

Imidazolium Chloroaluminate:

We found that ionic liquid 1-alkyl-3-alkylimidazolium chloroaluminate is generally useful in promoting the Friedel-Crafts type acylation of indoles and azaindoles. The ionic liquid is generated by mixing 1-alkyl-3-alkylimidazolium chloride with aluminium chloride at room temperature with vigorous stirring. 1:2 or 1:3 molar ratio of 1-alkyl-3-alkylimidazolium chloride to aluminium chloride is preferred. One particular useful imidazolium chloroaluminate for the acylation of azaindole with methyl or ethyl chlorooxoacetate is the 1-ethyl-3-methylimidazolium chloroaluminate. The reaction is typically performed at ambient temperature and the azaindoleglyoxyl ester can be isolated. More conveniently, we found that the glyoxyl ester can be hydrolyzed *in situ* at ambient temperature on prolonged reaction time (typically overnight) to give the corresponding glyoxyl acid for amide formation (Scheme 1).

Scheme 1

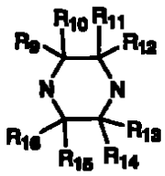


A representative experimental procedure is as follows: 1-ethyl-3-methylimidazolium chloride (2 equiv.; purchased from TCI; weighted under a stream of nitrogen) was stirred in an oven-dried round bottom flask at r.t. under a nitrogen atmosphere, and added aluminium chloride (6 equiv.; anhydrous powder packaged under argon in ampules purchased from Aldrich preferred; weighted under a stream of nitrogen). The mixture was vigorously stirred to form a liquid, which was then added azaindole (1 equiv.) and stirred until a homogenous mixture resulted. The reaction mixture was added dropwise ethyl or methyl chlorooxoacetate (2 equiv.) and then stirred at r.t. for 16 h. After which time, the mixture was cooled in an ice-water bath and the reaction quenched by carefully adding excess water. The precipitates were filtered, washed with water and dried under high vacuum to give the

azaindoleglyoxyl acid. For some examples, 3 equivalents of 1-ethyl-3-methylimidazolium chloride and chlorooxoacetate may be required.

Related references: (1) Welton, T. *Chem Rev.* **1999**, *99*, 2071; (2) Surette, J. K. D.; Green, L.; Singer, R. D. *Chem. Commun.* **1996**, 2753; (3) Saleh, R. Y. WO 0015594.

Step D. The acid intermediate, 4a, from step C of Scheme 1 is coupled with an amine A(C=O)WH preferably in the presence of DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one) and *N,N*-diisopropylethylamine, commonly known as Hunig's base, to provide azaindole piperazine diamides. DEPBT was prepared according to the procedure of Ref. 28, Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Organic Lett.*, **1999**, *1*, 91-93. Typically an inert solvent such as DMF or THF is used but other aprotic solvents could be used. The group W as referred to herein is

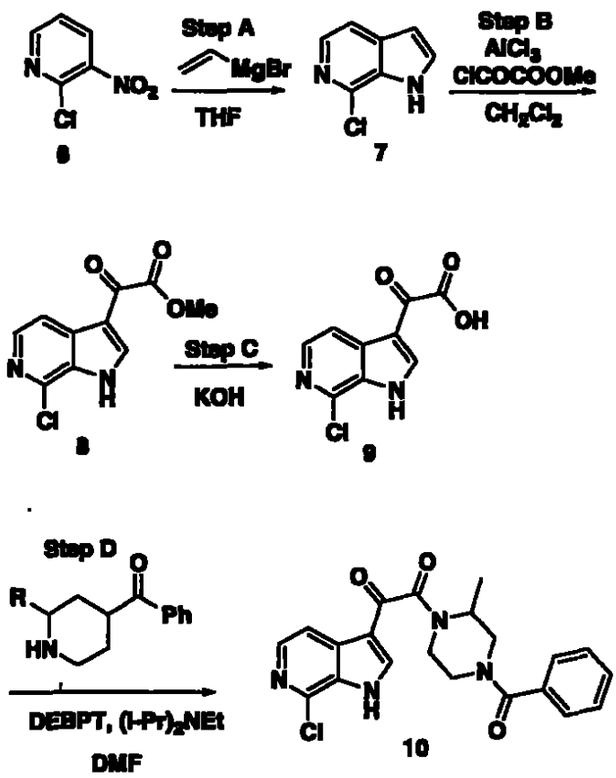


The amide bond construction reaction could be carried out using the preferred conditions described above, the EDC conditions described below, other coupling conditions described in this application, or alternatively by applying the conditions or coupling reagents for amide bond construction described later in this application for construction of substituents R_1-R_4. Some specific nonlimiting examples are given in this application.

The mono-substituted piperazine derivatives can be prepared according to well established procedures such as those described by Desai et al, Ref. 27(a), Adamczyk et al, Ref. 27(b), Rossen et al, Ref. 27(c), and Wang et al, 27(d).

Additional procedures for synthesizing, modifying and attaching groups : $(C=O)_m$-WC(O)-A are contained in PCT WO 00/71535.

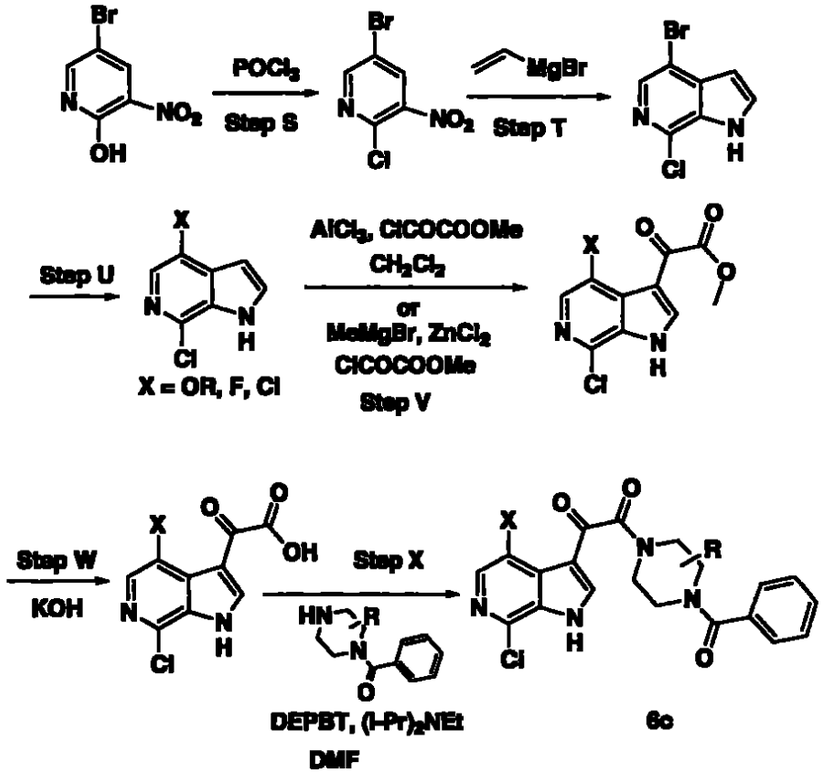
Scheme 2



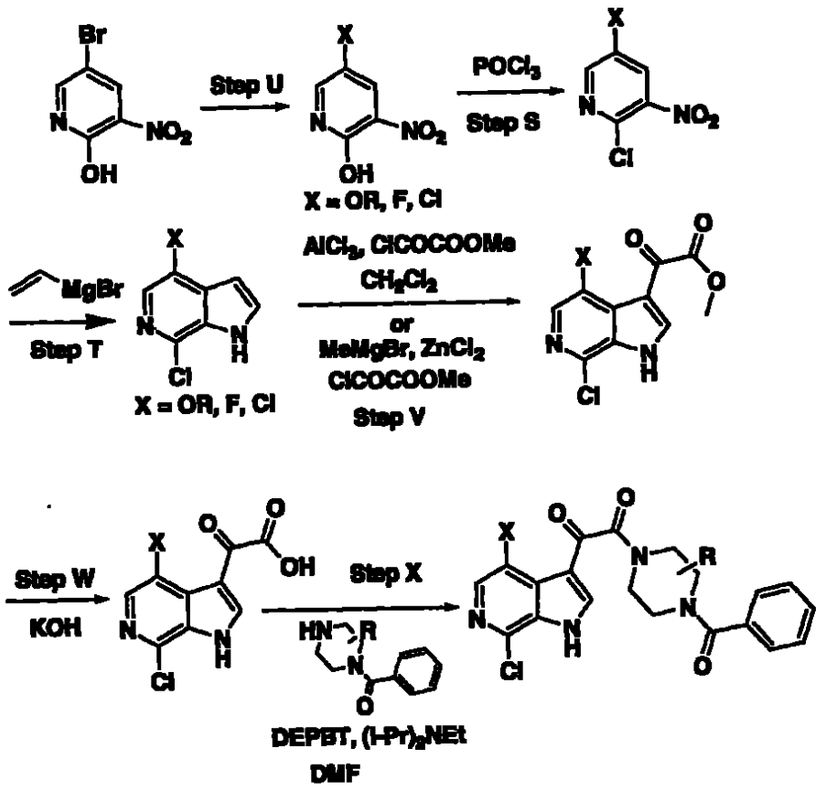
Scheme 2 provides a more specific example of the transformations previously described in Scheme 1. Intermediates 6-10 are prepared by the methodologies as described for intermediates 1a-5a in Scheme 1. Scheme 2A is another embodiment of the transformations described in Schemes 1 and 2. Conversion of the phenol to the chloride (Step S, Scheme 2A) may be accomplished according to the procedures described in Reimann, E.; Wichmann, P.; Hoefner, G.; Sci. Pharm. 1996, *64(3)*, 637-646; and Katritzky, A.R.; Rachwal, S.; Smith, T.P.; Steel, P.J.; *J. Heterocycl. Chem.* 1995, *32(3)*, 979-984. Step T of Scheme 2A can be carried out as described for Step A of Scheme 1. The bromo intermediate can then be converted into alkoxy, chloro, or fluoro intermediates as shown in Step U of Scheme 2A. Scheme 2A describes the

preferred method for preparing intermediate 6c or other closely related compounds containing a 4 methoxy group in the 6-azaindole system. When step U is the conversion of the bromide into alkoxy derivatives, the conversion may be carried out by reacting the bromide with an excess of sodium methoxide in methanol with cuprous salts, such as copper I bromide, copper I iodide, and copper I cyanide. The temperature may be carried out at temperatures of between ambient and 175° but most likely will be around 115°C or 100°C. The reaction may be run in a pressure vessel or sealed tube to prevent escape of volatiles such as methanol. The preferred conditions utilize 3eq of sodium methoxide in methanol, CuBr as the reaction catalyst (0.2 to 3 equivalents with the preferred being 1 eq or less) , and a reaction temperature of 115° C. The reaction is carried out in a sealed tube or sealed reaction vessel. The conversion of the bromide into alkoxy derivatives may also be carried out according to procedures described in Palucki, M.; Wolfe, J.P.; Buchwald, S.L.; *J. Am. Chem. Soc.* **1997**, *119(14)*, 3395-3396; Yamato, T.; Komine, M.; Nagano, Y.; *Org. Prep. Proc. Int.* **1997**, *29(3)*, 300-303; Rychnovsky, S.D.; Hwang, K.; *J. Org. Chem.* **1994**, *59(18)*, 5414-5418. Conversion of the bromide to the fluoro derivative (Step U, Scheme 2A) may be accomplished according to Antipin, I.S.; Vigalok, A.I.; Konovalov, A.I.; *Zh. Org. Khim.* **1991**, *27(7)*, 1577-1577; and Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H.; *Synlett.* **1992**, *4*, 345-346. Conversion of the bromide to the chloro derivative (Step U, Scheme 2A) may be accomplished according to procedures described in Gilbert, E.J.; Van Vranken, D.L.; *J. Am. Chem. Soc.* **1996**, *118(23)*, 5500-5501; Mongin, F.; Mongin, O.; Trecourt, F.; Godard, A.; Queguiner, G.; *Tetrahedron Lett.* **1996**, *37(37)*, 6695-6698; and O'Connor, K.J.; Burrows, C.J.; *J. Org. Chem.* **1991**, *56(3)*, 1344-1346. Steps V, W and X of Scheme 2A are carried out according to the procedures previously described for Steps B, C, and D of Scheme 1, respectively. The steps of Scheme 2A may be carried out in a different order as shown in Scheme 2B and Scheme 2C.

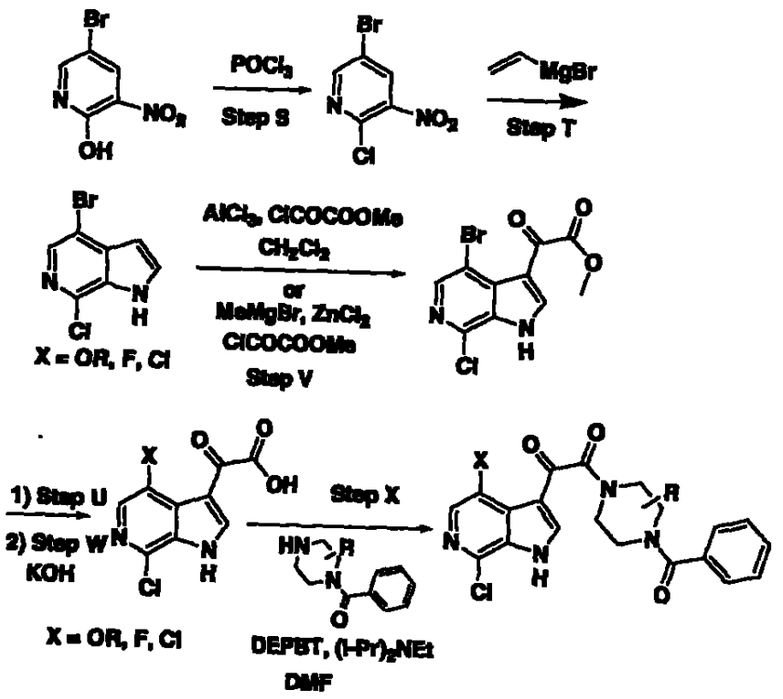
Scheme 2A


Br
N
NO2
OH
POCl3
Step S
Cl
MgBr
Step T
H
Step U
X
X = OR, F, Cl
AlCl3, ClCOCOOMe
CH2Cl2
or
MeMgBr, ZnCl2
ClCOCOOMe
Step V
O
OH
Step W
KOH
Step X
HN
R
DEPBT, (i-Pr)2NEt
DMF
6c

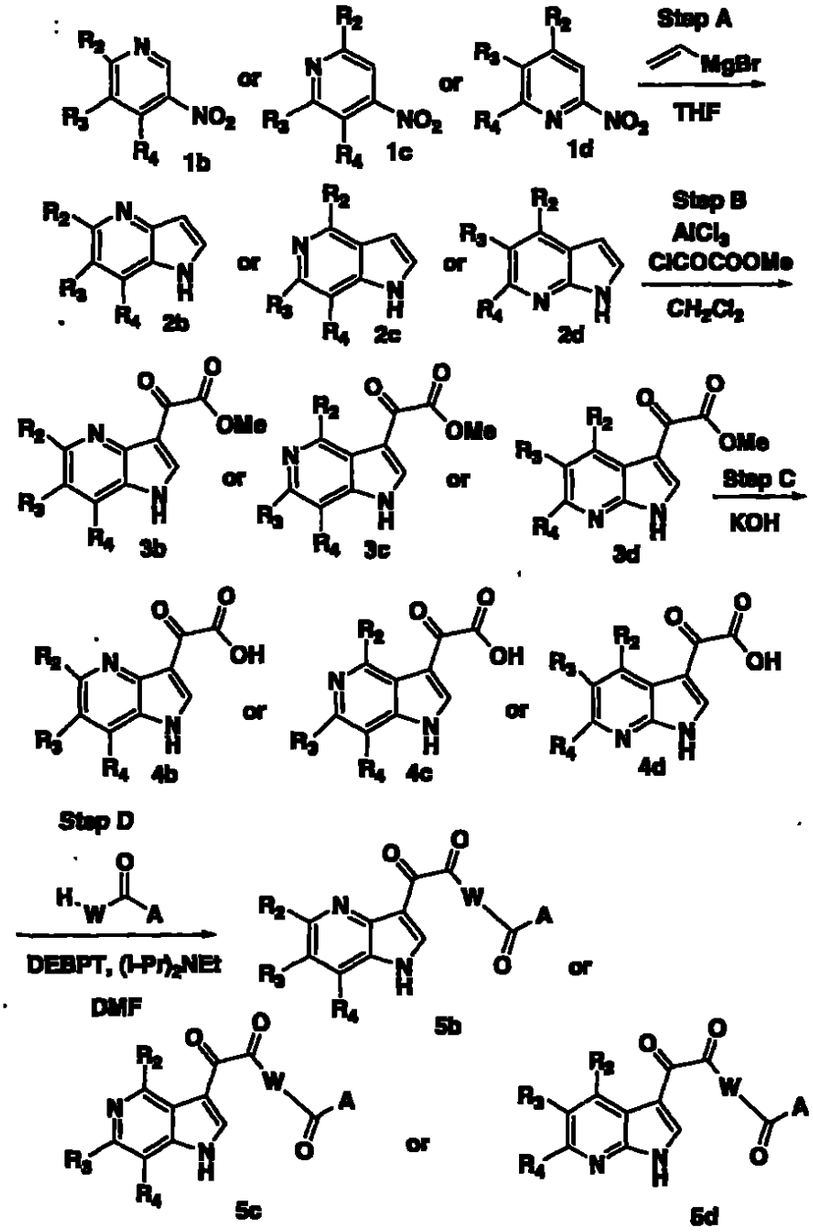
Scheme 2B


Br
Step U
X
POCl3
Step S
NO2
OH
Cl
X = OR, F, Cl
MgBr
Step T
AlCl3, ClCOCOOMe
CH2Cl2
or
MeMgBr, ZnCl2
ClCOCOOMe
Step V
Step W
KOH
Step X
HN
R
N
O
DEPBT, (i-Pr)2NEt
DMF

Scheme 2C


Br
NO2
OH
POCl3
Step S
Cl
MgBr
Step T
AlCl3, ClCOCOOMe
CH2Cl2
or
MeMgBr, ZnCl2
ClCOCOOMe
Step V
X = OR, F, Cl
1) Step U
2) Step W
KOH
Step X
DEPBT, (i-Pr)2NEt
DMF

Scheme 3

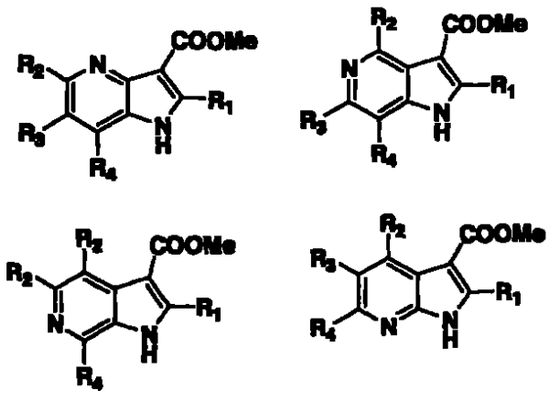


Scheme 3 shows the synthesis of 4-azaindole derivatives 1b-5b, 5-azaindole derivatives 1c-5c, and 7-azaindole derivatives 1d-5d. The methods used to synthesize 1b-5b, 1c-5c, and 1d-5d are the same methods described for the synthesis of 1a-5a as

described in Scheme 1. It is understood, for the purposes of Scheme 3, that 1b is used to synthesize 2b-5b, 1c provides 2c-5c and 1d provides 2d-5d.

The compounds where there is a single carbonyl between the azaindole and group W can be prepared by the method of Kelarev, V. I; Gasanov, S. Sh.; Karakhanov, R. A.; Polivin, Yu. N.; Knatbekova, K. P.; Panina, M. E.; *Zh. Org. Khim* 1992, *28(12)*, 2561-2568. In this method azaindoles are reacted with trichloroacetyl chloride in pyridine and then subsequently with KOH in methanol to provide the 3-carbomethoxy azaindoles shown in Scheme 4 which can then be hydrolyzed to the acid and carried through the coupling sequence with HW(C=O)A to provide the compounds of Formula I wherein a single carbonyl links the azaindole moiety and group W.

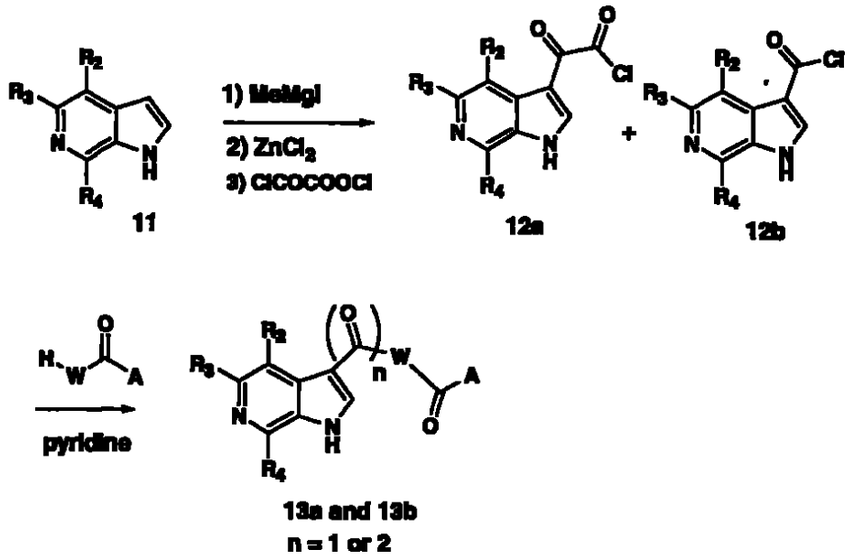
Scheme 4



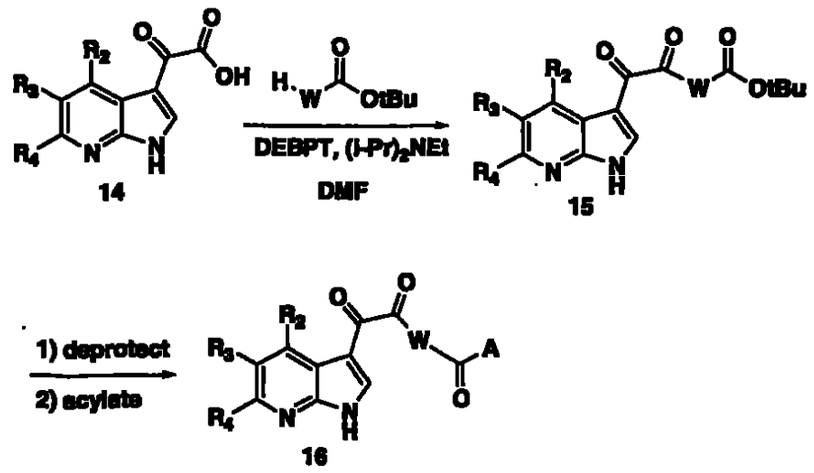
An alternative method for carrying out the sequence outlined in steps B-D (shown in Scheme 5) involves treating an azaindole, such as 11, obtained by procedures described in the literature or from commercial sources, with MeMgI and $ZnCl_2$, followed by the addition of ClCOCOCl (oxalyl chloride) in either THF or Et_2O to afford a mixture of a glyoxyl chloride azaindole, 12a, and an acyl chloride azaindole, 12b. The resulting mixture of glyoxyl chloride azaindole and acyl chloride azaindole is then coupled with mono-benzoylated piperazine derivatives under basic conditions to afford the products of step D as a mixture of compounds, 13a and 13b,

where either one or two carbonyl groups link the azaindole and group W. Separation via chromatographic methods which are well known in the art provides the pure 13a and 13b. This sequence is summarized in Scheme 5, below.

Scheme 5



Scheme 6



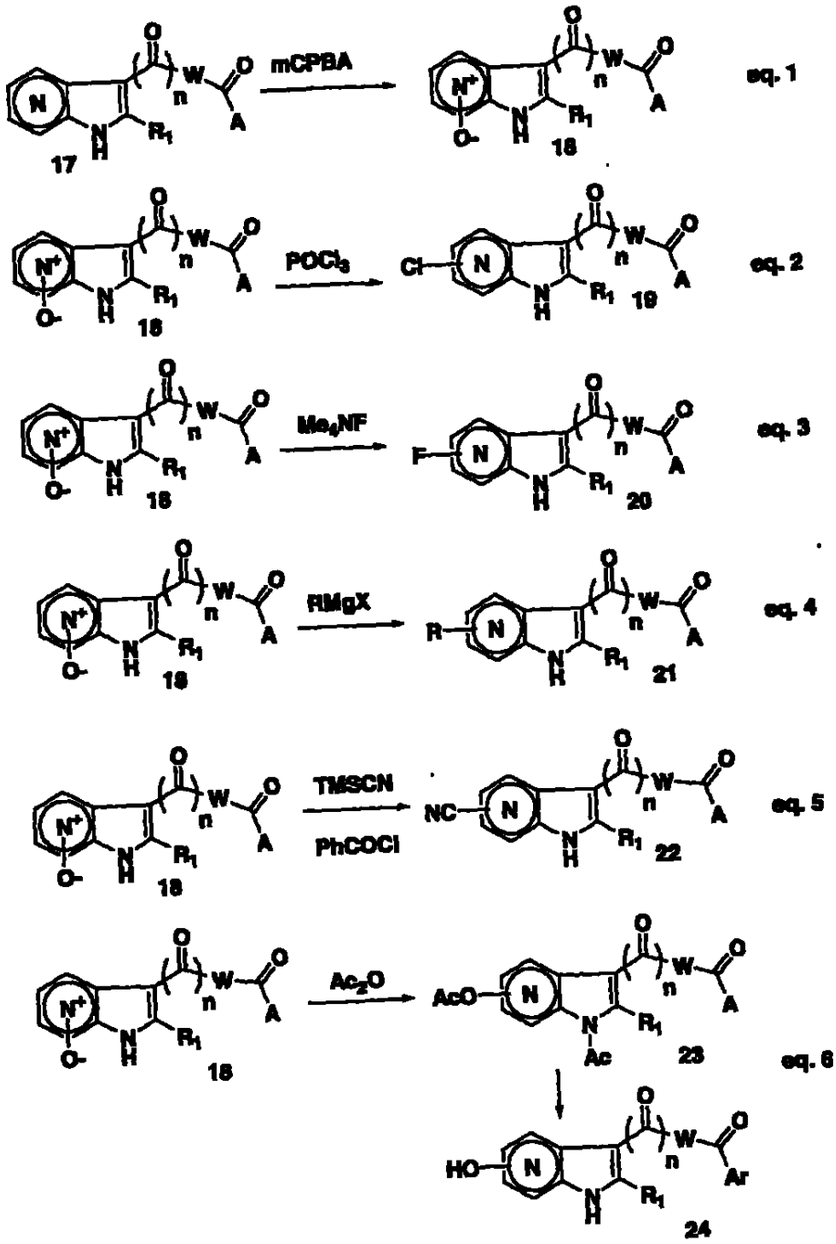
Scheme 6 depicts a general method for modifying the substituent A. Coupling of H-W-C(O)OtBu using the conditions described previously for W in Scheme 1, Step D provides Boc protected intermediate, 15. Intermediate 15 is then deprotected by treatment with an acid such as TFA, hydrochloric acid or formic acid using standard solvents or additives such as CH_2Cl_2 , dioxane, or anisole and temperatures between –78 °C and 100 °C. Other acids such as aq hydrochloric or perchloric may also be used for deprotection. Alternatively other nitrogen protecting groups on W such as Cbz or TROC, may be utilized and could be removed via hydrogenation or treatment with zinc respectively. A stable silyl protecting group such as phenyl dimethylsilyl could also be employed as a nitrogen protecting group on W and can be removed with fluoride sources such as tetrabutylammonium fluoride. Finally, the free amine is coupled to acid A-C(O)OH using standard amine-acid coupling conditions such as those used to attach group W or as shown below for amide formation on positions R_1-R_4 to provide compound 16.

Some specific examples of general methods for preparing functionalized azaindoles or for interconverting functionality on aza indoles which will be useful for preparing the compounds of this invention are shown in the following sections for illustrative purposes. It should be understood that this invention covers substituted 4, 5, 6, and 7 azaindoles and that the methodology shown below may be applicable to all of the above series while other shown below will be specific to one or more. A typical practioner of the art can make this distinction when not specifically delineated. Many methods are intended to be applicable to all the series, particularly functional group installations or interconversions. For example, a general strategy for providing further functionality of this invention is to position or install a halide such as bromo, chloro, or iodo, aldehyde, cyano, or a carboxy group on the azaindole and then to convert that functionality to the desired compounds. In particular, conversion to substituted heteroaryl, aryl, and amide groups on the ring are of particular interest.

General routes for functionalizing azaindole rings are shown in Schemes 7, 8 and 9. As depicted in Scheme 7, the azaindole, 17, can be oxidized to the corresponding *N*-oxide derivative, 18, by using mCPBA (meta-Chloroperbenzoic Acid) in acetone or DMF (eq. 1, Harada et al, Ref. 29 and Antonini et al, Ref. 34).

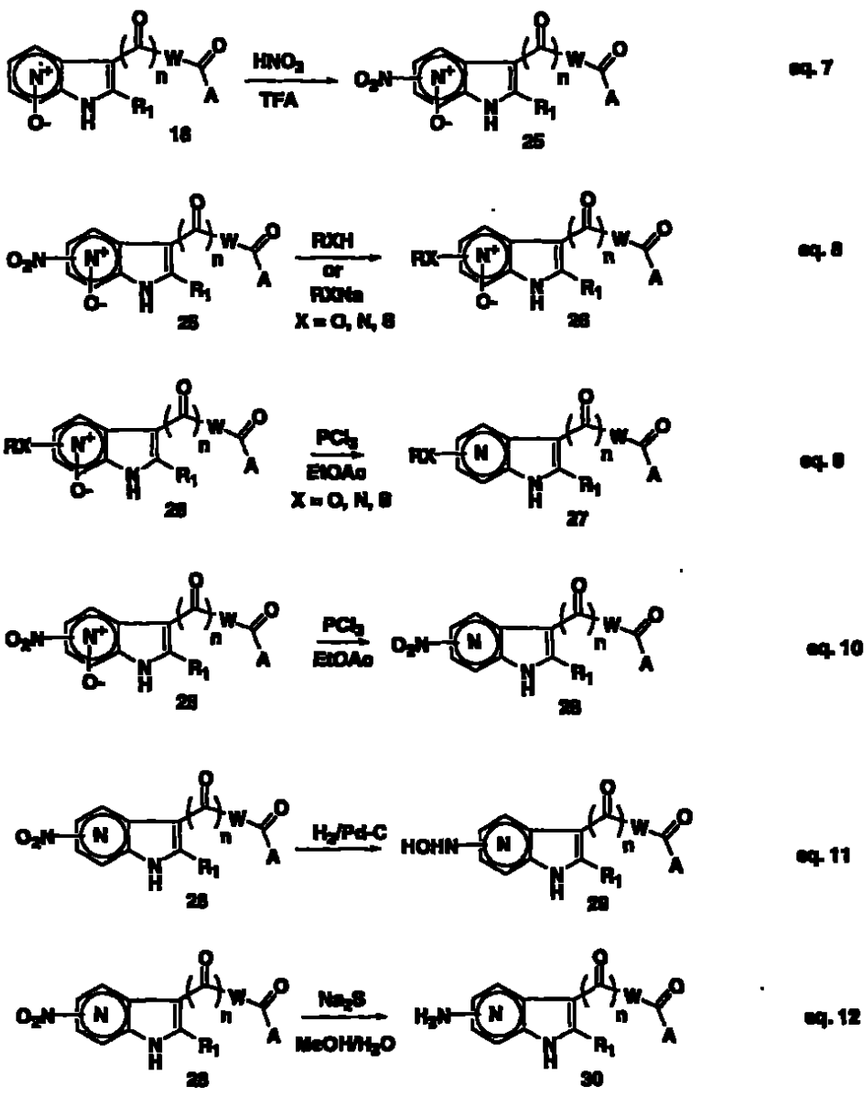
The *N*-oxide, 18, can be converted to a variety of substituted azaindole derivatives by using well documented reagents such as phosphorus oxychloride ($POCl_3$) (eq. 2, Schneller et al, Ref. 30), tetramethylammonium fluoride (Me_4NF) (eq. 3), Grignard reagents RMgX (R = alkyl or aryl, X = Cl, Br or I) (eq. 4, Shiotani et al, Ref. 31), trimethylsilyl cyanide (TMSCN) (eq. 5, Minakata et al, Ref. 32) or Ac_2O (eq. 6, Klemm et al, Ref. 33). Under such conditions, a chlorine (in 19), fluorine (in 20), nitrile (in 22), alkyl (in 21), aromatic (in 21) or hydroxyl group (in 24) can be introduced to the pyridine ring. Nitration of azaindole *N*-oxides results in introduction of a nitro group to azaindole ring, as shown in Scheme 8 (eq. 7, Antonini et al, Ref. 34). The nitro group can subsequently be displaced by a variety of nucleophilic agents, such as OR, NR^1R^2 or SR, in a well established chemical fashion (eq. 8, Regnouf De Vains et al, Ref. 35(a), Miura et al, Ref. 35(b), Proffit et al, Ref. 35(c)). The resulting N-oxides, 26, are readily reduced to the corresponding azaindole, 27, using phosphorus trichloride (PCl_3) (eq. 9, Antonini et al, Ref .34 and Nesi et al, Ref. 36). Similarly, nitro-substituted *N*-oxide, 25, can be reduced to the azaindole, 28, using phosphorus trichloride (eq. 10). The nitro group of compound 28 can be reduced to either a hydroxylamine (NHOH), as in 29, (eq. 11, Walser et al, Ref. 37(a) and Barker et al, Ref. 37(b)) or an amino (NH_2) group, as in 30, (eq. 12, Nesi et al , Ref. 36 and Ayyangar et al, Ref. 38) by carefully selecting different reducing conditions.

Scheme 7


mCPBA
eq. 1
POCl3
eq. 2
Me4NF
eq. 3
RMgX
eq. 4
TMSCN
PhCOCl
eq. 5
Ac2O
eq. 6

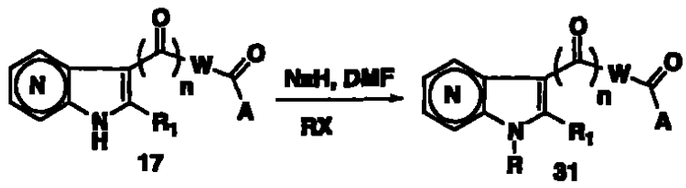
5

Scheme 8



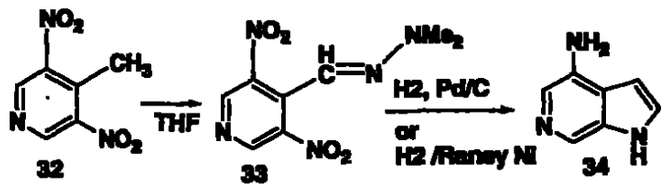
The alkylation of the nitrogen atom at position 1 of the azaindole derivatives can be achieved using NaH as the base, DMF as the solvent and an alkyl halide or sulfonate as alkylating agent, according to a procedure described in the literature (Mahadevan et al, Ref. 39) (Scheme 9).

Scheme 9



In the general routes for substituting the azaindole ring described above, each process can be applied repeatedly and combinations of these processes is permissible in order to provide azaindoles incorporating multiple substituents. The application of such processes provides additional compounds of Formula I.

Scheme 10



The synthesis of 4-aminoazaindoles which are useful precursors for 4, 5, and/or 7-substituted azaindoles is shown in Scheme 10 above.

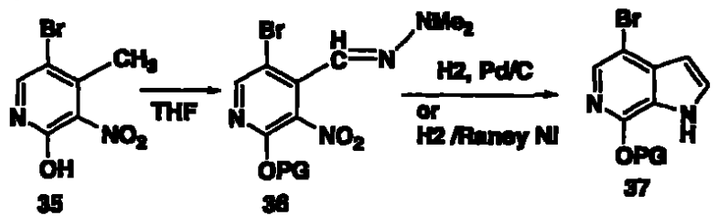
The synthesis of 3, 5-dinitro-4-methylpyridine, 32, is described in the following two references by Achremowicz et.al.: Achremowicz, Lucjan. *Pr. Nauk. Inst. Chem. Org. Fiz. Politech. Wroclaw.* 1982, *23*, 3-128; Achremowicz, Lucjan. *Synthesis* 1975, 10, 653-4. In the first step of Scheme 10, the reaction with dimethylformamide dimethyl acetal in an inert solvent or neat under conditions for forming Batcho-Leimgruber precursors provides the cyclization precursor, 33, as shown. Although the step is anticipated to work as shown, the pyridine may be oxidized to the N-oxide prior to the reaction using a peracid such as MCPBA or a more potent oxidant like meta-trifluoromethyl or meta nitro peroxy benzoic acids. In the second step of Scheme 10, reduction of the nitro group using for example hydrogenation over Pd/C catalyst in a solvent such as MeOH, EtOH, or EtOAc provides the cyclized product, 34. Alternatively the reduction may be carried out using tin dichloride and HCl,

hydrogenation over Raney nickel or other catalysts, or by using other methods for nitro reduction such as described elsewhere in this application.

The amino indole, 34, can now be converted to compounds of Formula I via, for example, diazotization of the amino group, and then conversion of the diazonium salt to the fluoride, chloride or alkoxy group. See the discussion of such conversions in the descriptions for Schemes 17 and 18. The conversion of the amino moiety into desired functionality could then be followed by installation of the oxoacetopiperazine moiety by the standard methodology described above. 5 or 7-substitution of the azaindole can arise from N-oxide formation at position 6 and subsequent conversion to the chloro via conditions such as $POCl_3$ in chloroform, acetic anhydride followed by $POCl_3$ in DMF, or alternatively TsCl in DMF. Literature references for these and other conditions are provided in some of the later Schemes in this application. The synthesis of 4-bromo-7-hydroxy or protected hydroxy-4-azaindole is described below as this is a useful precursor for 4 and/or 7 substituted 6-aza indoles.

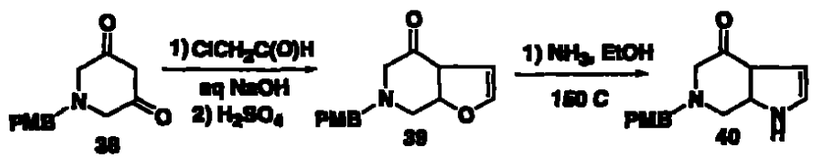
The synthesis of 5-bromo-2-hydroxy-4-methyl-3-nitro pyridine, 35, may be carried out as described in the following reference:Betageri, R.; Beaulieu, P.L.; Llinas-Brunet, M; Ferland, J.M.; Cardozo, M.; Moss, N.; Patel, U.; Proudfoot, J.R. PCT Int. Appl. WO 9931066, 1999. Intermediate 36 is prepared from 35 according to the method as described for Step 1 of Scheme 10. PG is an optional hydroxy protecting group such as triallylsilyl or the like. Intermediate 37 is then prepared from 36 by the selective reduction of the nitro group in the presence of bromide and subsequent cyclization as described in the second step of Scheme 10. $Fe(OH)_2$ in DMF with catalytic tetrabutylammonium bromide can also be utilized for the reduction of the nitro group. The bromide may then be converted to fluoride via displacement with fluoride anions or to other substituents. The compounds are then converted to compounds of Formula I as above.

Scheme 11



An alternate method for preparing substituted 6-azaindoles is shown below in Schemes 12 and 13. It should be recognized that slight modifications of the route depicted below are possible. For example, acylation reactions of the 3 position of what will become the azaindole five membered ring, prior to aromatization of the azaindole, may be carried out in order to obtain higher yields. In addition to a para-methoxybenzyl group (PMB), a benzyl group can be carried through the sequence and removed during azaindole formation by using TsOH, p-Chloranil, in benzene as the oxidant if DDQ is not optimal. The benzyl intermediate, 38, has been described by Ziegler et al. in *J. Am. Chem. Soc.* 1973, *95(22)*, 7458. The transformation of 38 to 40 is analogous to the transformation described in *Heterocycles* 1984, 22, 2313.

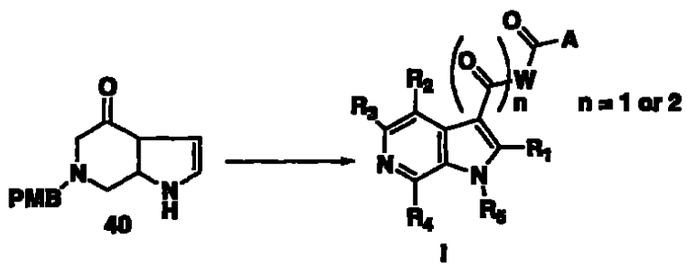
Scheme 12



Scheme 13 describes various transformations of intermediate 40 which ultimately provide compounds of Formula I. The conversions of the phenol moiety to other functionality at position 4 (R_2 position in Scheme 13) may be carried out by the following methods: 1) conversion of a phenol to methoxy group with silver oxide and MeI or diazomethane; 2) conversion of a phenolic hydroxy group to chloro using cat $ZnCl_2$, and N,N dimethylaniline in CH_2Cl_2 or PCl_5 and $POCl_3$ together; 3) conversion of a phenolic hydroxy group to fluoro using diethylamine-SF_3 as in *Org.Prep. Proc. Int.* 1992, *24(1)*, 55-57. The method described in EP 427603, 1991, using the

chloroformate and HF will also be useful. Other transformations are possible. For example the phenol can be converted to a triflate by standard methods and used in coupling chemistries described later in this application.

Scheme 13



1) Ketone alkylation to install R_3

2) DDQ oxidation to form azaindole

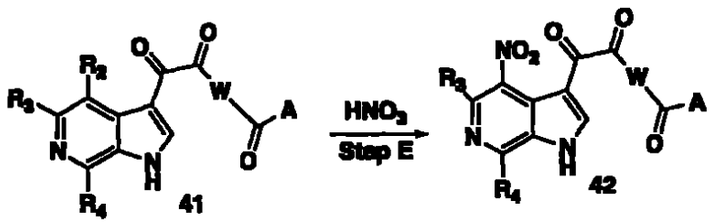
3) Transformation of-phenol (R_2 = OH) into methyl ether, or Fluoro, chloro, etc

4) Use of C-7 directing group to functionalize at R_4 or formation of N-oxide and $POCl_3$ to make R_4 = chloro

5) Conversion to compounds of Formula I as above

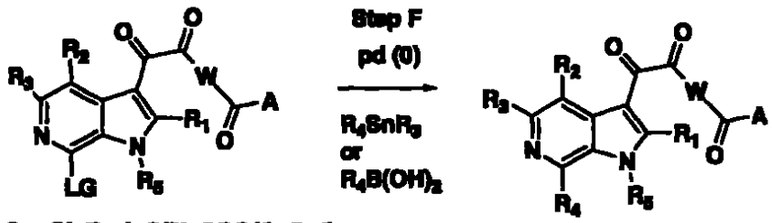
Step E. Scheme 14 depicts the nitration of an azaindole, 41, (R_2 = H). Numerous conditions for nitration of the azaindole may be effective and have been described in the literature. N_2O_5 in nitromethane followed by aqueous sodium bisulfite according to the method of Bakke, J. M.; Ranes, E.; *Synthesis* **1997**, *3*, 281-283 could be utilized. Nitric acid in acetic may also be employed as described in Kimura, H.; Yotsuya, S.; Yuki, S.; Sugi, H.; Shigehara, I.; Haga, T.; *Chem. Pharm. Bull.* **1995**, *43(10)*, 1696-1700. Sulfuric acid followed by nitric acid may be employed as in Ruefenacht, K.; Kristinsson, H.; Mattern, G.; *Helv Chim Acta* **1976**, *59*, 1593. Coombes, R. G.; Russell, L. W.; *J. Chem. Soc., Perkin Trans. 1* **1974**, 1751 describes the use of a Titatanium based reagent system for nitration. Other conditions for the nitration of the azaindole can be found in the following references: Lever, O.W.J.; Werblood, H. M.; Russell, R. K.; *Synth. Comm.* **1993**, *23(9)*, 1315-1320; Wozniak, M.; Van Der Plas, H. C.; *J. Heterocycl Chem.* **1978**, *15*, 731.

Scheme 14



41 42

Scheme 15



LG = Cl, Br, I, OTf, OPO(Oalkyl)$_2$

Step F

As shown above in Scheme 15, Step F, substituted azaindoles containing a chloride, bromide, iodide, triflate, or phosphonate undergo coupling reactions with a boronate (Suzuki type reactions) or a stannane to provide substituted azaindoles. Stannanes and boronates are prepared via standard literature procedures or as described in the experimental section of this application. The substitututed indoles may undergo metal mediated coupling to provide compounds of Formula I wherein R_4 is aryl, heteroaryl, or heteroalicyclic for example. The bromoazaindole intermediates, (or azaindole triflates or iodides) may undergo Stille-type coupling with heteroarylstannanes as shown in Scheme 15. Conditions for this reaction are well known in the art and the following are three example references a) Farina, V.; Roth, G.P. Recent advances in the Stille reaction; *Adv. Met.-Org. Chem.* **1996**, *5*, 1-53. b) Farina, V.; Krishnamurthy, V.; Scott, W.J. The Stille reaction ; *Org. React.* (N. Y.) **1997**, *50*, 1-652. and c) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524. Other references for general coupling conditions are also in the reference by Richard C. Larock Comprehensive Organic Transformations 2nd Ed. 1999, John

Wiley and Sons New York. All of these references provide numerous conditions at the disposal of those skilled in the art in addition to the specific examples provided in Scheme 15 and in the specific embodiments. It can be well recognized that an indole stannane could also couple to a heterocyclic or aryl halide or triflate to construct compounds of Formula I. Suzuki coupling (Norio Miyaura and Akiro Suzuki *Chem Rev.* **1995**, *95*, 2457.) between a triflate, bromo, or chloro azaindole intermediate and a suitable boronate could also be employed and some specific examples are contained in this application. Palladium catalyzed couplings of stannanes and boronates between chloro azaindole intermediates are also feasible and have been utilized extensively for this invention. Preferred procedures for coupling of a chloro azaindole and a stannane employ dioxane, stoichiometric or an excess of the tin reagent (up to 5 equivalents), 0.1 to 1 eq of Palladium (0) tetrakis triphenyl phosphine in dioxane heated for 5 to 15 h at 110 to 120°. Other solvents such as DMF, THF, toluene, or benzene could be employed. Preferred procedures for Suzuki coupling of a chloro azaindole and a boronate employ 1:1 DMF water as solvent, 2 equivalents of potassium carbonate as base stoichiometric or an excess of the boron reagent (up to 5 equivalents), 0.1 to 1 eq of Palladium (0) tetrakis triphenyl phosphine heated for 5 to 15 h at 110 to 120°. If standard conditions fail new specialized catalysts and conditions can be employed. Some references (and the references therein) describing catalysts which are useful for coupling with aryl and heteroaryl chlorides are:

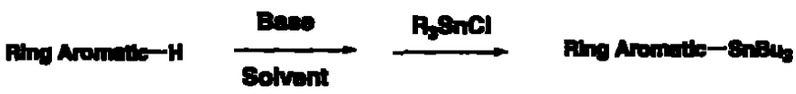
Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122(17)*, 4020-4028; Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1999**, *40(3)*, 439-442; Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59(17)*, 5034-7; Buchwald, S.; Old, D. W.; Wolfe, J. P.; Palucki, M.; Kamikawa, K.; Chieffi, A.; Sadighi, J. P.; Singer, R. A.; Ahman, J PCT Int. Appl. WO 0002887 **2000**; Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38(23)*, 3415; Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121(41)*, 9550-9561; Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38(16)*, 2413-2416; Bracher, F.; Hildebrand, D.; *Liebigs Ann. Chem.* **1992**, *12*, 1315-1319; and Bracher, F.; Hildebrand, D.; *Liebigs Ann. Chem.* **1993**, *8*, 837-839.

Alternatively, the boronate or stannane may be formed on the azaindole via methods known in the art and the coupling performed in the reverse manner with aryl or heteroaryl based halogens or triflates.

Known boronate or stannane agents could be either purchased from commercial resources or prepared following disclosed documents. Additional examples for the preparation of tin reagents or boronate reagents are contained in the experimental section.

Novel stannane agents could be prepared from one of the following routes.

Scheme Tin-01

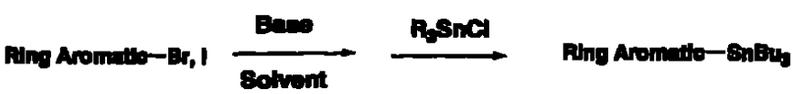


Base = LDA, TMP-Li, n-BuLi, S-BuLi, t-BuLi

Solvent = THF, ether, DME

R = Me, Bu

Scheme Tin-02

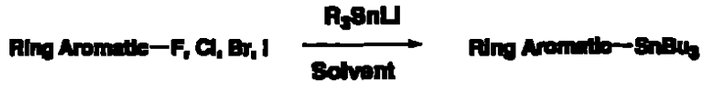


Base = n-BuLi, S-BuLi, t-BuLi

Solvent = THF, ether, DME

R = Me, Bu

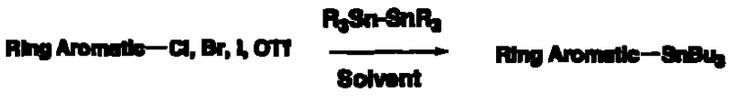
Scheme Tin-03



Solvent = THF, ether, DME

R = Me, Bu

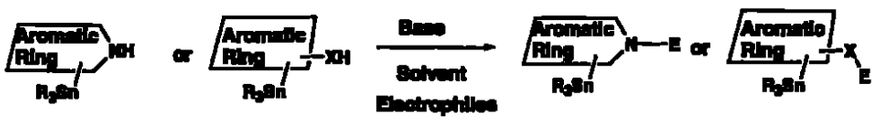
Scheme Tin-04



Solvent = Dioxane, Toluene

R = Me, Bu

Scheme Tin-05



E = Electrophile = R'-halide, R'COCl, R'OCOCl, R'R"NCOCl, RSO_2Cl, R'NCO, R'NSO, R'NCNR"

Solvent = CH_2Cl_2, THF, Ether, DMF

R = Me, Bu

Base = NaH, BuLi, LDA, K_2CO_3, Et_3N, DBU, DMAP, NaHMDS

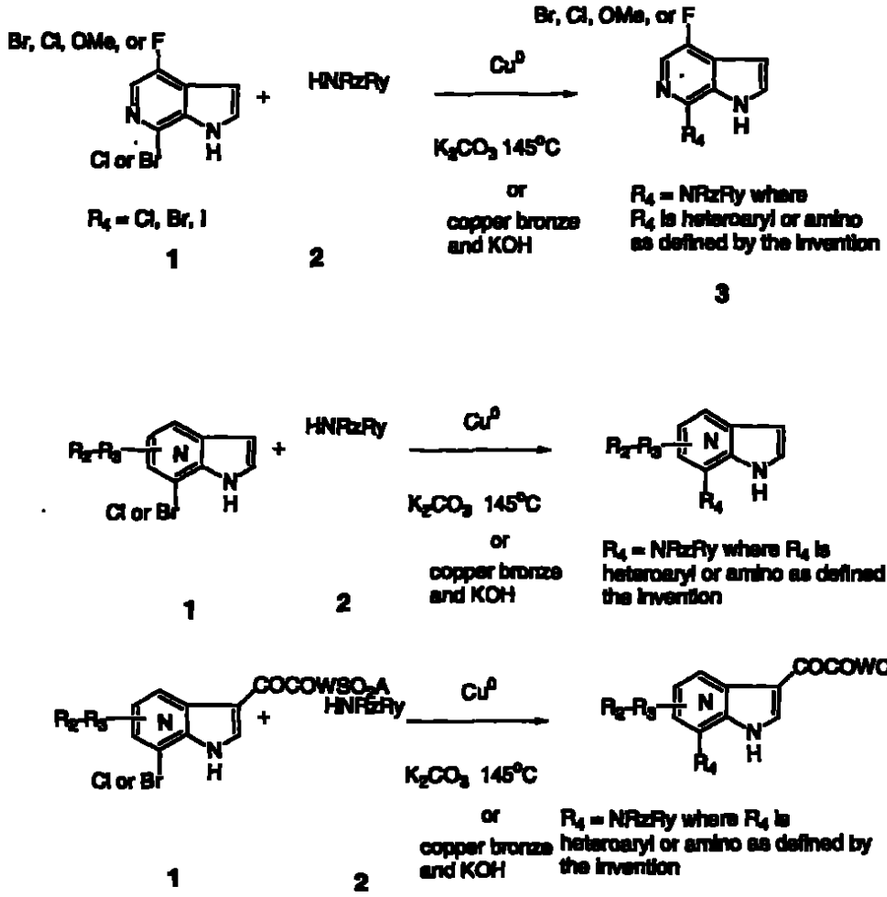
Boronate reagents are prepeared as described in reference 71. Reaction of lithium or Grignard reagents with trialkyl borates generates boronates. Alternatively, Palladium catalyzed couplings of alkoxy diboron or alkyl diboron reagents with aryl or heteroaryl halides can provide boron reagents for use in Suzuki type couplings. Some example conditions for coupling a halide with (MeO)BB(OMe)2 utilize PdCl2

(dppf), KOAc, DMSO, at 80°C until reaction is complete when followed by TLC or HPLC analysis.

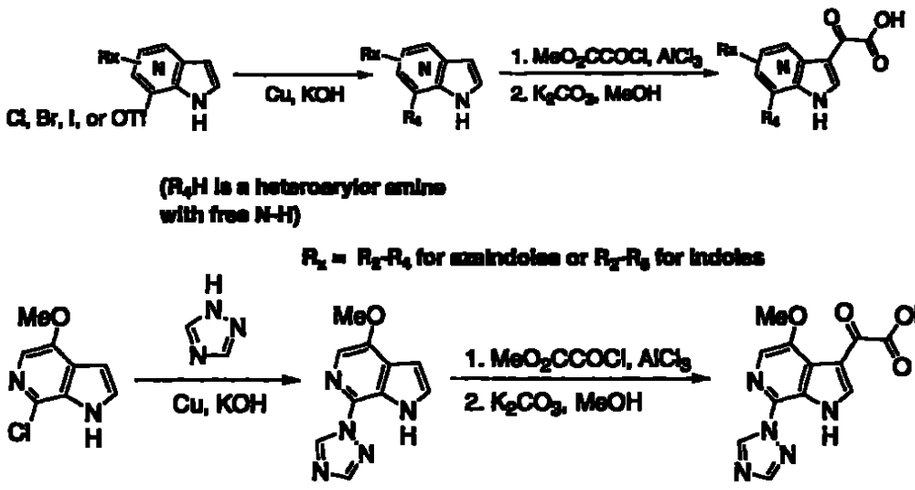
Related examples are provided in the following experimental section.

Methods for direct addition of aryl or heteroaryl organometallic reagents to alpha chloro nitrogen containing heterocyles or the N-oxides of nitrogen containing heterocycles are known and applicable to the azaindoles. Some examples are Shiotani et. Al. *J. Heterocyclic Chem.* **1997**, *34(3)*, 901-907; Fournigue et.al. *J.Org. Chem.* **1991**, *56(16)*, 4858-4864.

SCHEME 15aa



SCHEME 15bb

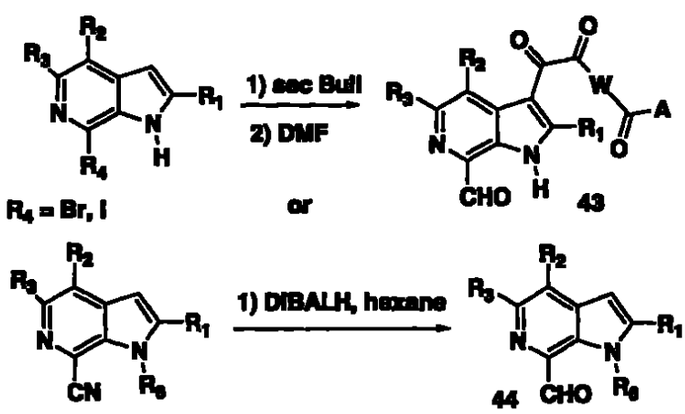


Direct displacements to install amine or N linked heteroaryl substituents can also be used to prepare compounds of Formula I. As shown in Schemes 15aa and 15bb, a mixture of halo-indole or halo-azaindole intermediate, 1-2 equivalents of copper powder, with 1 equivalent preferred for the 4-F,6-azaindole series and 2 equivalents for the 4-methoxy, 6-azaindole series; 1-2 equivalents of potassium carbonate, with 1 equivalent preferred for the 4-F,6-azaindole series and 2 equivalents for the 4-methoxy,6-azaindole series; and a 2-30 equivalents of the corresponding heterocyclic reagent, with 10 equivalents preferred; was heated at 135-160°C for 4 to 9 hours, with 5 hours at 160°C preferred for the 4-F,6-azaindole series and 7 hours at 135°C preferred for the 4-methoxy,6-azaindole series. The reaction mixture was cooled to room temperature and filtered through filter paper. The filtrate was diluted with methanol and purified either by preparative HPLC or silica gel. In many cases no chromatography is necessary, the product can be obtained by crystallization with methanol.

Alternatively, the installation of amines or N linked heteroaryls may be carried out by heating 1 to 40 equivalents of the appropriate amine and an equivalent of the appropriate aza indole chloride, bromide or iodide with copper bronze (from 0.1 to 10equivalents (preferably about 2 equivalents) and from 1 to 10 equivalents of finely pulverized potassium hydroxide (preferably about 2 equivalents).

Temperatures of 120° to 200° may be employed with 140-160° generally preferred. For volatile starting materials a sealed reactor may be employed. The reaction is most commonly used when the halogen being displaced is at the 7-position of a 6-aza (or 4-azaindole, not shown) but the method can work in the 5-azaseries or when the halogen is at a different position (4-7 position possible). As shown above the reaction can be employed on azaindoles unsubstituted at position 3 or intermediates which contain the dicarbonyl or the intact dicarbonyl piperazine urea or thioureas contained in compounds of formula I.

Scheme 16

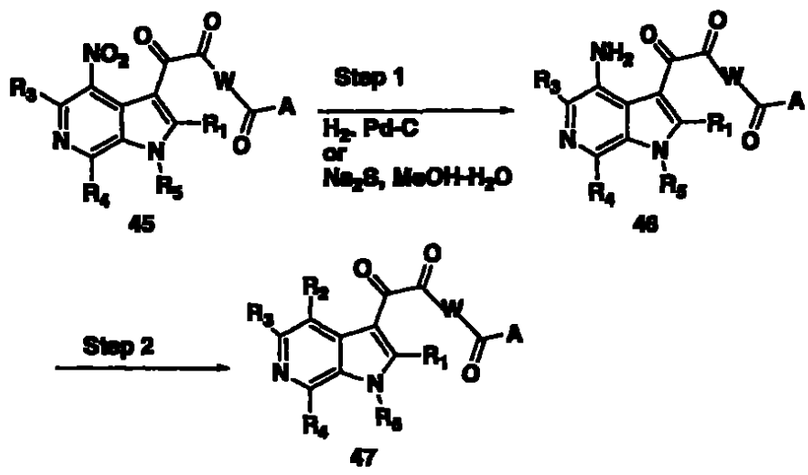


The preparation of a key aldehyde intermediate, 43, using a procedure adapted from the method of Gilmore et. Al. *Synlett* 1992, 79-80. Is shown in Scheme 16 above. The aldehyde substituent is shown only at the R_4 position for the sake of clarity, and should not be considered as a limitation of the methodology. The bromide or iodide intermediate is converted into an aldehyde intermediate, 43, by metal-halogen exchange and subsequent reaction with dimethylformamide in an appropriate aprotic solvent. Typical bases used include, but are not limited to, alkyl lithium bases such as n-butyl lithium, sec butyl lithium or tert butyl lithium or a metal such as lithium metal. A preferred aprotic solvent is THF. Typically the transmetallation is initiated at –78 °C. The reaction may be allowed to warm to allow the transmetalation to go to completion depending on the reactivity of the bromide intermediate. The reaction is then recooled to –78 °C and allowed to react with dimethylformamide. (allowing the reaction to warm may be required to enable

complete reaction) to provide an aldehyde which is elaborated to compounds of Formula I. Other methods for introduction of an aldehyde group to form intermediates of formula 43 include transition metal catalyzed carbonylation reactions of suitable bromo, trifluoromethane sulfonyl, or stannyl azaindoles. Alternative the aldehydes can be introduced by reacting indolyl anions or indolyl Grignard reagents with formaldehyde and then oxidizing with MnO_2 or TPAP/NMO or other suitable oxidants to provide intermediate 43.

The methodology described in T. Fukuda et.al. *Tetrahedron* **1999**, *55*, 9151 and M. Iwao et. Al. *Heterocycles* **1992**, *34(5)*, 1031 provide methods for preparing indoles with substituents at the 7-position. The Fukuda references provide methods for functionalizing the C-7 position of indoles by either protecting the indole nitrogen with 2,2-diethyl propanoyl group and then deprotonating the 7-position with sec/BuLi in TMEDA to give an anion. This anion may be quenched with DMF, formaldehyde, or carbon dioxide to give the aldehyde, benzyl alcohol, or carboxylic acid respectively and the protecting group removed with aqueous t butoxide. Similar tranformations can be achieved by converting indoles to indoline, lithiation at C-7 and then reoxidation to the indole such as described in the Iwao reference above. The oxidation level of any of these products may be adjusted by methods well known in the art as the interconversion of alcohol, aldehyde, and acid groups has been well studied. It is also well understood that a cyano group can be readily converted to an aldehyde. A reducing agent such as DIBALH in hexane such as used in Weyerstahl, P.; Schlicht, V.; *Liebigs Ann/Recl.* **1997**, *1*, 175-177 or alternatively catecholalane in THF such as used in Cha, J. S.; Chang, S. W.; Kwon, O. O.; Kim, J. M.; *Synlett.* **1996**, *2*, 165-166 will readily achieve this conversion to provide intermediates such as 44 (Scheme 16). Methods for synthesizing the nitriles are shown later in this application. It is also well understood that a protected alcohol, aldehyde, or acid group could be present in the starting azaindole and carried through the synthetic steps to a compound of Formula I in a protected form until they can be converted into the desired substituent at R_1 through R_4. For example, a benzyl alcohol can be protected as a benzyl ether or silyl ether or other alcohol protecting group; an aldehyde may be carried as an acetal, and an acid may be protected as an ester or ortho ester until deprotection is desired and carried out by literature methods.

Scheme 17



Step G. Step 1 of Scheme 17 shows the reduction of a nitro group on 45 to the amino group of 46. Although shown on position 4 of the azaindole, the chemistry is applicable to other nitro isomers. The procedure described in Ciurla, H.; Puszko, A.; *Khim Geterotsikl Soedin* **1996**, *10*, 1366-1371 uses hydrazine Raney-Nickel for the reduction of the nitro group to the amine. Robinson, R. P.; DonahueO, K. M.; Son, P. S.; Wagy, S. D.; *J. Heterocycl. Chem.* **1996**, *33(2)*, 287-293 describes the use of hydrogenation and Raney Nickel for the reduction of the nitro group to the amine. Similar conditions are described by Nicolai, E.; Clande, S.; Teulon, J. M.; *J. Heterocycl. Chem.* **1994**, *31(1)*, 73-75 for the same transformation. The following two references describe some trimethylsilyl sulfur or chloride based reagents which may be used for the reduction of a nitro group to an amine. Hwu, J.R.; Wong, F.F.; Shiao, M.J.; *J. Org. Chem.* **1992**, *57(19)*, 5254-5255; Shiao, M.J.; Lai, L.L.; Ku, W.S.; Lin, P.Y.; Hwu, J.R.; *J. Org. Chem.* **1993**, *58(17)*, 4742-4744.

Step 2 of Scheme 17 describes general methods for conversion of amino groups on azaindoles into other functionality. Scheme 18 also depicts transformations of an amino azaindole into various intermediates and compounds of Formula I.

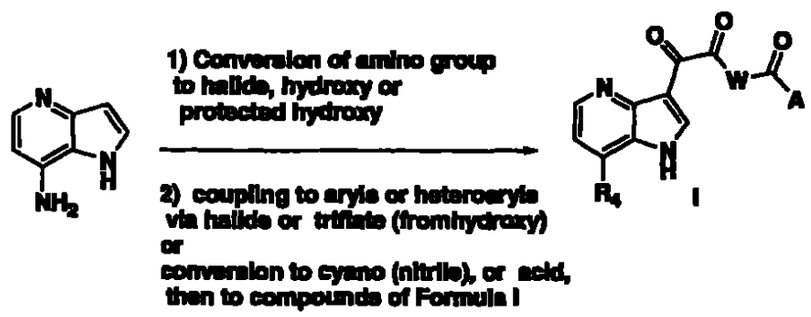
The amino group at any position of the azaindole, such as 46 (Scheme 17), may be converted to a hydroxy group using sodium nitrite, sulfuric acid, and water via the method of Klemm, L. H.; Zell, R.; *J. Heterocycl. Chem.* **1968**, *5*, 773. Bradsher, C. K.; Brown, F. C.; Porter, H. K.; *J. Am. Chem. Soc.* **1954**, *76*, 2357 describes how the hydroxy group may be alkylated under standard or Mitsonobu conditions to form ethers. The amino group may be converted directly into a methoxy group by diazotization (sodium nitrite and acid)and trapping with methanol.

The amino group of an azaindole, such as 46, can be converted to fluoro via the method of Sanchez using HPF_6, $NaNO_2$, and water by the method described in Sanchez, J. P.; Gogliotti, R. D.; *J. Heterocycl. Chem.* **1993**, *30(4)*, 855-859. Other methods useful for the conversion of the amino group to fluoro are described in Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G.; *Tetrahedron Lett.* **1993**, *34(18)*, 2937-2940 and Sanchez, J. P.; Rogowski, J.W.; *J. Heterocycl. Chem.* **1987**, *24*, 215.

The amino group of the azaindole, 46, can also be converted to a chloride via diazotization and chloride displacement as described in Ciurla, H.; Puszko, A.; *Khim Geterotsikl Soedin* **1996**, *10*, 1366-1371 or the methods in Raveglia, L.F.; Giardina, G.A..; Grugni, M.; Rigolio, R.; Farina, C.; *J. Heterocycl. Chem.* **1997**, *34(2)*, 557-559 or the methods in Matsumoto, J. I.; Miyamoto, T.; Minamida, A.; Mishimura, Y.; Egawa, H.; Mishimura, H.; *J. Med. Chem.* **1984**, *27(3)*, 292; or as in Lee, T.C.; Salemnick, G.; *J. Org. Chem.* **1975**, *24*, 3608.

The amino group of the azaindole, 46, can also be converted to a bromide via diazotization and displacement by bromide as described in Raveglia, L.F.; Giardina, G.A..; Grugni, M.; Rigolio, R.; Farina, C.; *J. Heterocycl. Chem.* **1997**, *34(2)*, 557-559; Talik, T.; Talik, Z.; Ban-Oganowska, H.; *Synthesis* **1974**, 293; and Abramovitch, R.A.; Saha, M.; *Can. J. Chem.* **1966**, *44*, 1765.

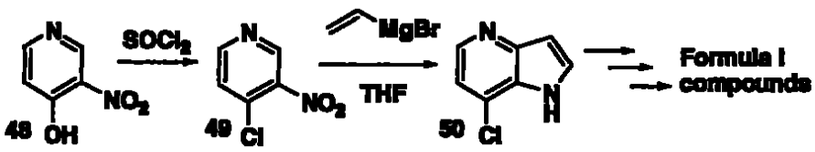
Scheme 18



The preparation of 4-amino 4-azaindole and 7-methyl-4-azaindole is described by Mahadevan, I; Rasmussen, M. *J. Heterocycl. Chem.* 1992, *29(2)*, 359-67. The amino group of the 4-amino 4-azaindole can be converted to halogens, hydroxy, protected hydroxy, triflate, as described above in Schemes 17-18 for the 4-amino compounds or by other methods known in the art. Protection of the indole nitrogen of the 7-methyl-4-azaindole via acetylation or other strategy followed by oxidation of the 7-methyl group with potassium permanganate or chromic acid provides the 7-acid /4-N-oxide. Reduction of the N-oxide, as described below, provides an intermediate from which to install various substituents at position R_4. Alternatively the parent 4-azaindole which was prepared as described in Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* 1992, *29(2)*, 359-67 could be derivatized at nitrogen to provide the 1-(2,2-diethylbutanoyl)azaindole which could then be lithiated using TMEDA /sec BuLi as described in T. Fukuda et. Al. *Tetrahedron* 1999, *55*, 9151-9162; followed by conversion of the lithio species to the 7-carboxylic acid or 7-halogen as described. Hydrolysis of the N-amide using aqueous tert-butoxide in THF regenerates the free NH indole which can now be converted to compounds of Formula I. The chemistry used to functionalize position 7 can also be applied to the 5 and 6 indole series.

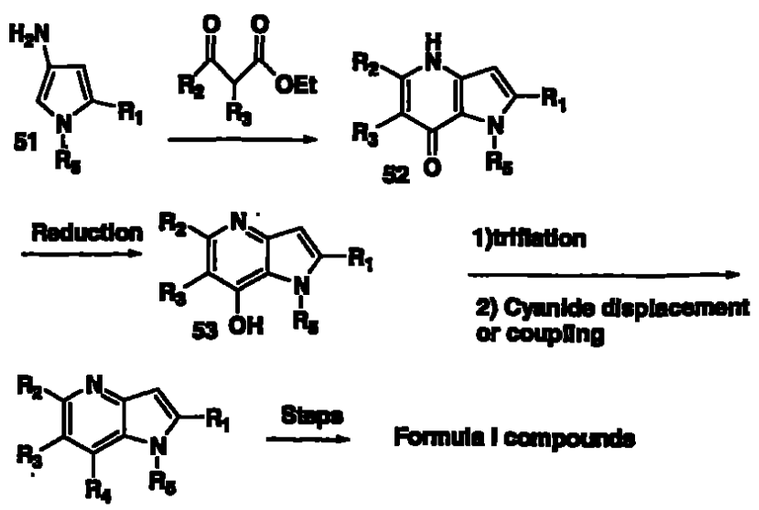
Scheme 19 shows the preparation of a 7-chloro-4-azaindole, 50, which can be converted to compounds of Formula I by the chemistry previously described, especially the palladium catalyzed tin and boron based coupling methodology described above. The chloro nitro indole, 49, is commercially available or can be prepared from 48 according to the method of Delarge, J.; Lapiere, C. L. *Pharm. Acta Helv.* 1975, *50(6)*, 188-91.

Scheme 19



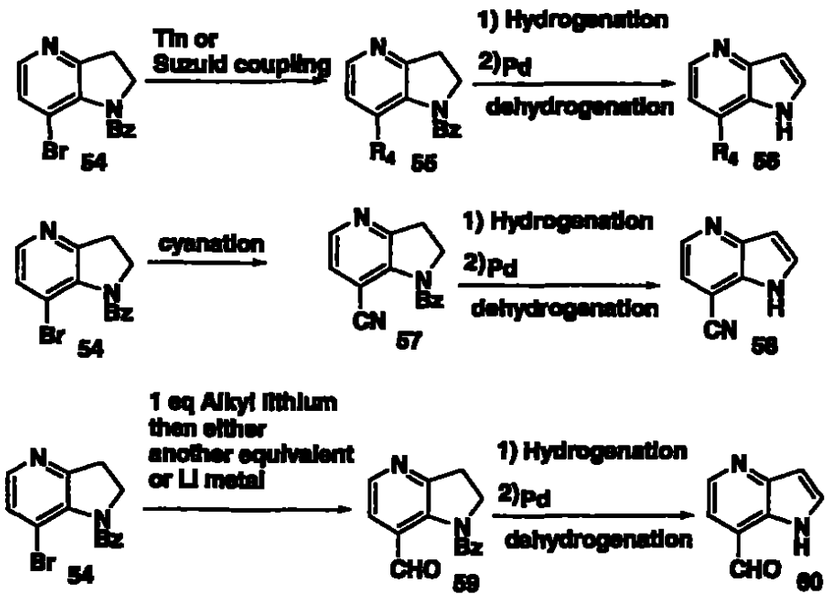
Scheme 20, below, shows another synthetic route to substituted 4-aza indoles. The 3-aminopyrrole, 51, was reacted to provide the pyrrolopyridinone, 52, which was then reduced to give the hydroxy azaindole, 53. The pyrrolo[2,3-b]pyridines described were prepared according to the method of Britten, A.Z.; Griffiths, G.W.G. *Chem. Ind.* (London) 1973, 6, 278. The hydroxy azaindole, 53, can then be converted to the triflate then further reacted to provide compounds of Formula I.

Scheme 20



The following references describe the synthesis of 7-halo or 7 carboxylic acid, or 7-amido derivatives of 5-azaindoline which can be used to construct compounds of Formula I. Bychikhina, N. N.; Azimov, V. A.; Yakhontov, L.N. *Khim. Geterotsikl. Soedin.* **1983**, *1*, 58-62; Bychikhina, N. N.; Azimov, V. A.; Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1982**, *3*, 356-60; Azimov, V. A.; Bychikhina, N. N.; Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1981**, 12, 1648-53; Spivey, A.C.; Fekner, T.; Spey, S.E.; Adams, H. *J. Org. Chem.* **1999**, *64(26)*, 9430-9443; Spivey, A.C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39(48)*, 8919-8922. The methods described in Spivey et al. (preceding two references) for the preparation of 1-methyl-7-bromo-4-azaindoline can be used to prepare the 1-benzyl-7-bromo-4-azaindoline, 54, shown below in Scheme 21. This can be utilized in Stille or Suzuki couplings to provide 55, which is deprotected and dehydrogenated to provide 56. Other useful azaindole intermediates, such as the cyano derivatives, 57 and 58, and the aldehyde derivatives, 59 and 60, can then be further elaborated to compounds of Formula I.

Scheme 21

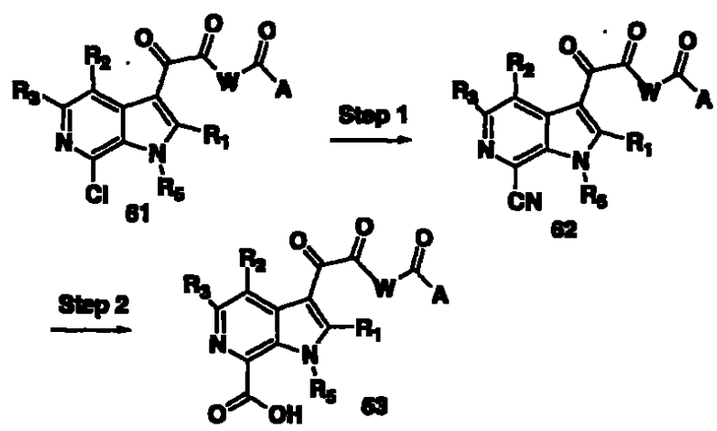


Alternatively the 7-functionalized 5-azaindole derivatives may be obtained by functionalization using the methodologies of T. Fukuda et.al. *Tetrahedron* **1999**, *55*, 9151 and M. Iwao et. Al. *Heterocycles* **1992**, *34(5)*, 1031described above for the 4 or

6 azaindoles. The 4 or 6 positions of the 5 aza indoles can be functionalized by using the azaindole N-oxide.

The conversion of indoles to indolines is well known in the art and can be carried out as shown or by the methods described in Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* 1987, *35(8)*, 3146-54; M. Iwao et. Al. *Heterocycles* 1992, *34(5)*, 1031; andAkagi, M.; Ozaki, K. *Heterocycles* 1987, *26(1)*, 61-4.

Scheme 22



The preparation of azaindole oxoacetyl or oxo piperidines with carboxylic acids can be carried out from nitrile, aldehyde, or anion precursors via hydrolysis, oxidation, or trapping with CO_2 respectively. As shown in the Scheme 22, Step 1, or the scheme below step a12 one method for forming the nitrile intermediate, 62, is by cyanide displacement of a halide in the aza-indole ring. The cyanide reagent used can be sodium cyanide, or more preferably copper or zinc cyanide. The reactions may be carried out in numerous solvents which are well known in the art. For example DMF is used in the case of copper cyanide. Additional procedures useful for carrying out step 1 of Scheme 24 are Yamaguchi, S.; Yoshida, M.; Miyajima, I.; Araki, T.; Hirai, Y.; *J. Heterocycl. Chem.* 1995, *32(5)*, 1517-1519 which describes methods for copper cyanide; Yutilov, Y.M.; Svertilova, I.A.; *Khim Geterotsikl Soedin* 1994, *8*, 1071-1075 which utilizes potassium cyanide; and Prager, R.H.; Tsopelas, C.; Heisler, T.; *Aust. J. Chem.* 1991, *44 (2)*, 277-285 which utilizes copper cyanide in the presence of

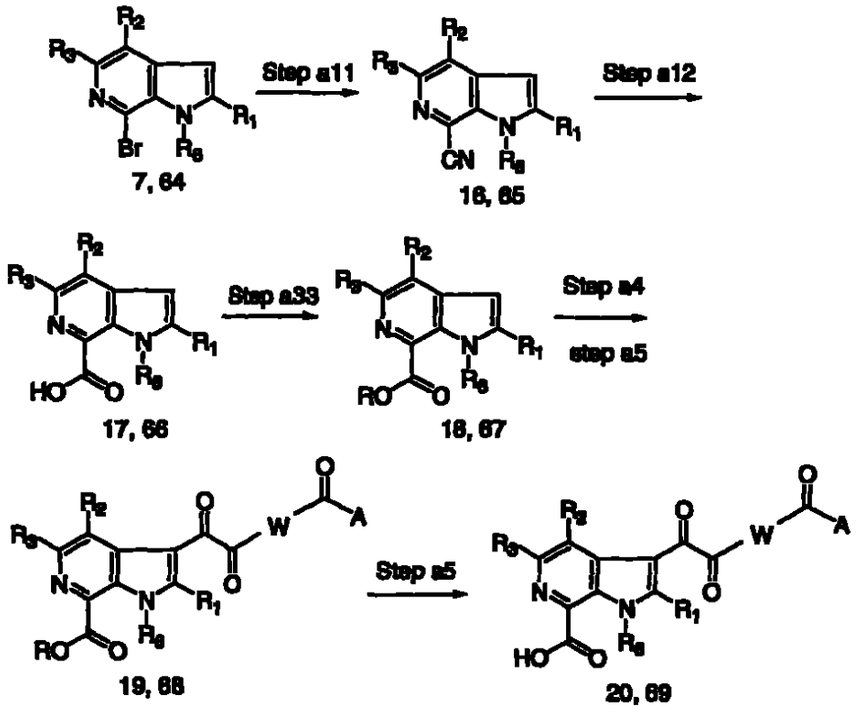
$MeOS(O)_2F$. The chloride or more preferably a bromide on the azaindole may be displaced by sodium cyanide in dioxane via the method described in *Synlett.* **1998**, *3*, 243-244. Alternatively, Nickel dibromide, Zinc, and triphenyl phosphine in can be used to activate aromatic and heteroaryl chlorides to displacement via potassium cyanide in THF or other suitable solvent by the methods described in Eur. Pat. Appl., 831083, 1998.

The conversion of the cyano intermediate, 62, to the carboxylic acid intermediate, 63, is depicted in step 2, Scheme 22 or in step a12, Scheme 23. Many methods for the conversion of nitriles to acids are well known in the art and may be employed. Suitable conditions for step 2 of Scheme 22 or the conversion of intermediate 65 to intermediate 66 below employ potassium hydroxide, water , and an aqueous alcohol such as ethanol. Typically the reaction must be heated at refluxing temperatures for one to 100 h. Other procedures for hydrolysis include those described in:

Shiotani, S.; Taniguchi, K.; *J. Heterocycl. Chem.* **1997**, *34(2)*, 493-499; Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J.; *Tetrahedron* **1994**, *50(8)*, 2551-2560; Rivalle, C.; Bisagni, E.; *Heterocycles* **1994**, *38(2)*, 391-397; Macor, J.E.; Post, R.; Ryan, K.; *J. Heterocycl. Chem.* **1992**, *29(6)*, 1465-1467.

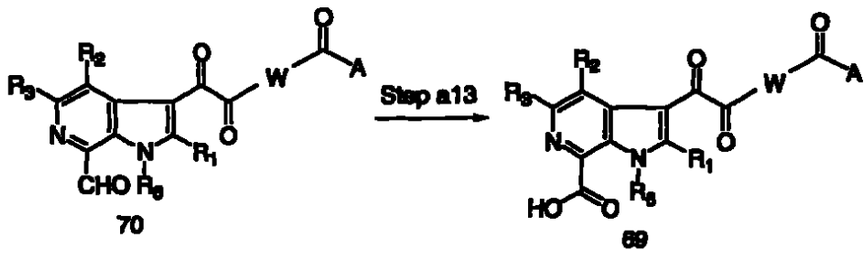
The acid intermediate, 66 (Scheme 23), may then be esterified using conditions well known in the art. For example, reaction of the acid with diazomethane in an inert solvent such as ether, dioxane, or THF would give the methyl ester. Intermediate 67 may then be converted to intermediate 68 according to the procedure described in Scheme 2. Intermediate 68 may then be hydrolyzed to provide intermediate 69.

Scheme 23



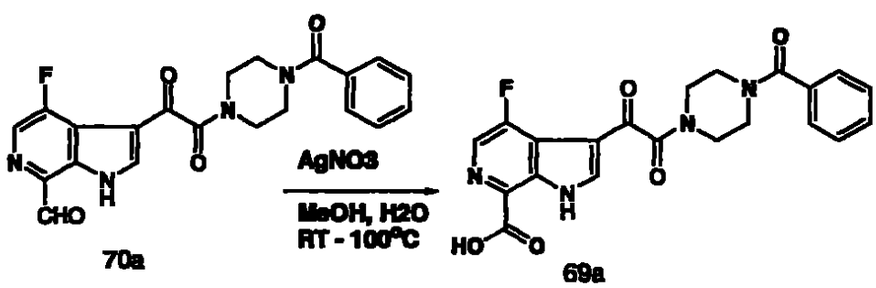
As shown in Scheme 24, step a13 another preparation of the indoleoxoacetylpiperazine 7-carboxylic acids, 69, is carried out by oxidation of the corresponding 7-carboxaldehyde, 70. Numerous oxidants are suitable for the conversion of aldehyde to acid and many of these are described in standard organic chemistry texts such as: Larock, Richard C., Comprehensive organic transformations : a guide to functional group preparations 2nd ed. New York : Wiley-VCH, 1999. One preferred method is the use of silver nitrate or silver oxide in a solvent such as aqueous or anhydrous methanol at a temperature of ~25 °C or as high as reflux. The reaction is typically carried out for one to 48 h and is typically monitored by TLC or LC/MS until complete conversion of product to starting material has occurred. Alternatively, $KmnO_4$ or CrO_3/H_2SO_4 could be utilized.

Scheme 24



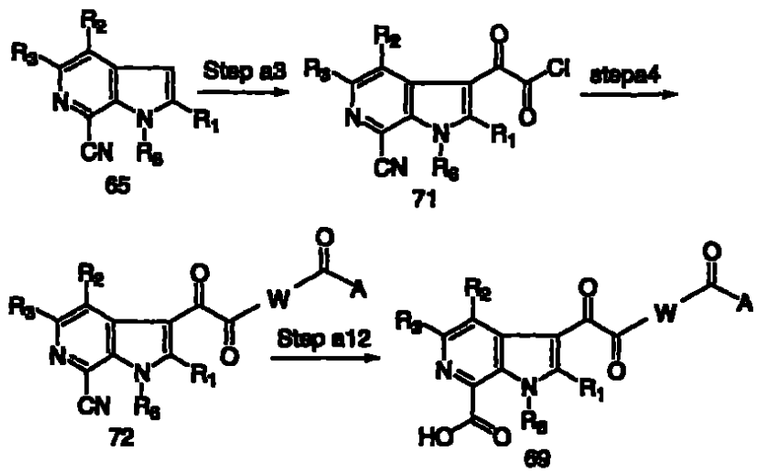
Scheme 25 gives a specific example of the oxidation of an aldehyde intermediate, 70a, to provide the carboxylic acid intermediate, 69a.

Scheme 25

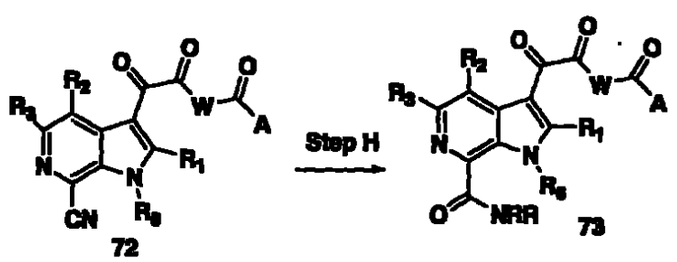


Alternatively, intermediate 69 can be prepared by the nitrile method of synthesis carried out in an alternative order as shown in Scheme 26. The nitrile hydrolyis step can be delayed and the nitrile carried through the synthesis to provide a nitrile which can be hydrolyzed to provide the free acid, 69, as above.

Scheme 26



Scheme 27



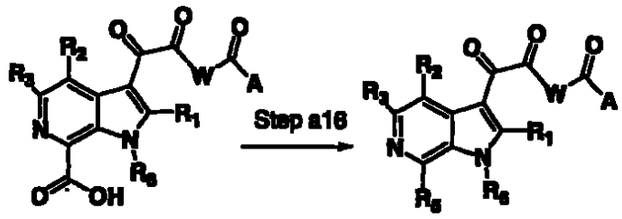
Step H. The direct conversion of nitriles, such as 72, to amides, such as 73, shown in Scheme 27, Step H, can be carried out using the conditions as described in Shiotani, S.; Taniguchi, K.; *J. Heterocycl. Chem.* **1996**, *33(4)*, 1051-1056 (describes the use of aqueous sulfuric acid); Memoli, K.A.; *Tetrahedron Lett.* **1996**, *37(21)*, 3617-3618; Adolfsson, H.; Waernmark, K.; Moberg, C.; *J. Org. Chem.* **1994**, *59(8)*, 2004-2009; and El Hadri, A.; Leclerc, G.; *J. Heterocycl. Chem.* **1993**, *30(3)*, 631-635.

Step I. For NH2

Shiotani, S.; Taniguchi, K.; *J. Heterocycl. Chem.* **1997**, *34(2)*, 493-499; Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J.; *Tetrahedron* **1994**, *50(8)*, 2551-2560; Rivalle, C.; Bisagni, E.; *Heterocycles* **1994**, *38(2)*, 391-397; Macor, J.E.; Post, R.; Ryan, K.; *J. Heterocycl. Chem.* **1992**, *29(6)*, 1465-1467.

Step J.

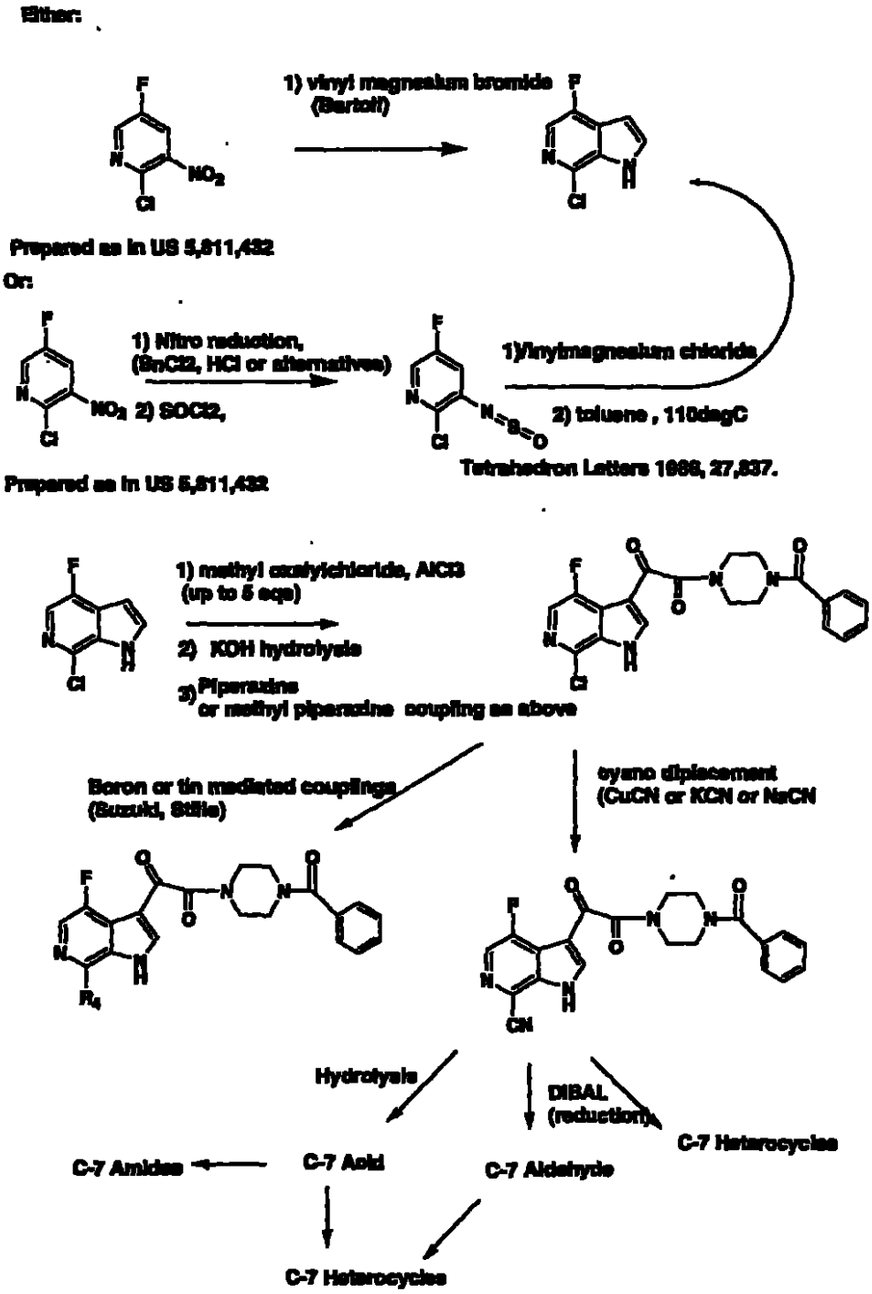
Scheme 28



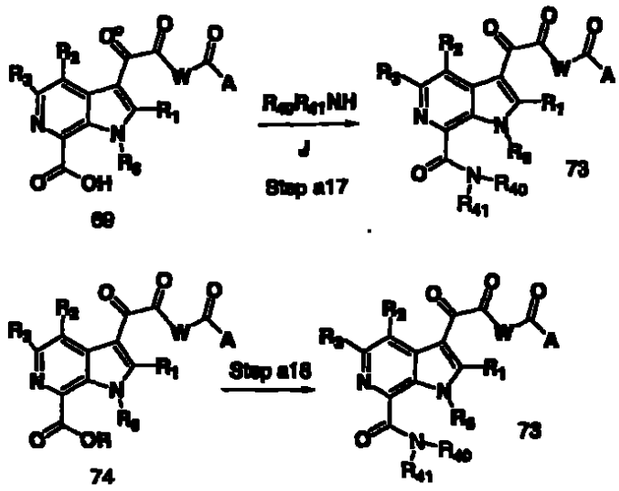
69 I

The following scheme (28A) shows an example for the preparation of 4-fluoro-7substituted azaindoles from a known starting materials. References for the Bartoli indole synthesis were mentioned earlier. The conditions for tranformation to the nitriles, acids, aldeheydes, heterocycles and amides have also been described in this application.

Scheme 28A


Either:
1) vinyl magnesium bromide (Bartoli)
Prepared as in US 5,811,432
Or:
1) Nitro reduction, (SnCl2, HCl or alternatives)
2) SOCl2,
1)Vinylmagnesium chloride
2) toluene , 110degC
Tetrahedron Letters 1986, 27,837.
Prepared as in US 5,811,432
1) methyl oxalylchloride, AlCl3 (up to 5 eqs)
2) KOH hydrolysis
3) Piperazine or methyl piperazine coupling as above
Boron or tin mediated couplings (Suzuki, Stille)
cyano displacement (CuCN or KCN or NaCN
Hydrolysis
DIBAL (reduction)
C-7 Amides
C-7 Acid
C-7 Aldehyde
C-7 Heterocycles
C-7 Heterocycles

Scheme 29

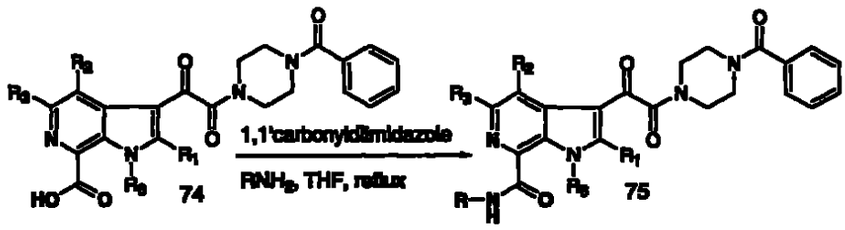


Steps a16, a17, and a18 encompasses reactions and conditions for 1^0, 2^0 and 3^0 amide bond formation as shown in Schemes 28 and 29 which provide compounds such as those of Formula 73.

The reaction conditions for the formation of amide bonds encompass any reagents that generate a reactive intermediate for activation of the carboxylic acid to amide formation, for example (but not limited to), acyl halide, from carbodiimide, acyl iminium salt, symmetrical anhydrides, mixed anhydrides (including phosphonic/phosphinic mixed anhydrides), active esters (including silyl ester, methyl ester and thioester), acyl carbonate, acyl azide, acyl sulfonate and acyloxy *N*-phosphonium salt. The reaction of the indole carboxylic acids with amines to form amides may be mediated by standard amide bond forming conditions described in the art. Some examples for amide bond formation are listed in references 41-53 but this list is not limiting. Some carboxylic acid to amine coupling reagents which are applicable are EDC, Diisopropylcarbodiimide or other carbodiimides, PyBop (benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate), 2-(1H-benzotriazole-1-yl)-1, 1, 3, 3-tetramethyl uronium hexafluorophosphate (HBTU). A particularly useful method for azaindole 7-carboxylic acid to amide reactions is the use of carbonyl imidazole as the coupling reagent as described in reference 53. The temperature of this reaction may be lower than in the cited reference , from 80 °C (or

possibly lower) to 150 °C or higher. A more specific application is depicted in Scheme 30.

Scheme 30



The following four general methods provide a more detailed description for the preparation of indolecarboamides and these methods were employed for the synthesis of compounds of Formula I.

Method 1:

To a mixture of an acid intermediate, such as 69, (1 equiv., 0.48 mmol), an appropriate amine (4 equiv.) and DMAP (58 mg, 0.47 mmol) dissolved CH_2Cl_2 (1 mL) was added EDC (90 mg, 0.47 mmol). The resulting mixture was shaken at rt for 12h, and then evaporated *in vacuo*. The residue was dissolved in MeOH, and subjected to preparative reverse phase HPLC purification.

Method 2:

To a mixture of an appropriate amine (4 equiv.) and HOBT (16 mg, 0.12 mmol) in THF (0.5 mL) was added an acid intermediate, such as 69, (25 mg, 0.06 mmol) and NMM (50 µl, 0.45 mmol), followed by EDC (23 mg, 0.12 mmol). The reaction mixture was shaken at rt for 12 h. The volatiles were evaporated *in vacuo*; and the residue dissolved in MeOH and subjected to preparative reverse phase HPLC purification.

Method 3:

To a mixture of an acid intermediate, such as 69, (0.047 mmol), amine (4 equiv.) and DEPBT (prepared according to Li, H.; Jiang, X. Ye, Y.; Fan, C.; Todd, R.; Goodman, M. *Organic Letters* 1999, *1*, 91; 21 mg, 0.071 mmol) in DMF (0.5 mL) was added TEA (0.03 mL, 0.22 mmol). The resulting mixture was shaken at rt for 12 h; and then diluted with MeOH (2 mL) and purified by preparative reverse phase HPLC.

Method 4:

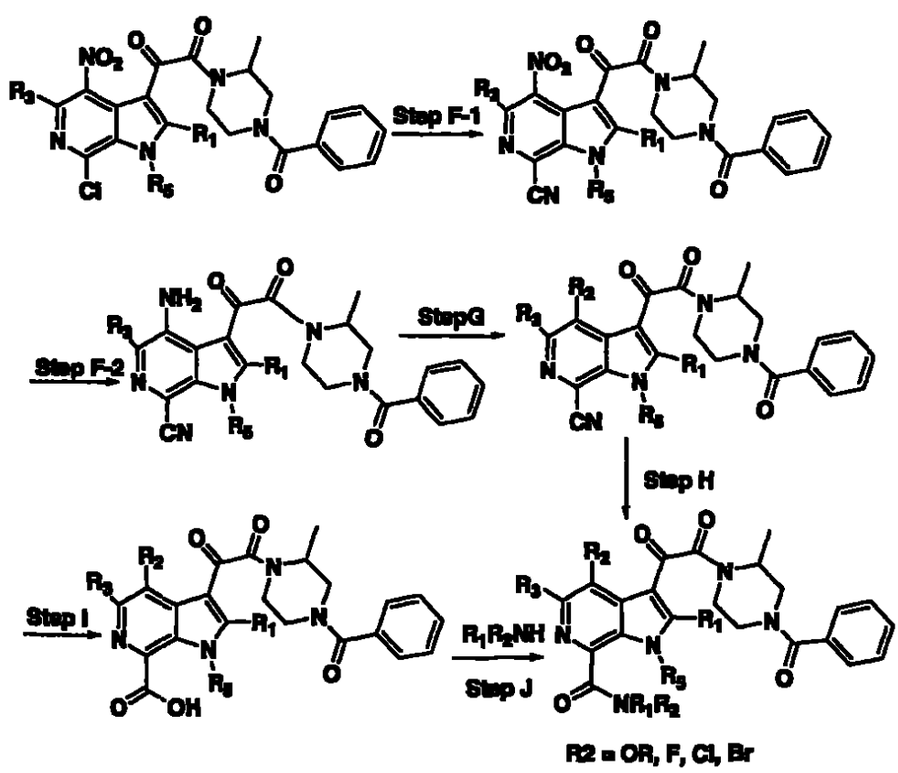
A mixture of an acid intermediate, such as 69, (0.047mmol) and 8.5 mg (0.052mmol) of 1,1-carbonyldiimidazole in anhydrous THF (2 mL) was heated to reflux under nitrogen. After 2.5h, 0.052 mmol of amine was added and heating continued. After an additional period of 3~20 h at reflux, the reaction mixture was cooled and concentrated in vacuo. The residue was purified by chromatography on silica gel to provide a compound of Formula I.

In addition, the carboxylic acid may be converted to an acid chloride using reagents such as thionyl chloride (neat or in an inert solvent) or oxalyl chloride in a solvent such as benzene, toluene, THF, or CH_2Cl_2. The amides may alternatively, be formed by reaction of the acid chloride with an excess of ammonia, primary, or secondary amine in an inert solvent such as benzene, toluene, THF, or CH_2Cl_2 or with stoichiometric amounts of amines in the presence of a tertiary amine such as triethylamine or a base such as pyridine or 2,6-lutidine. Alternatively, the acid chloride may be reacted with an amine under basic conditions (Usually sodium or potassium hydroxide) in solvent mixtures containing water and possibly a miscible co solvent such as dioxane or THF. Scheme 25B depicts a typical preparation of an acid chloride and derivatization to an amide of Formula I. Additionally, the carboxylic acid may be converted to an ester preferably a methyl or ethyl ester and then reacted with an amine. The ester may be formed by reaction with diazomethane or alternatively trimethylsilyl diazomethane using standard conditions which are well

known in the art. References and procedures for using these or other ester forming reactions can be found in reference 52 or 54.

Additional references for the formation of amides from acids are: Norman, M.H.; Navas, F. III; Thompson, J.B.; Rigdon, G.C.; *J. Med. Chem.* 1996, *39(24)*, 4692-4703; Hong, F.; Pang, Y.-P.; Cusack, B.; Richelson, E.; *J. Chem. Soc., Perkin Trans* 1 1997, *14*, 2083-2088; Langry, K.C.; *Org. Prep. Proc. Int.* 1994, *26(4)*, 429-438; Romero, D.L.; Morge, R.A.; Biles, C.; Berrios-Pena, N.; May, P.D.; Palmer, J.R.; Johnson, P.D.; Smith, H.W.; Busso, M.; Tan, C.-K.; Voorman, R.L.; Reusser, F.; Althaus, I.W.; Downey, K.M.; et al.; *J. Med. Chem.* 1994, *37(7)*, 999-1014; Bhattacharjee, A.; Mukhopadhyay, R.; Bhattacharjya, A.; *Indian J. Chem., Sect B* 1994, *33(7)*, 679-682.

Scheme 31



Scheme 31 shows synthetic transformations on a chloro nitro azaindole. Step F-1 of Scheme 31 can be carried may be carried out according to the following

procedures: Yamaguchi, S.; Yoshida, M.; Miyajima, I.; Araki, T.; Hirai, Y.; *J. Heterocycl. Chem.* **1995**, *32(5)*, 1517-1519;

Yutilov, Y.M.; Svertilova, I. A.; *Khim Geterotsikl Soedin* **1994**, *8*, 1071-1075; and Prager, R.H.; Tsopelas, C.; Heisler, T.; *Aust. J. Chem.* **1991**, *44(2)*, 277-285. Step F-2 of Scheme 31 may be accomplished according to the procedures set forth in: Ciurla, H.; Puszko, A.; *Khim Geterotsikl Soedin* **1996**, *10*, 1366-1371; Robinson, R.P.; Donahue, K.M.; Son, P.S.; Wagy, S.D.; J. Heterocycl. Chem. **1996**, *33(2)*, 287-293; Nicolai, E.; Claude, S.; Teulon, J. M.; *J. Heterocycl. Chem.* **1994**, *31(1)*, 73-75; Hwu, J.R.; Wong, F.F.; Shiao, M.-J.; *J. Org. Chem.* **1992**, *57(19)*, 5254-5255; Shiao, M.-J.; Lai, L.-L.; Ku, W.-S.; Lin, P.-Y.; Hwu, J.R.; *J. Org. Chem.* **1993**, *58(17)*, 4742-4744.

The introduction of an alkoxy or aryloxy substituent onto the azaindole (Step G, Scheme 31, R_2 is alkoxy or aryloxy) may be accomplished by the f procedures described in Klemm, L.H.; Zell, R.; *J. Heterocycl. Chem.* **1968**, *5*, 773; Bradsher, C. K.; Brown, F. C.; Porter, H. K.; *J. Am. Chem. Soc.* **1954**, *76*, 2357; and Hodgson, H. H.; Foster, C. K.; J. Chem. Soc. **1942**, 581.

The introduction of a fluorine substituent onto the azaindole (Step G, Scheme 31) may be accomplished according to the procedures as described in Sanchez, J. P.; Gogliotti, R. D.; *J. Heterocycl. Chem.* **1993**, *30(4)*, 855-859; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G.; *Tetrahedron Lett.* **1993**, *34(18)*, 2937-2940; and Sanchez, J.P.; Rogowski, J.W.; *J. Heterocycl. Chem.* **1987**, *24*, 215.

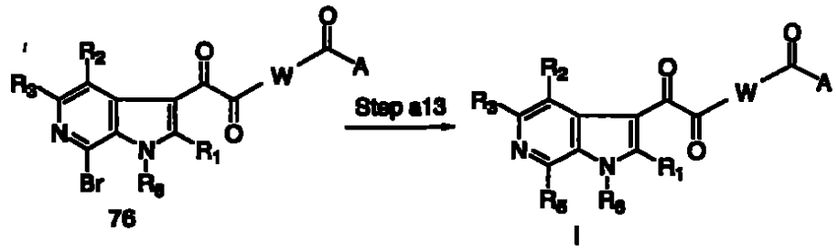
The introduction of a chlorine substituent onto the azaindole (Step G, Scheme 31) may be accomplished according to the procedures as described in Ciurla, H.; Puszko, A.; *Khim Geterotsikl Soedin* **1996**, *10*, 1366-1371; Raveglia, L.F.; Giardinal, G.A.M.; Grugni, M.; Rigolio, R.; Farina, C. ; *J. Heterocycl. Chem.* **1997**, *34(2)*, 557-559; Matsumoto, J.I.; Miyamoto, T.; Minamida, A.; Mishimura, Y.; Egawa, H.; Mishimura, H.; *J. Med. Chem.* **1984**, *27(3)*, 292; Lee, T.-C.; Salemnick, G.; J. Org. Chem. **1975**, *24*, 3608.

The introduction of a bromine substituent onto the azaindole (Step G, Scheme 31) may be accomplished according to the procedures as described in Raveglia, L.F.; Giardina, G.A.M.; Grugni, M.; Rigolio, R.; Farina, C. ; J. Heterocycl. Chem. 1997, *34(2)*, 557-559; Talik, T.; Talik, Z.; Ban-Oganowska, H.; *Synthesis* 1974, 293; Abramovitch, R. A.; Saha, M.; Can. J. Chem. 1966, *44*, 1765.

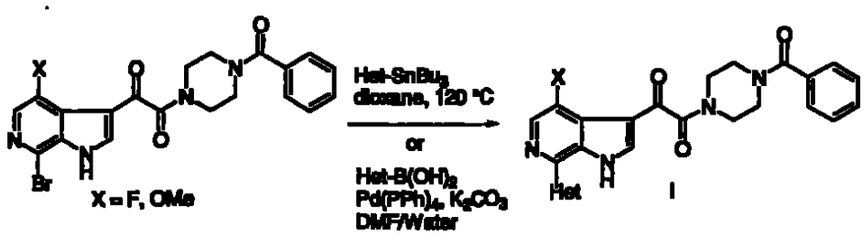
It is well known in the art that heterocycles may be prepared from an aldehyde, carboxylic acid, carboxylic acid ester, carboxylic acid amide, carboxylic acid halide, or cyano moiety or attached to another carbon substituted by a bromide or other leaving group such as a triflate, mesylate, chloride, iodide, or phosponate. The methods for preparing such intermediates from intermediates typified by the carboxylic acid intermediate, 69, bromo intermediate, 76, or aldehyde intermediate, 70 described above are known by a typical chemist practitioner. The methods or types of heterocycles which may be constructed are described in the chemical literature. Some representative references for finding such heterocycles and their construction are included in reference 55 through 67 but should in no way be construed as limiting. However, examination of these references shows that many versatile methods are available for synthesizing diversely substituted heterocycles and it is apparent to one skilled in the art that these can be applied to prepare compounds of Formula I. Chemists well versed in the art can now easily, quickly, and routinely find numerous reactions for preparing heterocycles, amides, oximes or other substituents from the above mentioned starting materials by searching for reactions or preparations using a conventional electronic database such as Scifinder (American Chemical Society), Crossfire (Beilstein), Theilheimer, or Reaccs (MDS). The reaction conditions identified by such a search can then be employed using the substrates described in this application to produce all of the compounds envisioned and covered by this invention. In the case of amides, commercially available amines can be used in the synthesis. Alternatively, the above mentioned search programs can be used to locate literature preparations of known amines or procedures to synthesize new amines. These procedures are then carried out by one with typical skill in the art to provide the compounds of Formula I for use as antiviral agents.

As shown below in Scheme 32, step a13, suitable substituted azaindoles, such as the bromoazaindole intermediate, 76, may undergo metal mediated couplings with aryl groups, heterocycles, or vinyl stannanes to provide compounds of Formula I wherein R_5 is aryl, heteroaryl, or heteroalicyclic for example. The bromoazaindole intermediates, 76 (or azaindole triflates or iodides) may undergo Stille-type coupling with heteroarylstannanes as shown in Scheme 32, step a13. Conditions for this reaction are well known in the art and references 68-70 as well as reference 52 provide numerous conditions in addition to the specific examples provided in Scheme 14 and in the specific embodiments. It can be well recognized that an indole stannane could also couple to a heterocyclic or aryl halide or triflate to construct compounds of Formula I. Suzuki coupling (reference 71) between the bromo intermediate, 76, and a suitable boronate could also be employed and some specific examples are contained in this application.

Scheme 32



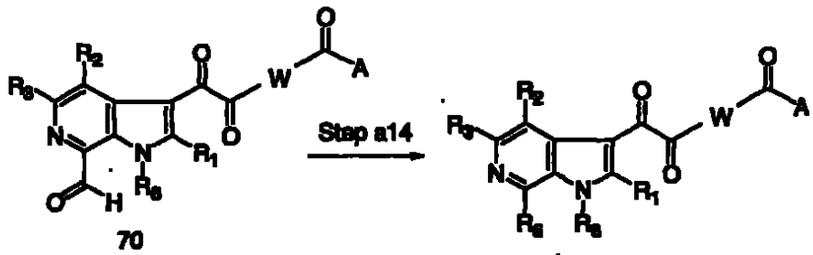
Scheme 33



As shown in Scheme 34, step a14, aldehyde intermediates, 70, may be used to generate numerous compounds of Formula I. The aldehyde group may be a precursor

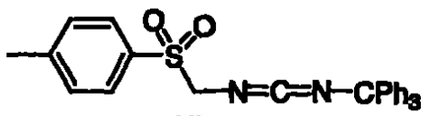
for any of the substituents R_1 through R_5 but the transormation for R_5 is depicted above for simplicity. The aldehyde intermediate 70, may be reacted to become incorporated into a ring as

Scheme 34



70 I

described in the claims or be converted into an acyclic group. The aldehyde, 70, may be reacted with a Tosmic based reagent to generate oxazoles (references 42 and 43 for example). The aldehyde, 70, may be reacted with a Tosmic reagent and than an amine to give imidazoles as in reference 72 or the aldehyde intermediate, 70, may be reacted with hydroxylamine to give an oxime which is a compound of Formula I as described below. Oxidation of the oxime with NBS, t-butyl hypochlorite, or the other known reagents would provide the N-oxide which react with alkynes or 3 alkoxy vinyl esters to give isoxazoles of varying substitution. Reaction of the aldehyde intermediate 70, with the known reagent, 77 (reference 70) shown below under basic conditions would provide 4-aminotrityl oxazoles.



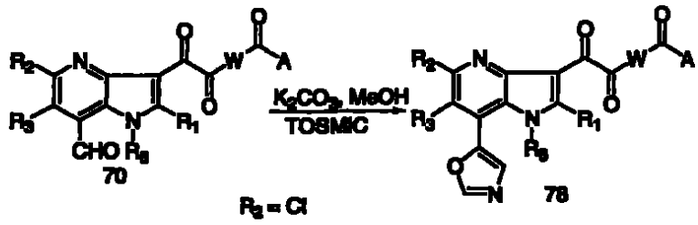
77

Removal of the trityl group would provide 4-amino oxazoles which could be substituted by acylation, reductive alkylation or alkylation reactions or heterocycle forming reactions. The trityl could be replaced with an alternate protecting group such as a monomethoxy trityl, CBZ, benzyl, or appropriate silyl group if desired. Reference 73 demonstrates the preparation of oxazoles containing a trifluoromethyl

moiety and the conditions described therein demonstrates the synthesis of oxazoles with fluorinated methyl groups appended to them.

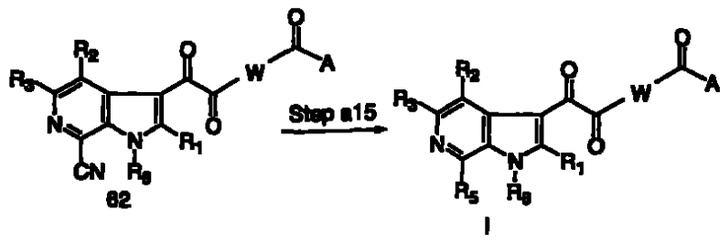
The aldehyde could also be reacted with a metal or Grignard (alkyl, aryl, or heteroaryl) to generate secondary alcohols. These would be efficacious or could be oxidized to the ketone with TPAP or MnO_2 or PCC for example to provide ketones of Formula I which could be utilized for treatment or reacted with metal reagents to give tertiary alcohols or alternatively converted to oximes by reaction with hydroxylamine hydrochlorides in ethanolic solvents. Alternatively the aldehyde could be converted to benzyl amines via reductive amination. An example of oxazole formation via a Tosmic reagent is shown below in Scheme 35. The same reaction would work with aldehydes at other positions and also in the 5 and 6 aza indole series.

Scheme 35



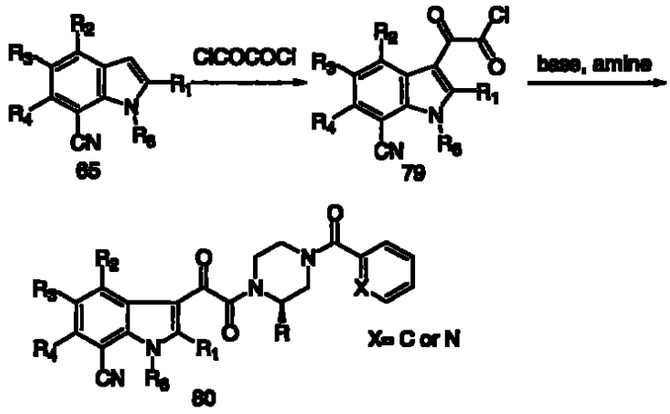
Scheme 36 shows in step a15, a cyano intermediate, such as 62, which could be directly converted to compounds of Formula I via heterocycle formation or reaction with organometallic reagents.

Scheme 36



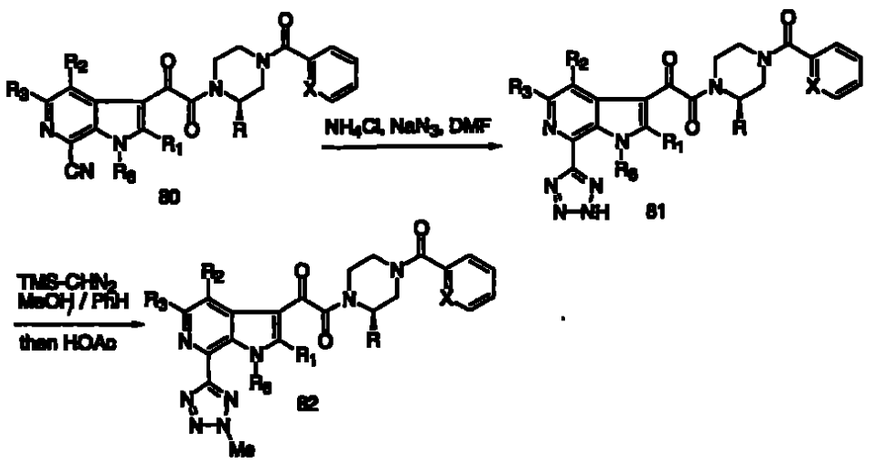
Scheme 37 shows a method for acylation of a cyanoindole intermediate of formula 65 with oxalyl chloride which would give acid chloride, 79, which could then be coupled with the appropriate amine in the presence of base to provide 80.

Scheme 37



The nitrile intermediate, 80, could be converted to the tetrazole of formula 81, which could then be alkylated with trimethylsilyldiazomethane to give the compound of formula 82 (Scheme 38).

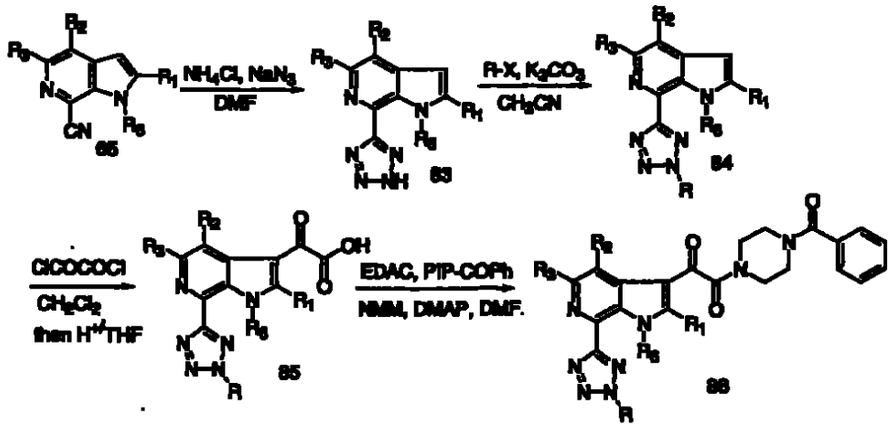
Scheme 38



Tetrazole alkylation with alkyl halides would be carried out prior to azaindole acylation as shown in Scheme 39. Intermediate 65 could be converted to tetrazole,

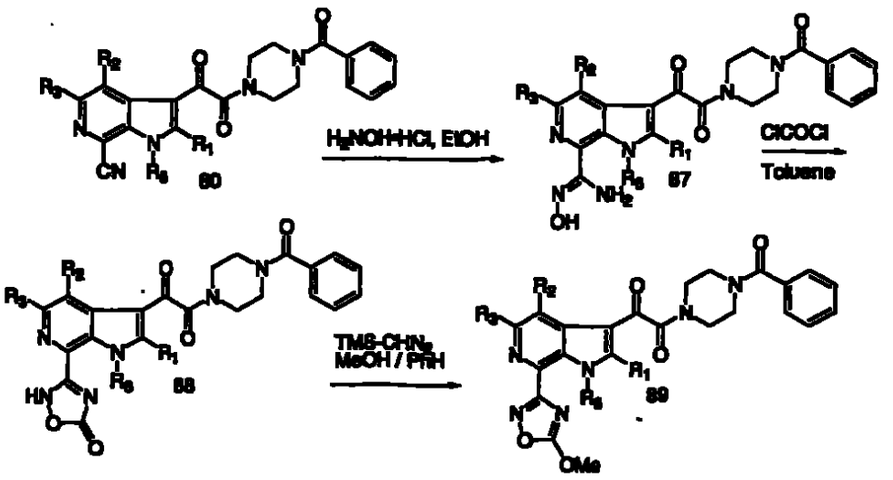
83, which could be alkylated to provide 84. Intermediate 84 could then be acylated and hydrolyzed to provide 85 which could be subjected to amide formation conditions to provide 86. The group appended to the tetrazole may be quite diverse and still exhibit impressive potency.

Scheme 39



Scheme 40 shows that an oxadiazole such as , 88, may be prepared by the addition of hydroxylamine to the nitrile, 80, followed by ring closure of intermediate 87 with phosgene. Alkylation of oxadiazole, 88, with trimethylsilyldiazomethane would give the compound of formula 89.

Scheme 40



A 7-cyanoindole, such as 80, could be efficiently converted to the imidate ester under conventional Pinner conditions using 1,4-dioxane as the solvent. The imidate ester can be reacted with nitrogen, oxygen and sulfur nucleophiles to provide C7-substituted indoles, for example: imidazolines, benzimidazoles, azabenzimidazoles, oxazolines, oxadiazoles, thiazolines, triazoles, pyrimidines and amidines etc. For example the imidate may be reacted with acetyl hydrazide with heating in a nonparticipating solvent such as dioxane, THF, or benzene for example. (aqueous base or aqueous base in an alcoholic solvent may need to be added to effect final dehydrative cyclization in some cases) to form a methyl triazine. Other hydrazines can be used. Triazines can also be installed via coupling of stannyl triazines with 4,5,6,or 7-bromo or chloro azaindoles. The examples give an example of the formation of many of these heterocycles.

References:

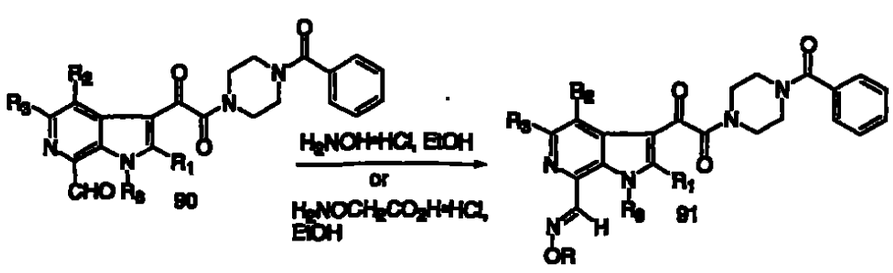
(1) Das, B. P.; Boykin, D. W. *J. Med. Chem.* **1977**, *20*, 531.

(2) Czarny, A.; Wilson, W. D.; Boykin, D. W. *J. Heterocyclic Chem.* **1996**, *33*, 1393.

(3) Francesconi, I.; Wilson, W. D.; Tanious, F. A.; Hall, J. E.; Bender, B. C.; Tidwell, R. R.; McCurdy, D.; Boykin, D. W. *J. Med. Chem.* **1999**, *42*, 2260.

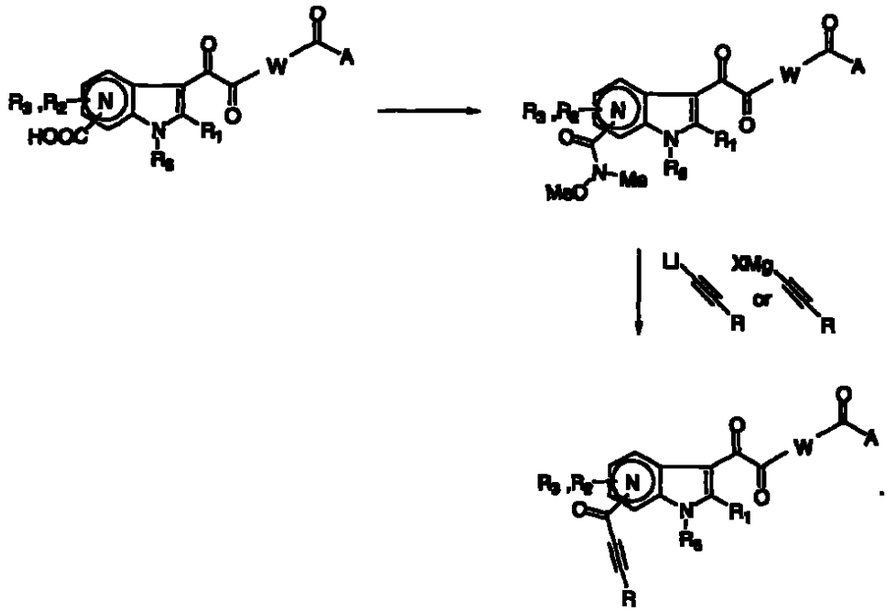
Scheme 41 shows addition of either hydroxylamine or hydroxylamine acetic acid to aldehyde intermediate 90 may give oximes of Formula 91.

Scheme 41

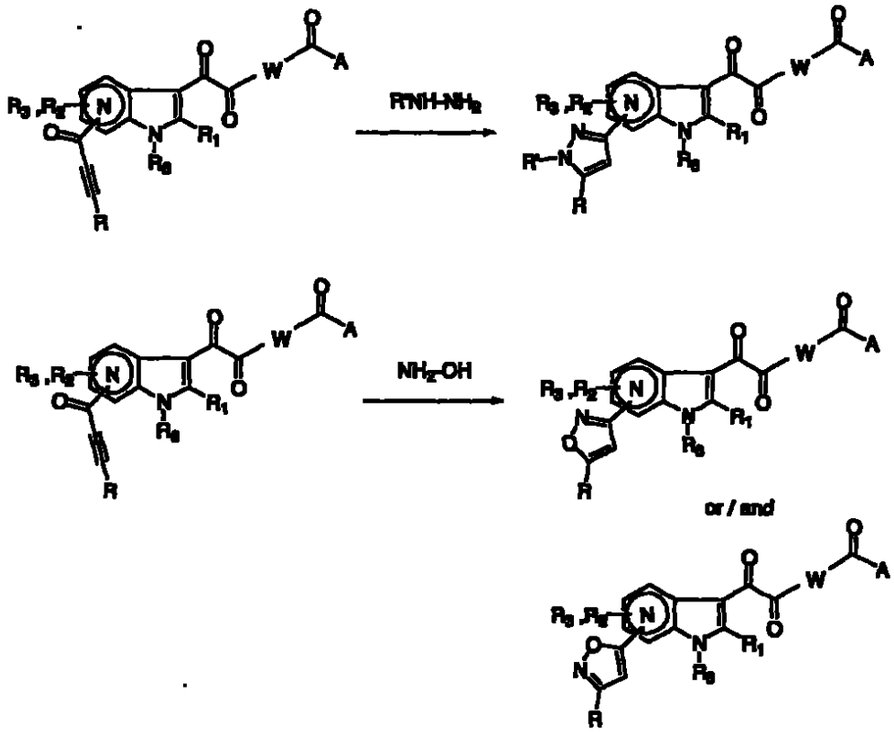


An acid may be a precursor for substituents R_1 through R_5 when it occupies the corresponding position such as R_5 as shown in Scheme 42.

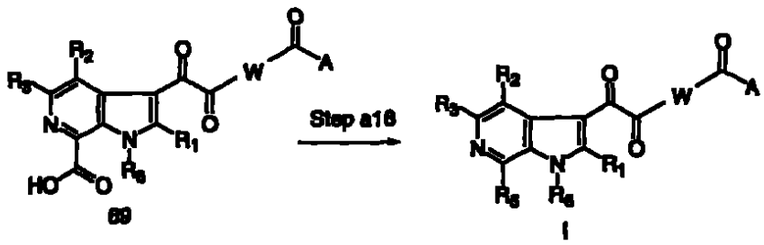
Scheme 41a



Scheme 41a (continued)



Scheme 42



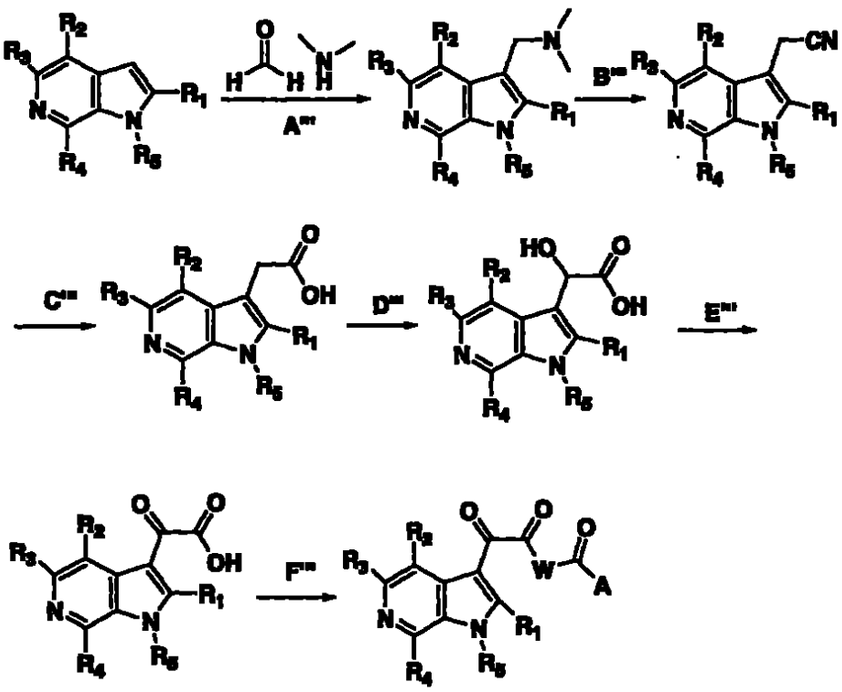
An acid intermediate, such as 69, may be used as a versatile precursor to generate numerous substituted compounds. The acid could be converted to hydrazonyl bromide and then a pyrazole via reference 74. One method for general heterocycle synthesis would be to convert the acid to an alpha bromo ketone (ref 75) by conversion to the acid chloride using standard methods, reaction with diazomethane, and finally reaction with HBr. The alpha bromo ketone could be used

to prepare many different compounds of Formula I as it can be converted to many heterocycles or other compounds of Formula I. Alpha amino ketones can be prepared by displacement of the bromide with amines. Alternatively, the alpha bromo ketone could be used to prepare heterocycles not available directly from the aldehyde or acid. For example, using the conditions of Hulton in reference 76 to react with the alpha bromo ketone would provide oxazoles. Reaction of the alpha bromoketone with urea via the methods of reference 77 would provide 2-amino oxazoles. The alpha bromoketone could also be used to generate furans using beta keto esters(ref 78-80) or other methods, pyrroles (from beta dicarbonyls as in ref 81 or by Hantzsch methods (ref 82) thiazoles , isoxazoles and imidazoles (ref 83) example using literature procedures. Coupling of the aforementioned acid chloride with N-methyl-O-methyl hydroxyl amine would provide a "Weinreb Amide" which could be used to react with alkyl lithiums or Grignard reagents to generate ketones. Reaction of the Weinreb anion with a dianion of a hydroxyl amine would generate isoxazoles (ref 84). Reaction with an acetylenic lithium or other carbanion would generate alkynyl indole ketones. Reaction of this alkynyl intermediate with diazomethane or other diazo compounds would give pyrazoles (ref 85). Reaction with azide or hydroxyl amine would give heterocycles after elimination of water. Nitrile oxides would react with the alkynyl ketone to give isoxazoles (ref 86). Reaction of the initial acid to provide an acid chloride using for example oxalyl chloride or thionyl chloride or triphenyl phosphine/ carbon tetrachloride provides a useful intermediate as noted above. Reaction of the acid chloride with an alpha ester substituted isocyanide and base would give 2-substituted oxazoles (ref 87): These could be converted to amines, alcohols, or halides using standard reductions or Hoffman/Curtius type rearrangements.

Scheme 43 describes alternate chemistry for installing the oxoacetyl piperazine moiety onto the 3 position of the azaindoles. StepA''' in Scheme 43 depicts reaction with formaldehyde and dimethylamine using the conditions in Frydman, B.; Despuy, M.E.; Rapoport, H.; *J. Am. Chem. Soc.* 1965, *87*, 3530 will provide the dimethylamino compound shown.

Step B''' shows displacement with potassium cyanide would provide the cyano derivative according to the method described in Miyashita, K.; Kondoh, K.; Tsuchiya, K.; Miyabe, H.; Imanishi, T.; *Chem. Pharm. Bull.* 1997, *45(5)*, 932-935 or in Kawase, M.; Sinhababu, A.K.; Borchardt, R.T.; *Chem. Pharm. Bull.* 1990, *38(11)*, 2939-2946. The same transformation could also be carried out using TMSCN and a tetrabutylammonium flouride source as in Iwao, M.; Motoi, O.; *Tetrahedron Lett.* 1995, *36(33)*, 5929-5932. Sodium cyanide could also be utilized.

Scheme 43



Step C''' of Scheme 43 depicts hydrolysis of the nitrile with sodium hydroxide and methanol would provide the acid via the methods described in Iwao, M.; Motoi, O.; *Tetrahedron Lett.* 1995, *36(33)*, 5929-5932 for example. Other basic hydrolysis conditions using either NaOH or KOH as described in Thesing, J.; et al.; *Chem. Ber.* 1955, *88*, 1295 and Geissman, T.A.; Armen, A.; *J. Am. Chem. Soc.* 1952, *74*, 3916. The use of a nitrilase enzyme to achieve the same transformation is

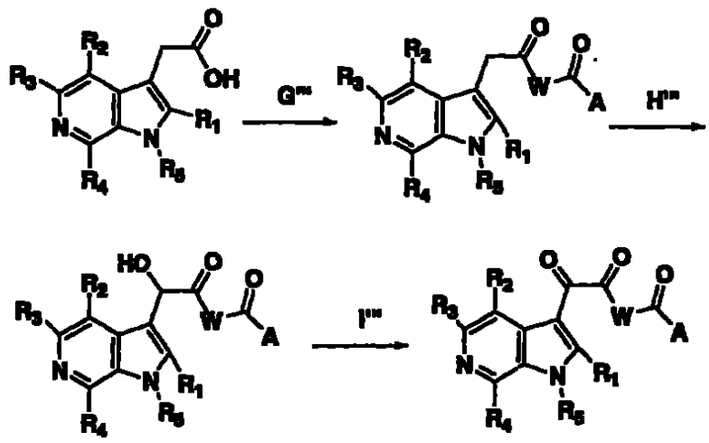
described by Klempier N, de Raadt A, Griengl H, Heinisch G, *J. Heterocycl. Chem.*, 1992 *29*, 93, and may be applicable.

Step D''' of Scheme 43 depicts an alpha hydroxylation which may be accomplished by methods as described in Hanessian, S.; Wang, W.; Gai, Y.; *Tetrahedron Lett.* 1996, *37(42)*, 7477-7480; Robinson, R. A.; Clark, J. S.; Holmes, A. B.; *J. Am. Chem. Soc.* 1993, *115(22)*, 10400-10401 ($KN(TMS)_2$ and then camphorsulfonyloxaziridine or another oxaziridine; andDavis, F.A.; Reddy, R.T.; Reddy, R.E.; *J. Org. Chem.* 1992, *57(24)*, 6387-6389.

Step E''' of Scheme 43 shows methods for the oxidation of the alpha hydroxy ester to the ketone which may be accomplished according to the methods described in Mohand, S.A.; Levina, A.; Muzart, J.; Synth. Comm. 1995, 25 (14), 2051-2059. A preferred method for step E''' is that of Ma, Z.; Bobbitt, J.M.; *J. Org. Chem.* 1991, *56(21)*, 6110-6114 which utilizes 4-(NH-Ac)-TEMPO in a solvent such as CH_2Cl_2 in the presence of para toluenesulfonic acid. The method described in Corson, B.B.; Dodge, R.A.; Harris, S.A.; Hazen, R.K.; *Org. Synth.* 1941, *I*, 241 for the oxidation of the alpha hydroxy ester to the ketone uses $KmnO_4$ as oxidant. Other methods for the oxidation of the alpha hydroxy ester to the ketone include those described in Humaeus, ; Zincke,; *Ber. Dtsch Chem. Ges.* 1877, *10*, 1489; Acree,; *Am. Chem.* 1913, *50*, 391; and Claisen,; *Ber. Dtsch. Chem. Ges.* 1877, *10*, 846.

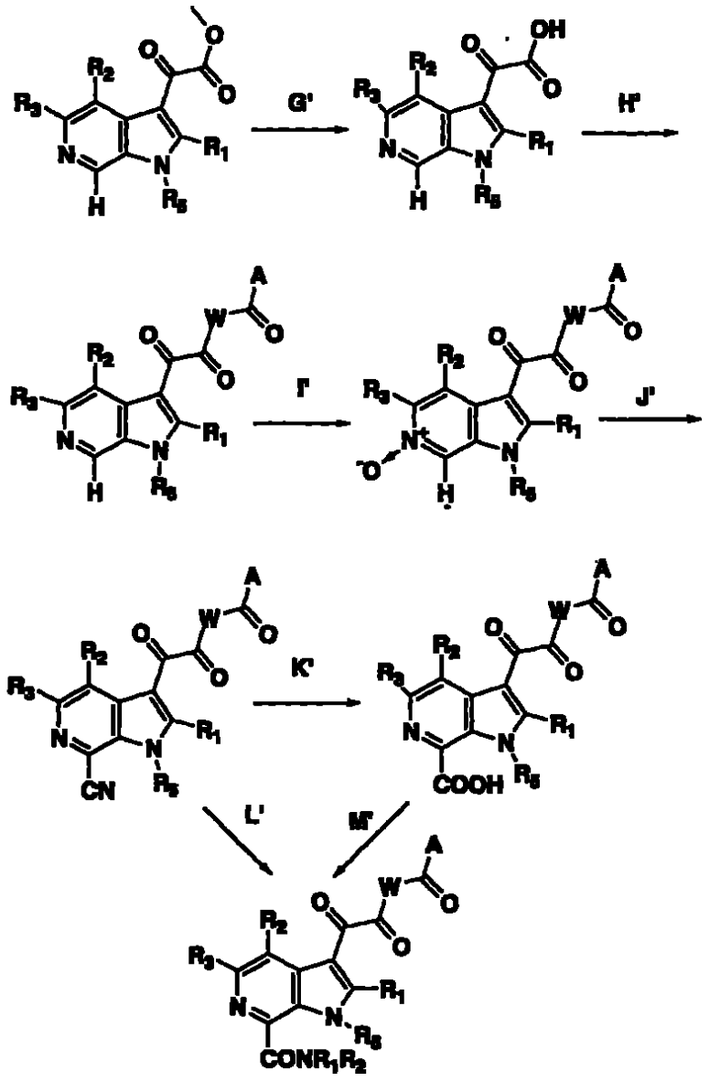
Step F''' of Scheme 43 depicts the coupling reactions which may be carried out as described previously in the application and by a preferred method which is described in Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Organic Lett.*, 1999, *1*, 91-93 and employs 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT); a new coupling reagent with remarkable resistance to racemization.

Scheme 44



Scheme 44 depicts the preparation of Formula I compounds by coupling HWC(O)A to the acid as described in Step F''' of Scheme 43, followed by hydroxylation as in Step D''' of Scheme 43 and oxidation as described in Step E''' of Scheme 43.

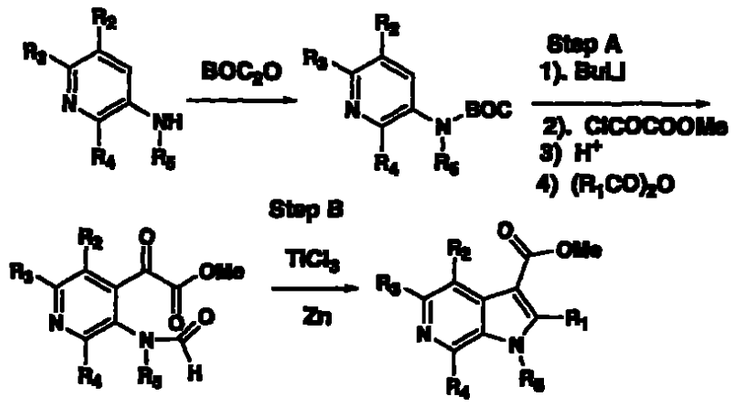
Scheme 45



Scheme 45 depicts a method for the preparation which could be used to obtain amido compounds of Formula I. Step G' represents ester hydrolysis followed by amide formation (Step H' as described in Step F''' of Scheme 43). Step I' of Scheme 45 depicts the preparation of the N-oxide which could be accomplished according to the procedures in Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y.; *Tetrahedron* **1997**, *53(5)*, 1593-1606; Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y.; Chem. Pharm. Bull. **1991**, *39(8)*, 2170-2172; and Ohmato, T.; Koike, K.; Sakamoto, Y.; Chem. Pharm. Bull.

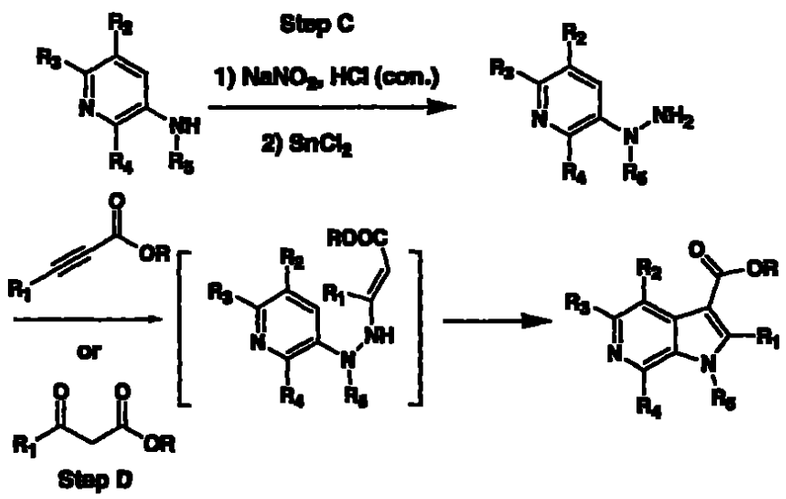
1981, *29*, 390. Cyanation of the N-oxide is shown in Step J' of Scheme 45 which may be accomplished according to Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y.; *Tetrahedron* 1997, *53(5)*, 1593-1606 and Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y.; Chem. Pharm. Bull. 1991, *39(8)*, 2170-2172. Hydrolysis of the nitrile to the acid is depicted in Step K' of Scheme 45 according to procedures such as Shiotani, S.; Taniguchi, K.; *J. Heterocycl. Chem.* 1996, *33(4)*, 1051-1056; Memoli, K.A.; *Tetrahedron Lett.* 1996, *37(21)*, 3617-3618; Adolfsson, H.; Waernmark, K.; Moberg, C.; *J. Org. Chem.* 1994, *59(8)*, 2004-2009; and El Hadri, A.; Leclerc, G.; *J. Heterocycl. Chem.* 1993, *30(3)*, 631-635. Step L' of Scheme 45 depicts a method which could be utilized for the preparation of amido compounds of Formula I from the cyano derivative which may be accomplished according to procedures described in Shiotani, S.; Taniguchi, K.; *J. Heterocycl. Chem.* 1997, *34(2)*, 493-499; Boogaard, A.T.; Pandit, U.K.; Koomen, G.-J.; *Tetrahedron* 1994, *50(8)*, 2551-2560; Rivalle, C.; Bisagni, E.; *Heterocycles* 1994, *38(2)*, 391-397; and Macor, J.E.; Post, R.; Ryan, K.; *J. Heterocycl. Chem.* 1992, *29(6)*, 1465-1467. Step M' of Scheme 45 shows a method which could be used for the preparation of amido compounds of Formula I from the acid derivative which may be accomplished according to procedures described in Norman, M.H.; Navas, F. III; Thompson, J.B.; Rigdon, G.C.; *J. Med. Chem.* 1996, *39(24)*, 4692-4703; Hong, F.; Pang, Y.-P.; Cusack, B.; Richelson, E.; *J. Chem. Soc., Perkin Trans 1* 1997, *14*, 2083-2088; Langry, K. C.; *Org. Prep. Proced. Int.* 1994, *26(4)*, 429-438; Romero, D.L.; Morge, R.A.; Biles, C.; Berrios-Pena, N.; May, P.D.; Palmer, J.R.; Johnson, P.D.; Smith, H.W.; Busso, M.; Tan, C.-K.; Voorman, R.L.; Reusser, F.; Althaus, I.W.; Downey, K.M.; et al.; *J. Med. Chem.* 1994, *37(7)*, 999-1014 and Bhattacharjee, A.; Mukhopadhyay, R.; Bhattacharjya, A.; *Indian J. Chem.*, Sect B 1994, *33(7)*, 679-682.

Scheme 46



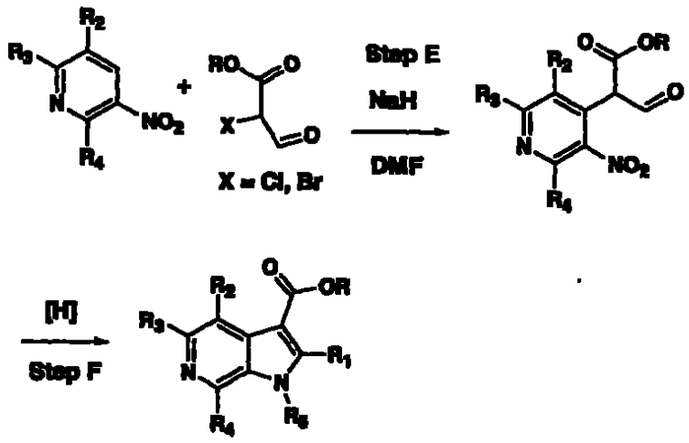
Scheme 46 shows a method which could be used for the synthesis of an azaindole acetic acid derivative. Protection of the amine group could be effected by treatment with di-tert-butyldicarbonate to introduce the t-Butoxycarbonyl (BOC) group. Introduction of the oxalate moiety may then be accomplished as shown in Step A of Scheme 46 according to the procedures described in Hewawasam, P.; Meanwell, N. A.; *Tetrahedron Lett.* 1994, *35(40)*, 7303-7306 (using t-Buli, or s-buli, THF); or Stanetty, P.; Koller, H.; Mihovilovic, M.; *J. Org. Chem.* 1992, *57(25)*, 6833-6837 (using t-Buli). The intermediate thus formed could then be cyclized to form the azaindole as shown in Step B of Scheme 46 according to the procedures described in Fuerstner, A.; Ernst, A.; Krause, H.; Ptock, A.; *Tetrahedron* 1996, *52(21)*, 7329-7344 (using. TiCl3, Zn, DME); or Fuerstner, A.; Hupperts, A.; *J. Am. Chem. Soc.* 1995, *117(16)*, 4468-4475 (using Zn, excess Tms-Cl, TiCl3 (cat.), MeCN).

Scheme 47



Scheme 47 describes an alternate synthesis which could be used to prepare azaindole acetic acid derivatives. Step C of Scheme 47 could be accomplished by using the procedures described in Harden, F.A.; Quinn, R.J.; Scammells, P.J.; *J. Med. Chem.* **1991**, *34(9)*, 2892-2898 [use of 1. $NaNO_2$, conc. HCl 2. $SnCl_2$, conc. HCl (cat.)]. Typically, 10 equivalents of $NaNO_2$ and 1.0 equivalents of substrate reacted at 0 °C for 0.25 to 1h and to this reaction mixture was added 3.5 equivalents of $SnCl_2$. Alternatively, the procedure described in De Roos, K.B.; Salemink, C.A.; *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1181 (use of $NaNO_2$, AcOH, H_2O) could be used. The intermediate thus formed could be further reacted and cyclized to provide azaindole acetic acid derivatives as shown in Step D of Scheme 47 and according to the procedures described inAtkinson, C. M.; Mattocks, A. R.; *J. Chem. Soc.* **1957**, 3722; Ain Khan, M.; Ferreira Da Rocha, J.; *Heterocycles* **1978**, *9*, 1617; Fusco, R.; Sannicolo, F.; *Tetrahedron* **1980**, *36*, 161[use of HCl (conc)]; Abramovitch, R. A.; Spenser, I. D.; *Adv. Heterocycl. Chem.* **1964**, *3*, 79 (use of $ZnCl_2$, p-Cymene); and Clemo, G. R.; Holt, R. J. W.; *J. Chem. Soc.* **1953**, 1313; (use of $ZnCl_2$, EtOH, Sealed tube).

Scheme 48

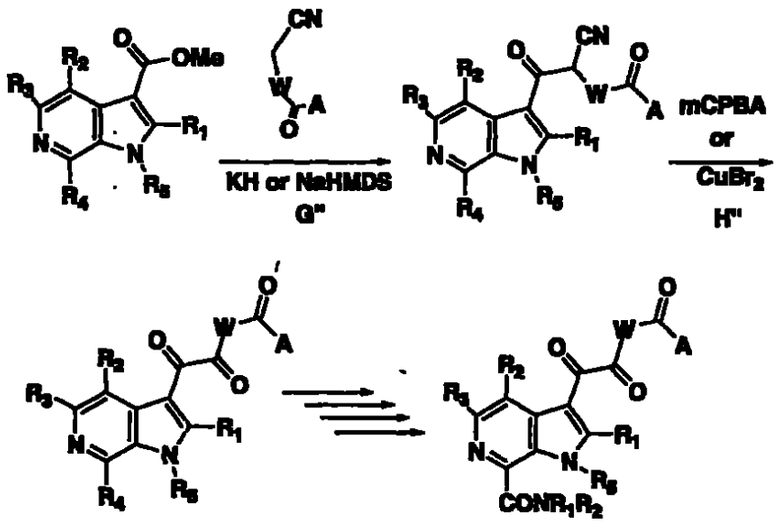


Scheme 48 depicts another possible route to azaindole acetic acid derivatives. Step B of Scheme 48 could be carried out as shown or according to procedures such as those described in Yurovskaya, M.A.; Khamlova, I.G.; Nesterov, V.N.; Shishkin, O.V.; Struchkov, T.; Khim Geterotsikl Soedin 1995, *11*, 1543-1550; Grzegozek, M.; Wozniak, M.; Baranski, A.; Van Der Plas, H.C.; *J. Heterocycl. Chem.* 1991, *28(4)*, 1075-1077 (use of NaOH, DMSO); Lawrence, N.J.; Liddle, J.; Jackson, D.A.; *Tetrahedron Lett.* 1995, *36(46)*, 8477-8480 (use of. NaH, DMSO); Haglund, O.; Nilsson, M.; Synthesis 1994, 3, 242-244; (use of 2.5 equiv. CuCl, 3.5 equiv. TBu-OK, DME, Py); Makosza, M.; Sienkiewicz, K.; Wojciechowski, K.; *Synthesis* 1990, *9*, 850-852; (use of KO-tBu, DMF); Makosza, M.; Nizamov, S.; *Org. Prep. Proceed. Int.* 1997, *29(6)*, 707-710; (use of tBu-OK, THF). Step F of Scheme 48 shows the cyclization reaction which could provide the azaindole acetic acid derivatives. This reaction could be accomplished according to procedures such as those described in Frydman, B.; Baldain, G.; Repetto, J. C.; *J. Org. Chem.* 1973, *38*, 1824 (use of H_2, Pd-C, EtOH); Bistryakova, I. D.; Smirnova, N. M.; Safonova, T. S.; Khim Geterotsikl Soedin 1993, *6*, 800-803 (use of H_2, Pd-C (cat.), MeOH); Taga, M.; Ohtsuka, H.; Inoue, I.; Kawaguchi, T.; Nomura, S.; Yamada, K.; Date, T.; Hiramatsu, H.; Sato, Y.; *Heterocycles* 1996, *42(1)*, 251-263 (use of $SnCl_2$, HCl, Et_2O); Arcari, M.; Aveta, R.; Brandt, A.; Cecchetelli, L.; Corsi, G.B.; Dirella, M.; *Gazz. Chim. Ital.* 1991, *121(11)*, 499-504 [use of $Na_2S_2O_6$, THF/EtOH/H_2O (2:2:1)]; Moody, C. J.;

Rahimtoola, K. F.; *J. Chem. Soc., Perkin Trans 1* 1990, 673 (use of $TiCl_3$, NH_4OAc, acetone, H_2O).

Scheme 49 provides another route to azaindole intermediates which could then be further elaborated to provide compounds of Formula I, such as the amido derivatives shown. Steps G'' and H'' of Scheme 49 may be carried out according to the procedures described in Takahashi, K.; Shibasaki, K.; Ogura, K.; Iida, H.; *Chem. Lett.* 1983, 859; and Itoh, N.; Chem. Pharm. Bull. 1962, *10*, 55. Elaboration of the intermediate to the amido compound of Formula I could be accomplished as previously described for Steps I'- M' of Scheme 45.

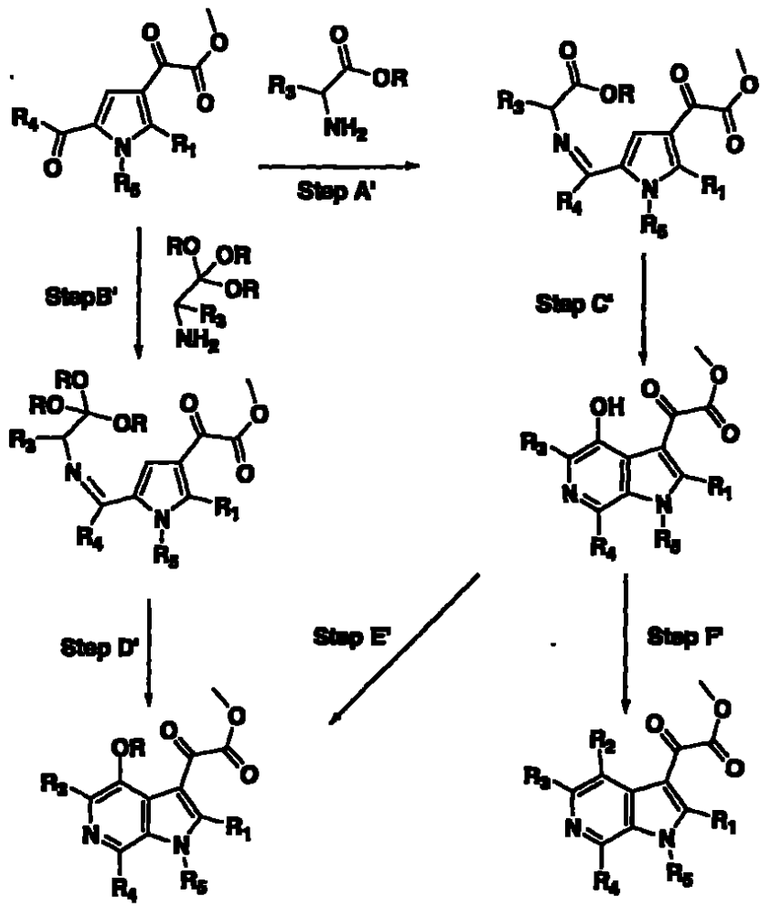
Scheme 49



Scheme 50 shows the preparation of azaindole oxalic acid derivatives. The starting materials in Scheme 50 may be prepared according to *Tetrahedron Lett.* 1995, *36*, 2389-2392. Steps A', B', C', and D' of Scheme 50 may be carried out according to procedures described in Jones, R.A.; Pastor, J.; Siro, J.; Voro, T.N.; *Tetrahedron* 1997, *53(2)*, 479-486; and Singh, S.K.; Dekhane, M.; Le Hyaric, M.; Potier, P.; Dodd, R.H.; *Heterocycles* 1997, *44(1)*, 379-391. Step E' of Scheme 50 could be carried out according to the procedures described in Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami,

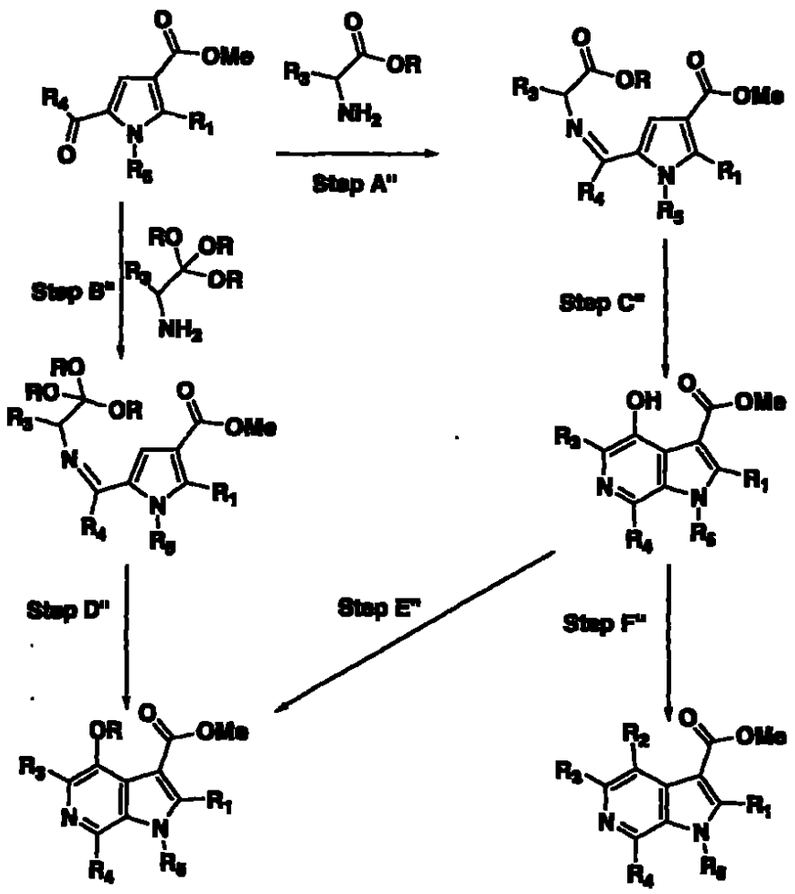
Y.; *Tetrahedron* 1997, *53(5)*, 1593-1606; Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y.; *Chem. Pharm. Bull.* 1991, *39(8)*, 2170-2172; Hagen, T.J.; Narayanan, K.; Names, J.; Cook, J.M.; *J. Org. Chem.* 1989, *54*, 2170; Murakami, Y.; Yokoyama, Y.; Watanabe, T.; Aoki, C.; et al.; *Heterocycles* 1987, *26*, 875; and Hagen, T. J.; Cook, J.M.; *Tetrahedron Lett.* 1988, *29(20)*, 2421. Step F' of Scheme 50 shows the conversion of the phenol to a fluoro, chloro or bromo derivative. Conversion of the phenol to the fluoro derivative could be carried out according to procedures described in Christe, K.O.; Pavlath, A.E.; *J. Org. Chem.* 1965, *30*, 3170; Murakami, Y.; Aoyama, Y.; Nakanishi, S.; *Chem. Lett.* 1976, 857; Christe, K. O.; Pavlath, A. E.; *J. Org. Chem.* 1965, *30*, 4104; and Christe, K.O.; Pavlath, A.E.; *J. Org. Chem.* 1966, *31*, 559. Conversion of the phenol to the chloro derivative could be carried out according to procedures described in Wright, S.W.; Org. Prep. Proc. Int. 1997, 29(1), 128-131; Hartmann, H.; Schulze, M.; Guenther, R.; *Dyes Pigm* 1991, *16(2)*, 119-136; Bay, E.; Bak, D. A.; Timony, P. E.; Leone-Bay, A.; J. Org. Chem. 1990, *55*, 3415; Hoffmann, H.; et al.; *Chem. Ber.* 1962, *95*, 523; and Vanallan, J.A.; Reynolds; G.A.; *J. Org. Chem.* 1963, *28*, 1022. Conversion of the phenol to the bromo derivative may be carried out according to procedures described in Katritzky, A.R.; Li, J.; Stevens, C.V.; Ager, D.J.; *Org. Prep. Proc. Int.* 1994, *26(4)*, 439-444; Judice, J.K.; Keipert, S.J.; Cram, D.J.; *J. Chem. Soc., Chem. Commun.* 1993, *17*, 1323-1325; Schaeffer, J.P.; Higgins, J.; *J. Org. Chem.* 1967, *32*, 1607; Wiley, G.A.; Hershkowitz, R.L.; Rein, R.M.; Chung, B.C.; *J. Am. Chem. Soc.* 1964, *86*, 964; and Tayaka, H.; Akutagawa, S.; Noyori, R.; *Org. Syn.* 1988, *67*, 20.

Scheme 50



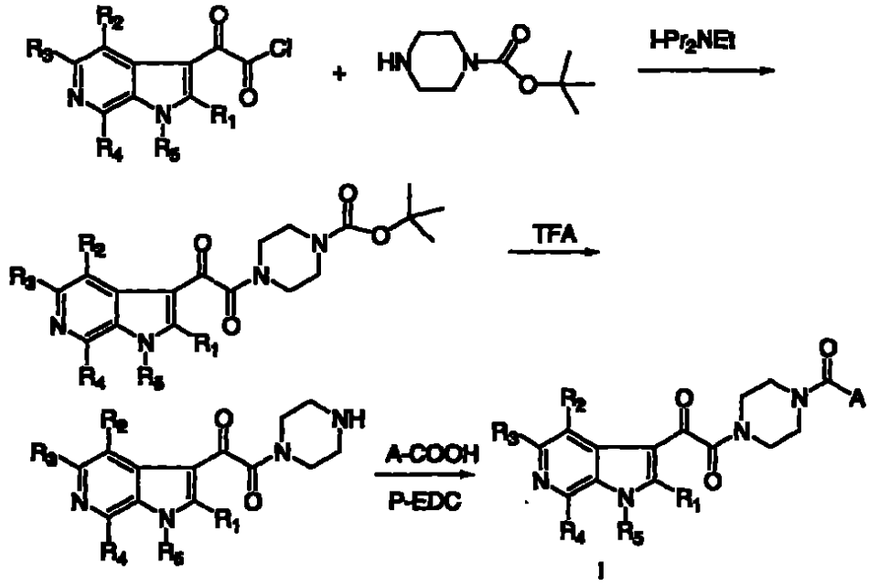
Scheme 51 describes methods for the preparation of azaindole acetic acid derivatives by the same methods employed for the preparation of azaindole oxalic acid derivatives as shown and described in Scheme 50 above. The starting material employed in Scheme 51 could be prepared according to *J. Org. Chem.* 1999, *64*, 7788-7801. Steps A'', B'', C'', D'', and E'' of Scheme 51 could be carried out in the same fashion as previously described for Steps Steps A', B', C', D', and E' of Scheme 50.

Scheme 51



The remaining schemes provide additional background, examples, and conditions for carrying out this invention. Specific methods for preparing W and modifying A are presented. As shown in Scheme 52, the azaindoles may be treated with oxalyl chloride in either THF or ether to afford the desired glyoxyl chlorides according to literature procedures (Lingens, F.; Lange, J. *Justus Liebigs Ann. Chem.* 1970, *738*, 46-53). The intermediate glyoxyl chlorides may be coupled with benzoyl piperazines (Dessi, M.; Watthey, J.W. *Org. Prep. Proc. Int.* 1976, *8*, 85-86) under basic conditions to afford compounds of Formula I directly.

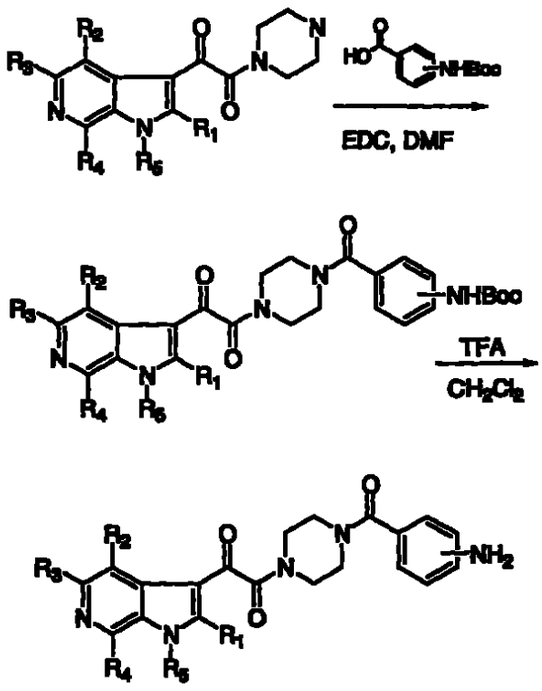
Scheme 52



I

Alternatively, Scheme 52 treatment of the azaindole-3-glyoxyl chloride, (Scheme 52) with *tert*-butyl 1-piperazinecarboxylate affords the piperazine coupled product. It is apparent to one skilled in the art that use of an alternative Boc protected piperazine which are synthesized as shown below would provide compounds of formula I with alternative groups of formula W. As discussed earlier, other amine protecting groups which do not require acidic deprotection conditions could be utilized if desired. Deprotection of the Boc group is effected with 20% TFA/CH_2Cl_2 to yield the free piperazine. This product is then coupled with carboxylic acid in the presence of polymer supported 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (P-EDC) to afford products of Formula I. This sequence provides a general method for synthesizing compounds of varied A in formula I.

Scheme 53

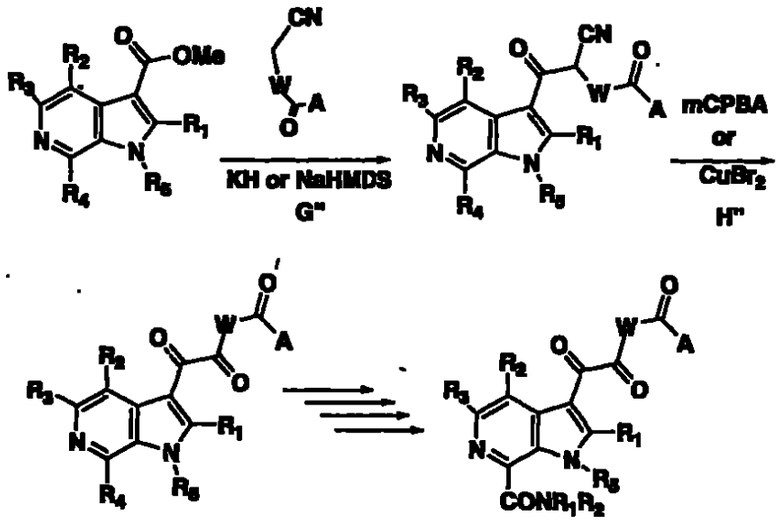


An example for preparing compounds of Formula I which possess substituents in A (or other parts of the molecule) which might interfere with the standard reaction schemes reactions is shown in Scheme 53. The piperazine derivative (Scheme 53) was treated with Boc-protected aminobenzoic acid in the presence of EDC to afford the piperazine diamide. A portion of the resulting product was separated and subjected to TFA in order to remove the Boc group, thus yielding amino derivatives.

Rahimtoola, K. F.; *J. Chem. Soc., Perkin Trans 1* 1990, 673 (use of $TiCl_3$, NH_4Oac, acetone, H_2O).

Scheme 49 provides another route to azaindole intermediates which could then be further elaborated to provide compounds of Formula I, such as the amido derivatives shown. Steps G''.and H'' of Scheme 49 may be carried out according to the procedures described in Takahashi, K.; Shibasaki, K.; Ogura, K.; Iida, H.; *Chem. Lett.* 1983, 859; and Itoh, N.; Chem. Pharm. Bull. 1962, *10*, 55. Elaboration of the intermediate to the amido compound of Formula I could be accomplished as previously described for Steps I'- M' of Scheme 45.

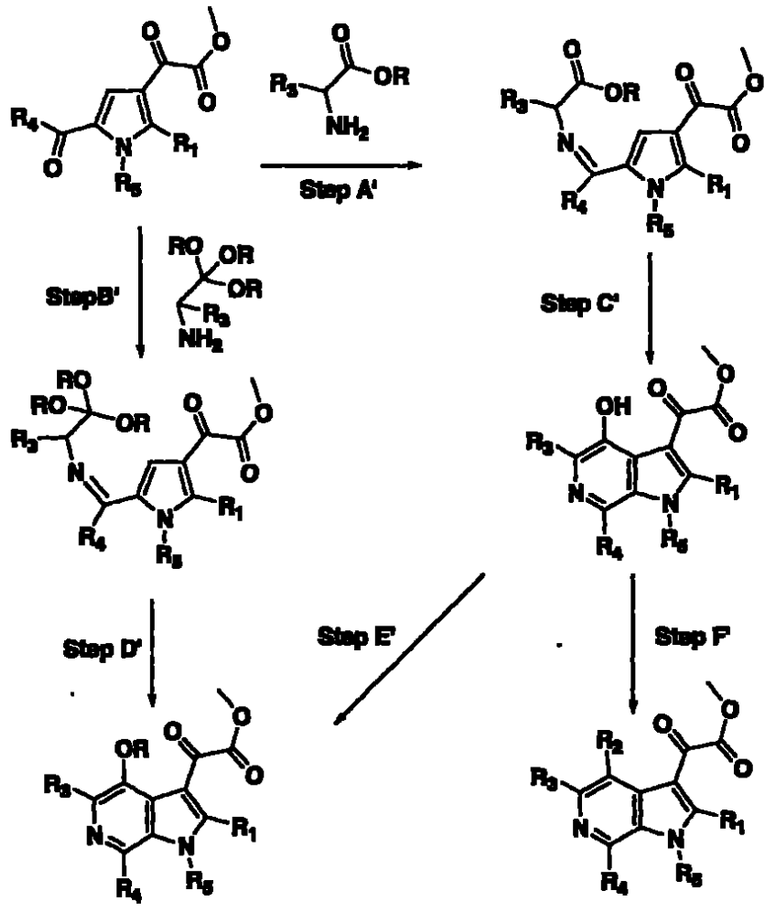
Scheme 49



Scheme 50 shows the preparation of azaindole oxalic acid derivatives. The starting materials in Scheme 50 may be prepared according to *Tetrahedron Lett.* 1995, *36*, 2389-2392. Steps A', B', C', and D' of Scheme 50 may be carried out according to procedures described in Jones, R.A.; Pastor, J.; Siro, J.; Voro, T.N.; *Tetrahedron* 1997, *53(2)*, 479-486; and Singh, S.K.; Dekhane, M.; Le Hyaric, M.; Potier, P.; Dodd, R.H.; *Heterocycles* 1997, *44(1)*, 379-391. Step E' of Scheme 50 could be carried out according to the procedures described in Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami,

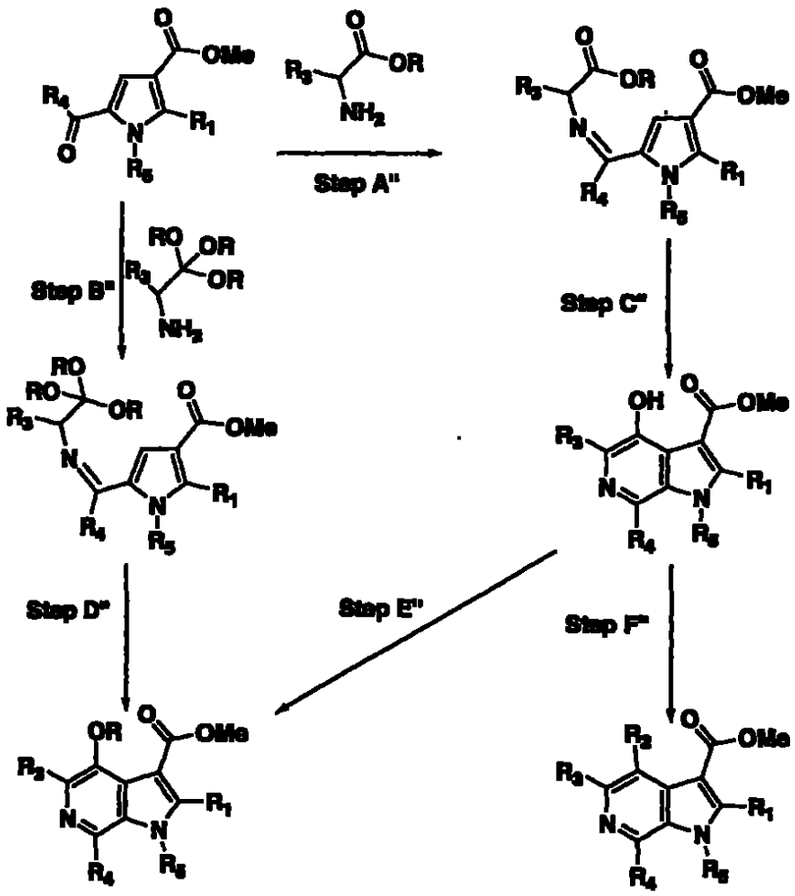
Y.; *Tetrahedron* 1997, *53(5)*, 1593-1606; Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y.; *Chem. Pharm. Bull.* 1991, *39(8)*, 2170-2172; Hagen, T.J.; Narayanan, K.; Names, J.; Cook, J.M.; *J. Org. Chem.* 1989, *54*, 2170; Murakami, Y.; Yokoyama, Y.; Watanabe, T.; Aoki, C.; et al.; *Heterocycles* 1987, *26*, 875; and Hagen, T. J.; Cook, J.M.; *Tetrahedron Lett.* 1988, *29(20)*, 2421. Step F' of Scheme 50 shows the conversion of the phenol to a fluoro, chloro or bromo derivative. Conversion of the phenol to the fluoro derivative could be carried out according to procedures described in Christe, K.O.; Pavlath, A.E.; *J. Org. Chem.* 1965, *30*, 3170; Murakami, Y.; Aoyama, Y.; Nakanishi, S.; *Chem. Lett.* 1976, 857; Christe, K. O.; Pavlath, A. E.; *J. Org. Chem.* 1965, *30*, 4104; and Christe, K.O.; Pavlath, A.E.; *J. Org. Chem.* 1966, *31*, 559. Conversion of the phenol to the chloro derivative could be carried out according to procedures described in Wright, S.W.; Org. Prep. Proc. Int. 1997, 29(1), 128-131; Hartmann, H.; Schulze, M.; Guenther, R.; *Dyes Pigm* 1991, *16(2)*, 119-136; Bay, E.; Bak, D. A.; Timony, P. E.; Leone-Bay, A.; J. Org. Chem. 1990, *55*, 3415; Hoffmann, H.; et al.; *Chem. Ber.* 1962, *95*, 523; and Vanallan, J.A.; Reynolds, G.A.; *J. Org. Chem.* 1963, *28*, 1022. Conversion of the phenol to the bromo derivative may be carried out according to procedures described in Katritzky, A.R.; Li, J.; Stevens, C.V.; Ager, D.J.; *Org. Prep. Proc. Int.* 1994, *26(4)*, 439-444; Judice, J.K.; Keipert, S.J.; Cram, D.J.; *J. Chem. Soc., Chem. Commun.* 1993, *17*, 1323-1325; Schaeffer, J.P.; Higgins, J.; *J. Org. Chem.* 1967, *32*, 1607; Wiley, G.A.; Hershkowitz, R.L.; Rein, R.M.; Chung, B.C.; *J. Am. Chem. Soc.* 1964, *86*, 964; and Tayaka, H.; Akutagawa, S.; Noyori, R.; *Org. Syn.* 1988, *67*, 20.

Scheme 50



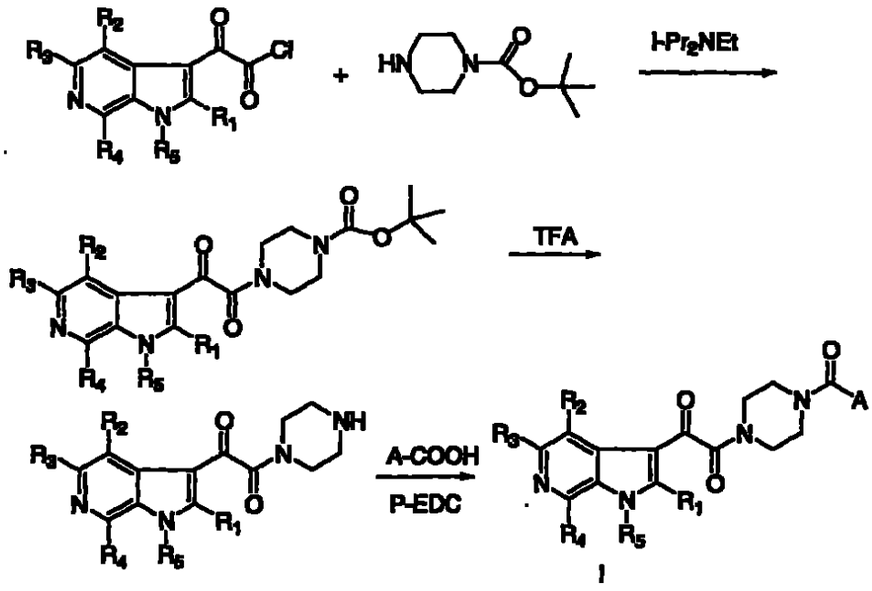
Scheme 51 describes methods for the preparation of azaindole acetic acid derivatives by the same methods employed for the preparation of azaindole oxalic acid derivatives as shown and described in Scheme 50 above. The starting material employed in Scheme 51 could be prepared according to *J. Org. Chem.* 1999, *64*, 7788-7801. Steps A'', B'', C'', D'', and E'' of Scheme 51 could be carried out in the same fashion as previously described for Steps Steps A', B', C', D', and E' of Scheme 50.

Scheme 51



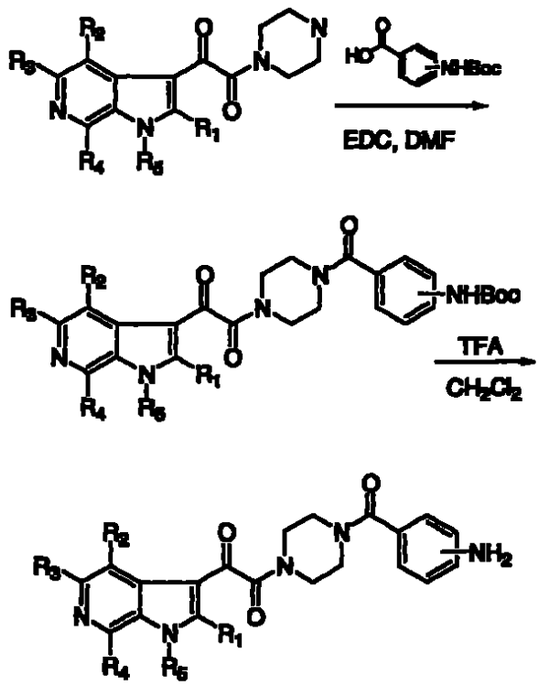
The remaining schemes provide additional background, examples, and conditions for carrying out this invention. Specific methods for preparing W and modifying A are presented. As shown in Scheme 52, the azaindoles may be treated with oxalyl chloride in either THF or ether to afford the desired glyoxyl chlorides according to literature procedures (Lingens, F.; Lange, J. *Justus Liebigs Ann. Chem.* 1970, *738*, 46-53). The intermediate glyoxyl chlorides may be coupled with benzoyl piperazines (Desai, M.; Watthey, J.W. *Org. Prep. Proc. Int.* 1976, *8*, 85-86) under basic conditions to afford compounds of Formula I directly.

Scheme 52



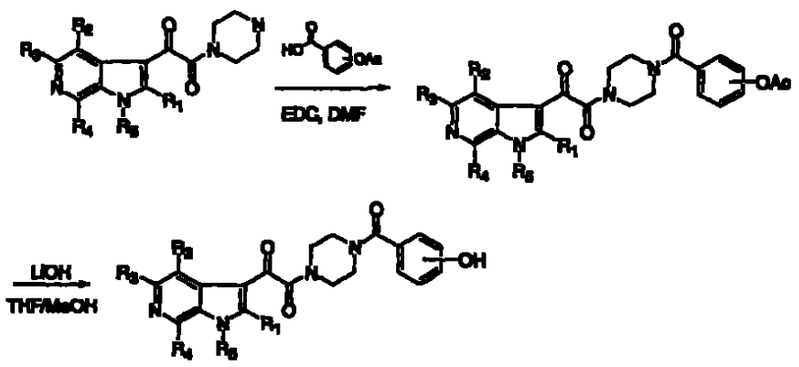
Alternatively, Scheme 52 treatment of the azaindole-3-glyoxyl chloride, (Scheme 52) with *tert*-butyl 1-piperazinecarboxylate affords the piperazine coupled product. It is apparent to one skilled in the art that use of an alternative Boc protected piperazine which are synthesized as shown below would provide compounds of formula I with alternative groups of formula W. As discussed earlier, other amine protecting groups which do not require acidic deprotection conditions could be utilized if desired. Deprotection of the Boc group is effected with 20% TFA/CH_2Cl_2 to yield the free piperazine. This product is then coupled with carboxylic acid in the presence of polymer supported 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (P-EDC) to afford products of Formula I. This sequence provides a general method for synthesizing compounds of varied A in formula I.

Scheme 53



An example for preparing compounds of Formula I which possess substituents in A (or other parts of the molecule) which might interfere with the standard reaction schemes reactions is shown in Scheme 53. The piperazine derivative (Scheme 53) was treated with Boc-protected aminobenzoic acid in the presence of EDC to afford the piperazine diamide. A portion of the resulting product was separated and subjected to TFA in order to remove the Boc group, thus yielding amino derivatives.

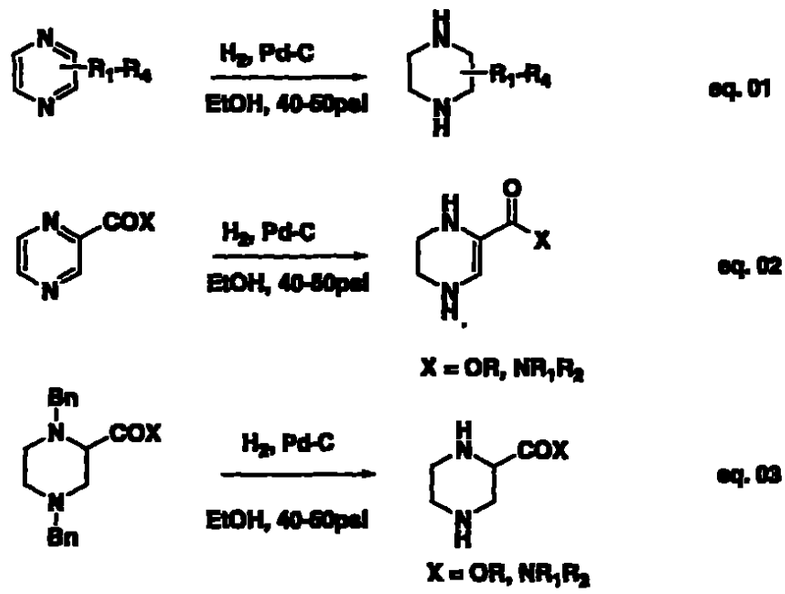
Scheme 54



Similarly, substituents which possess a reactive alcohol can be incorporated as below. The piperazine derivative (Scheme 54) was treated with acetoxybenzoic acid in the presence of EDC to afford the piperazine diamide derivative. A portion of the resulting product was separated and subjected to LiOH hydrolysis in order to remove the acetate group, thus yielding hydroxy derivatives.

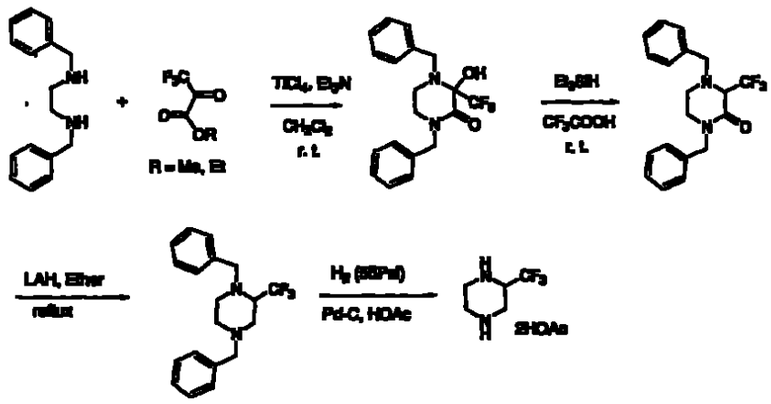
Examples containing substituted piperazines are prepared using the general procedures outlined in Schemes 55-38. Substituted piperazines are either commercially available from Aldrich, Co. or prepared according to literature procedures (Behun et al, Ref. 88(a), Scheme 31, eq. 01). Hydrogenation of alkyl substituted pyrazines under 40 to 50 psi pressure in EtOH afforded substituted piperazines. When the substituent was an ester or amide, the pyrazine systems could be partially reduced to the tetrahydropyrazine (Rossen et al, Ref. 88(b), Scheme 55, eq. 02). The carbonyl substituted piperazines could be obtained under the same conditions described above by using commercially available dibenzyl piperazines (Scheme 55, eq. 03).

Scheme 55



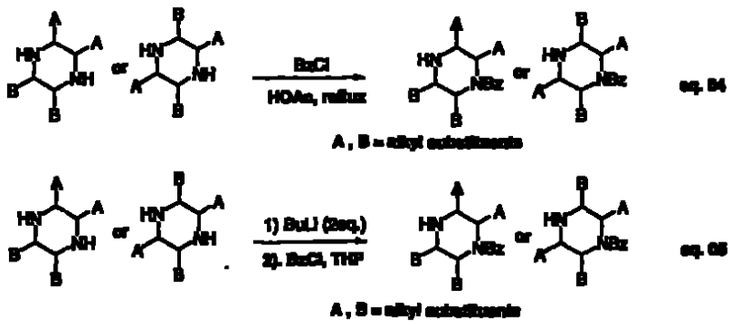
2-Trifluoromethylpiperazine (Jenneskens et al., Ref. 88c) was prepared through a four step route (Scheme 56). Using Lewis acid $TiCl_4$, N,N'-dibenzylethylenediamine reacted with trifluoropyruvates to afford the hemiacetal, which was reduced at room temperature by Et_3SiH in TFA to afford the lactam. $LiAlH_4$ treatment then reduced the lactam to 1,4-dibenzyl-2-trifluoromethylpiperazine. Finally, hydrogenation of the dibenzyl-2-trifluoromethylpiperazine in HOAc gave the desired product, 2-trifluoromethylpiperazine.

Scheme 56



Mono-benzoylation of symmetric substituted piperazines could be achieved by using one of the following procedures (Scheme 57). (a) Treatment of a solution of piperazine in acetic acid with acetyl chloride afforded the desired mon-benzoylated piperazine (Desai et al. Ref. 27, Scheme 57, eq. 04). (b) Symmetric piperazines were treated with 2 equivalents of *n*-butyllithium, followed by the addition of benzoyl chloride at room temperature (Wang et al, Ref. 89, Scheme 57, eq. 05).

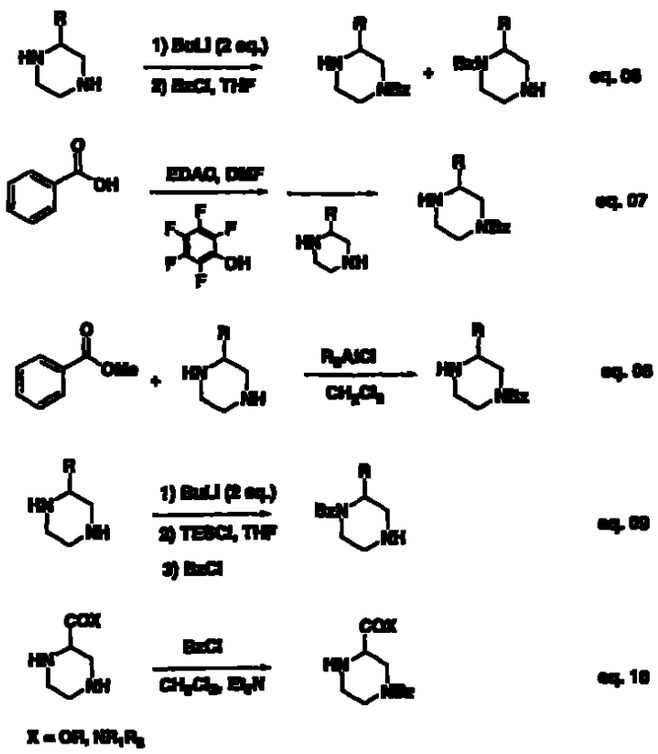
Scheme 57



Mono-benzoylation of unsymmetric substituted piperazines could be achieved by using one of the following procedures (Scheme 57), in which all the methods were exemplified by mono-alkyl substituted piperazines. (a) Unsymmetric piperazines were treated with 2 equivalents of *n*-butyllithium, followed by the addition of benzoyl chloride at room temperature to afford a mixture of two

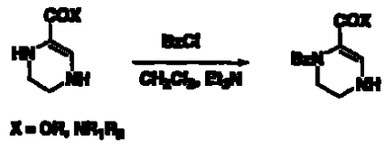
regioisomers, which could be separated by chromatography (Wang et al, Ref. 89 and 90(b), Scheme 58 eq. 06); (b) Benzoic acid was converted to its pentafluorophenyl ester, and then further reaction with 2-alkylpiperazine to provide the mono-benzoylpiperazines with the benzoyl group at the less hindered nitrogen (Adamczyk et al, Ref. 90(a), Scheme 58, eq. 07); (c) A mixture of piperazine and methyl benzoate was treated with dialkylaluminum chloride in methylene chloride for 2-4 days to yield the mono-benzoylpiperazine with the benzoyl group at the less hindered nitrogen (Scheme 58 eq. 08); (d) Unsymmetric piperazines were treated with 2 equivalents of *n*-butyllithium, followed by subsequent addition of triethylsilyl chloride and benzoyl chloride in THF at room temperature to afford mono-benzoylpiperazines with the benzoyl group at the more hindered nitrogen (Wang et al, Ref. 90(b), Scheme 58, eq. 09). When the substituent at position 2 was a ester or amide, the mono-benzoylation with benzoyl chloride occurred at the less hindered nitrogen of the piperazine with triethylamine as base in THF (Scheme 58, eq. 10).

Scheme 58



In the case of tetrahydropyrazines (Scheme 59, eq. 11), mono-benzoylation occurred at the more hindered nitrogen under the same conditions as those in equation 10 of Scheme 58, in the well precedented manner. (Rossen et al, Ref. 88(b)).

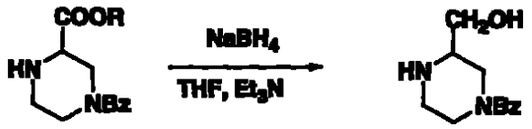
Scheme 59



eq. 11

Furthermore, the ester group can be selectively reduced by $NaBH_4$ in the presence of the benzamide (Masuzawa et al, Ref. 91), which is shown in Scheme 60.

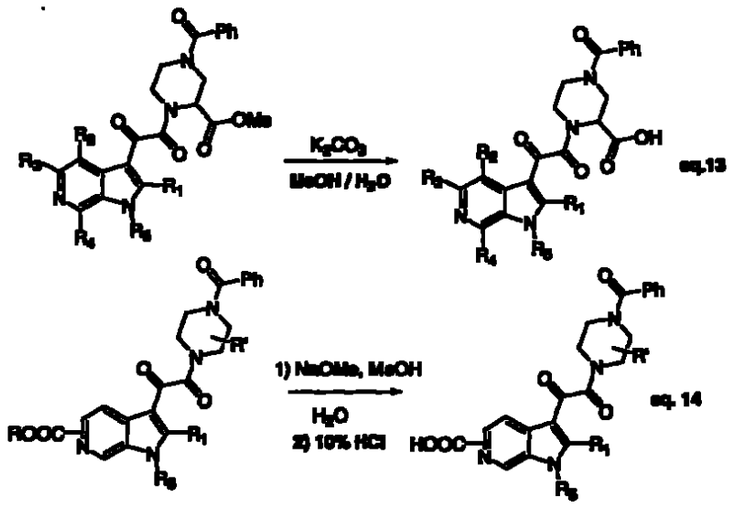
Scheme 60



eq. 12

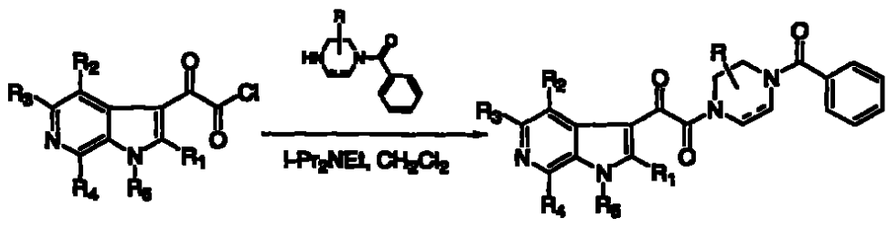
The ester groups on either the piperazine linkers or on the azaindole nucleus could be hydrolyzed to the corresponding acid under basic conditions such as K_2CO_3 (Scheme 61, eq. 13) or NaOMe (Scheme 61, eq. 14) as bases in MeOH and water.

Scheme 61



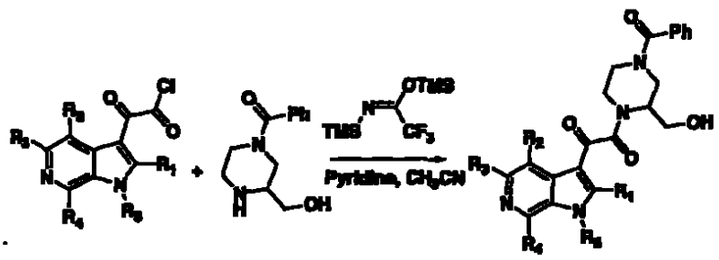
Reaction of an azaindole glyoxyl chloride with substituted benzoyl piperazines or tetrahydropyrazines in CH_2Cl_2 using I-Pr_2Net as base afforded the coupled products as shown in Scheme 62.

Scheme 62



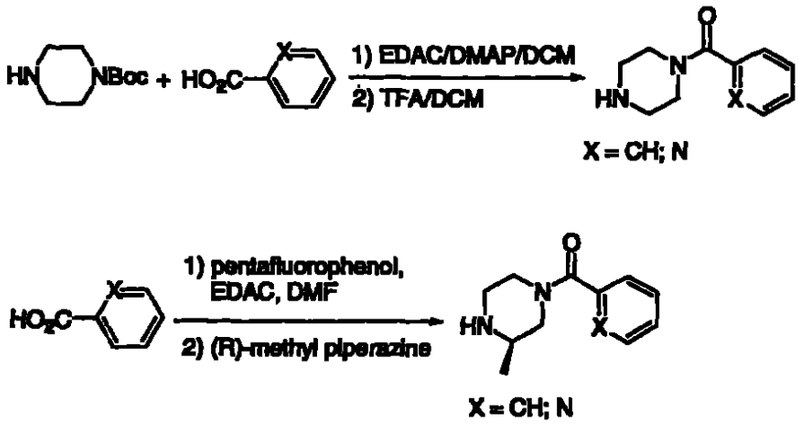
In the case of coupling reactions using 3-hydroxylmethyl-benzoylpiperazine, the hydroxyl group was temporarily protected as its TMS ether with BSTFA (N,O-bistrimethylsilyl)trifluoroacetamide) (Furber et al, Ref. 92). The unprotected nitrogen atom can then be reacted with glyoxyl chlorides to form the desired diamides. During workup, the TMS masking group was removed to give free hydroxylmethylpiperazine diamides as shown in Scheme 63.

Scheme 63



Piperazine intermediates were prepared using standard chemistry as shown in Scheme 64.

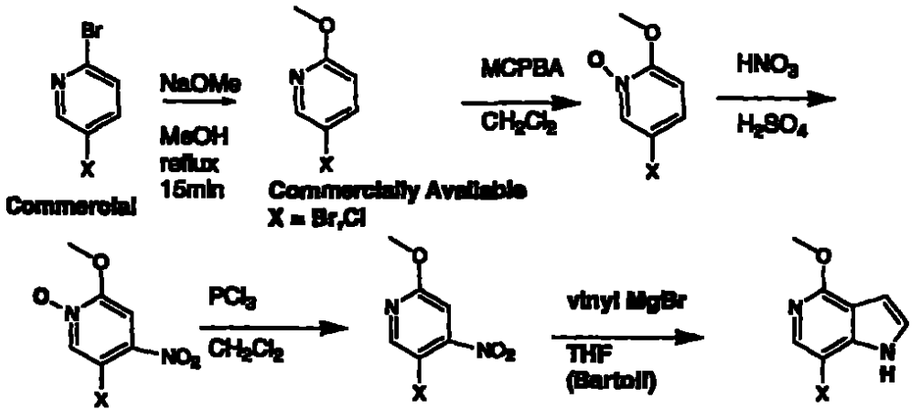
Scheme 64



Scheme 65

Scheme 65 depicts some more specific methodology for preparing 5-azindoles for use in prpeartion of the claimed compounds. Some reductive cyclizations conditions include Fe in acetic acid, Tin II chloride in aq HCl, or Zinc powder in acetic acid. Hydrogenation condititons or other conditions used in LeimGruber-Batch indole synthesis sequences can alo be employed.

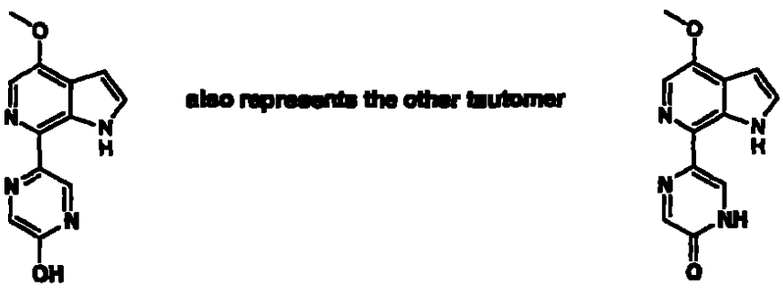
More specific route to 5-azaindoles:



X= chloro or bromo or may be converted to a substituent and then carried through the sequence

Tautomers of nitrogen containing heterocycles are covered by this patent application. For example, a hydroxy pyrazine is also known to represent its corresponding tautomer as well as shown in Scheme 66.

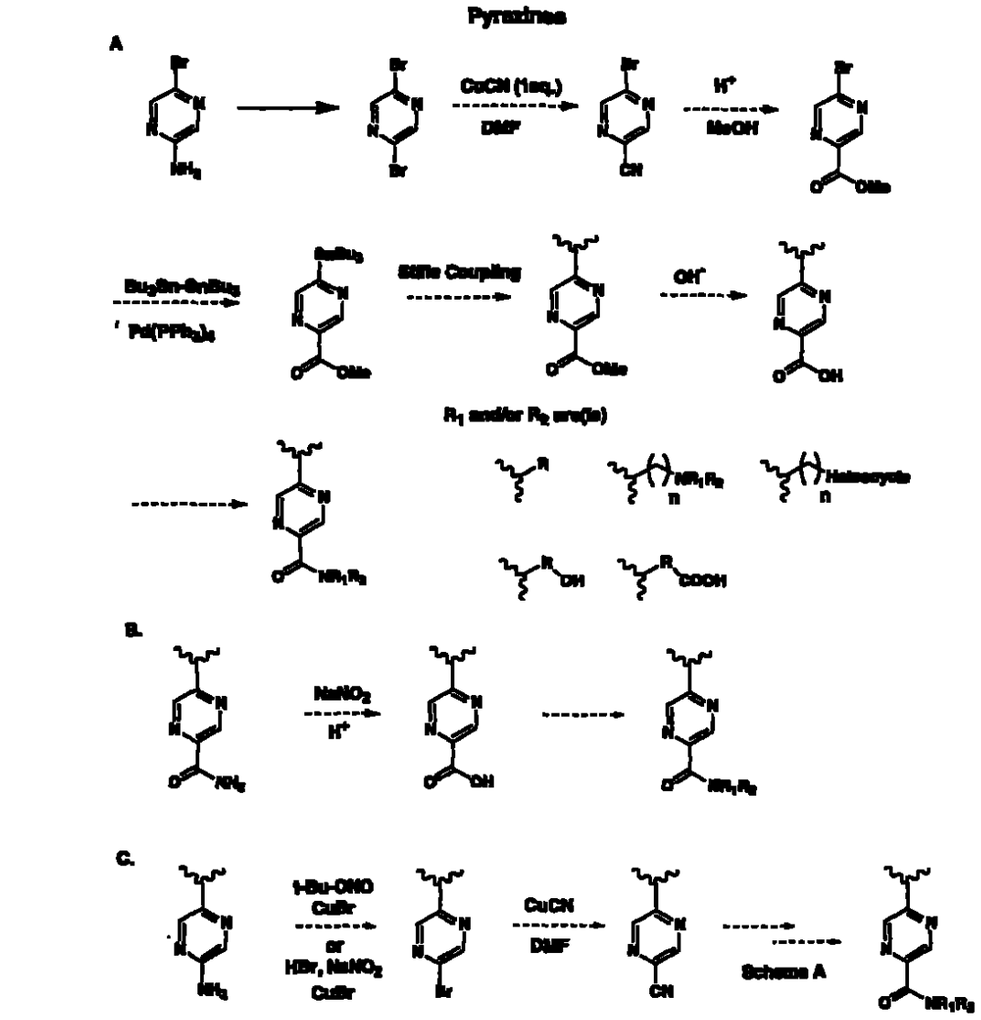
Scheme 66



Scheme 67-74 provides some nonlimiting methodology for the preparation of substituted pyrazines which can be incorporated into substituents of compounds of claim 1, particularly as part of R^4. It should be noted that the nomenclature in these schemes does not coincide with that of the claims but rather shows examples of methods which can be used to prepare pieces which make up the compounds of the claims. Thus R_1 and R_2 in these schemes does not refer to the R1 and R2 in the claims but for example refers to chemically compatible groups which might be

envisioned by chemists skilled in the art and which can be utilized to prepare compounds of the claims.

Scheme 67

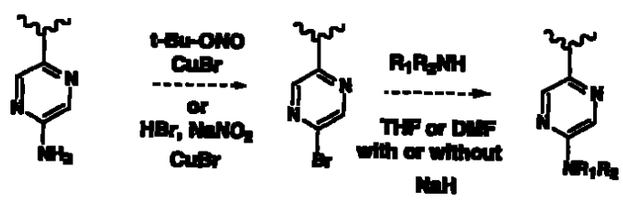


Scheme 68

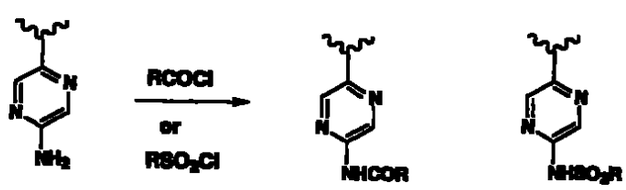
D.



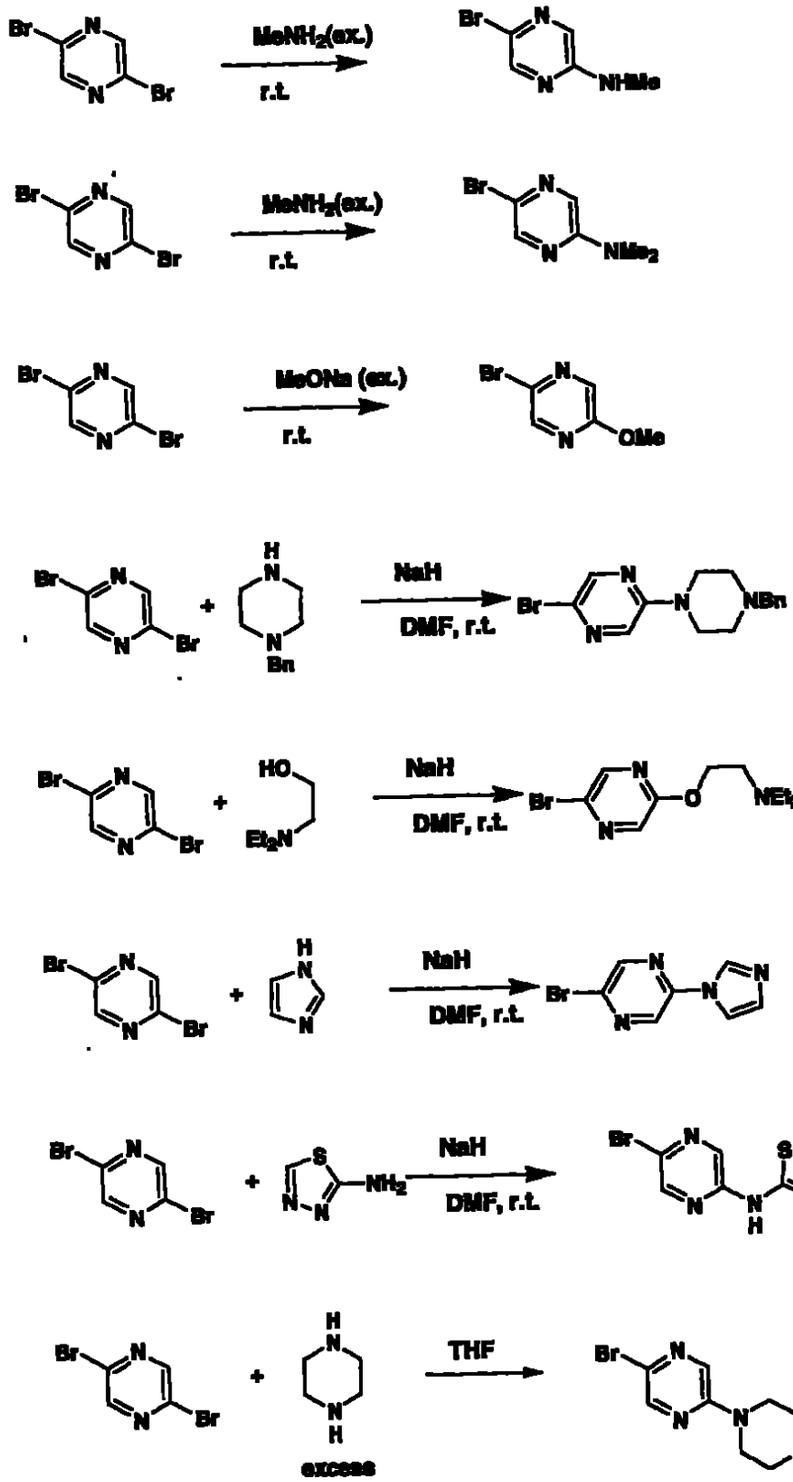
E.



F.



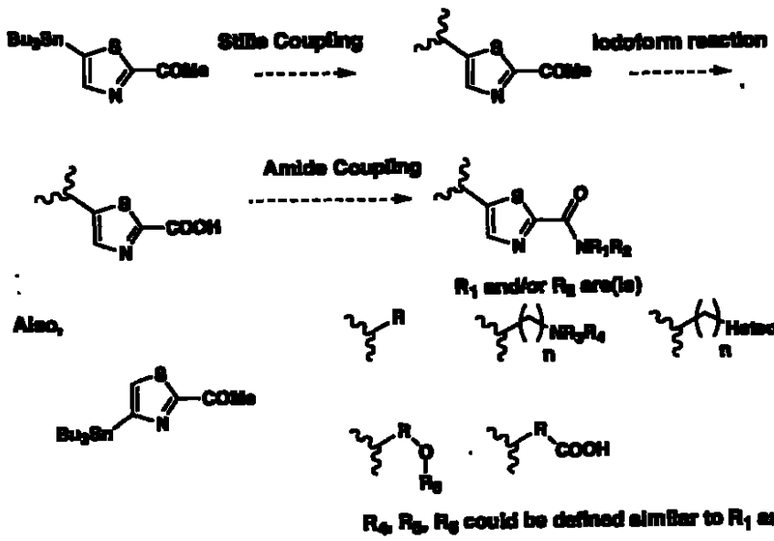
Scheme 69


MeNH2(ex.)
r.t.
NHMe
NMe2
MeONa (ex.)
OMe
NaH
DMF, r.t.
NBn
HO
Et2N
NEt2
NH2
THF
excess

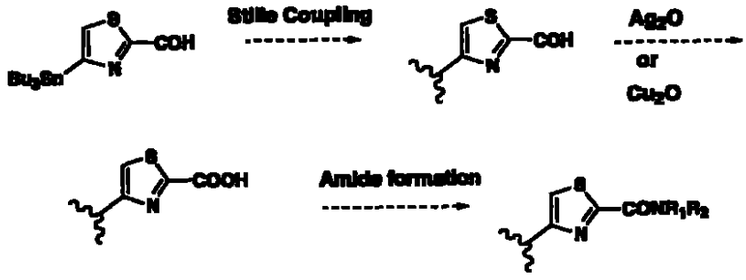
Scheme 70

Thiazole

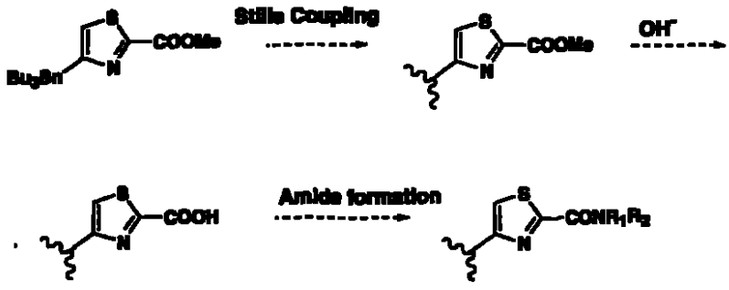
A



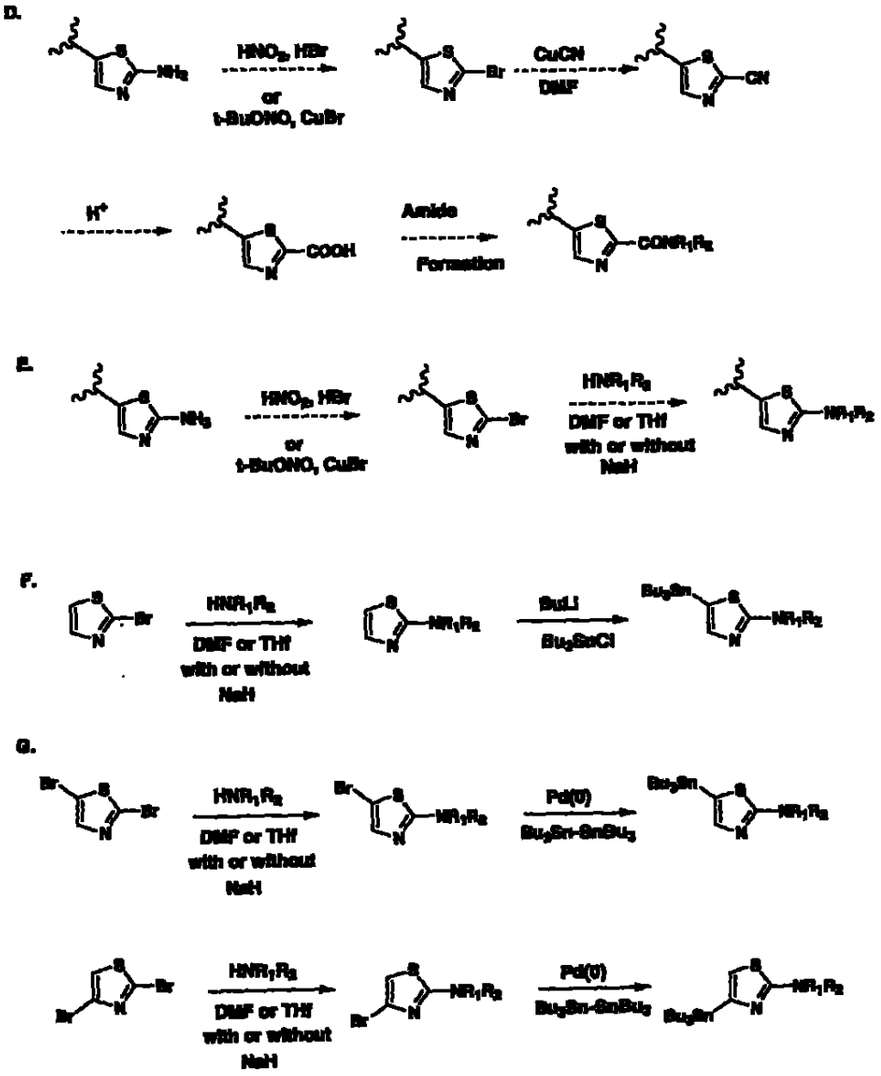
B.



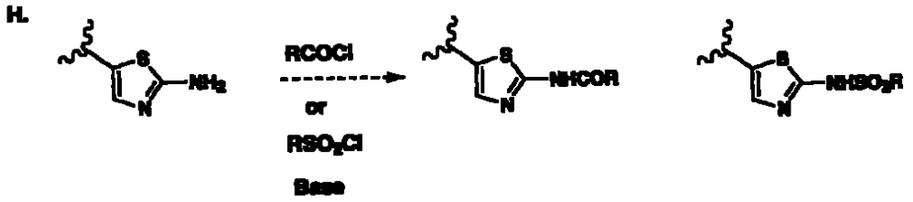
C.



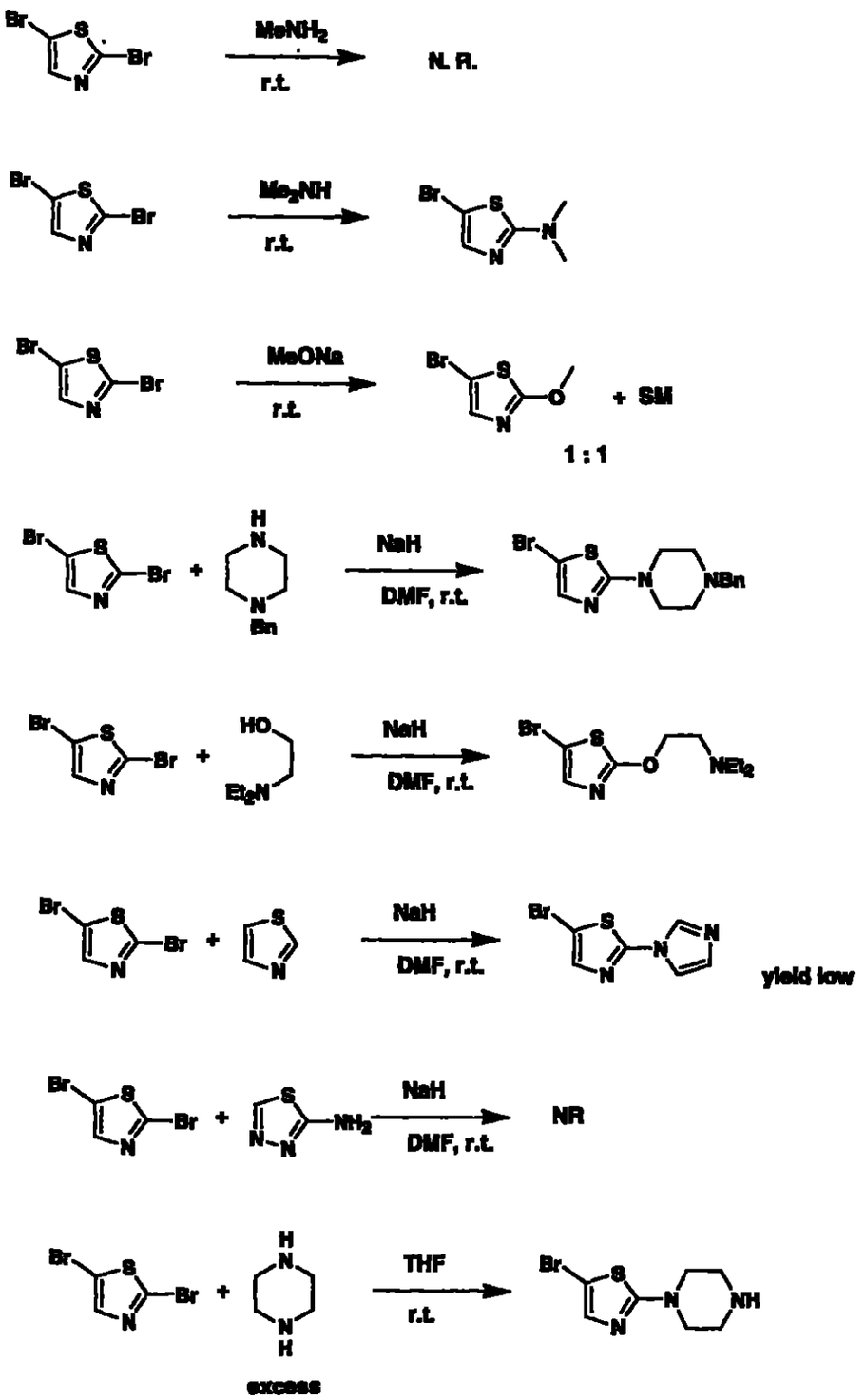
Scheme 71


D.
HNO2, HBr
or
t-BuONO, CuBr
CuCN
DMF
H+
Amide
Formation
E.
HNO2, HBr
or
t-BuONO, CuBr
HNR1R2
DMF or THF
with or without
NaH
F.
HNR1R2
DMF or THF
with or without
NaH
BuLi
Bu2SnCl
G.
HNR1R2
DMF or THF
with or without
NaH
Pd(0)
Bu3Sn-SnBu3

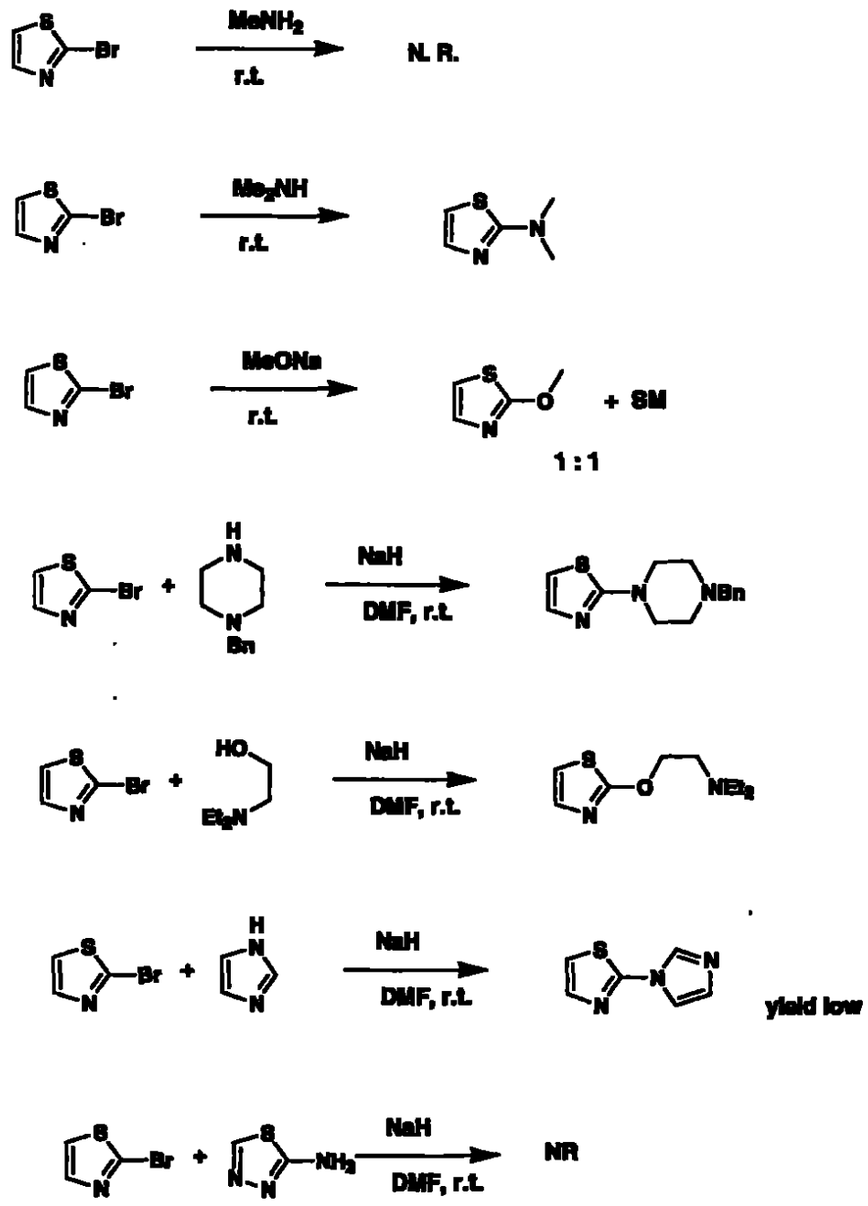
Scheme 72



Scheme 73


MeNH2
r.t.
N. R.
Me2NH
r.t.
MeONa
r.t.
+ SM
1 : 1
NaH
DMF, r.t.
Bn
HO
Et2N
NEt2
yield low
NH2
NR
THF
excess

Scheme 74

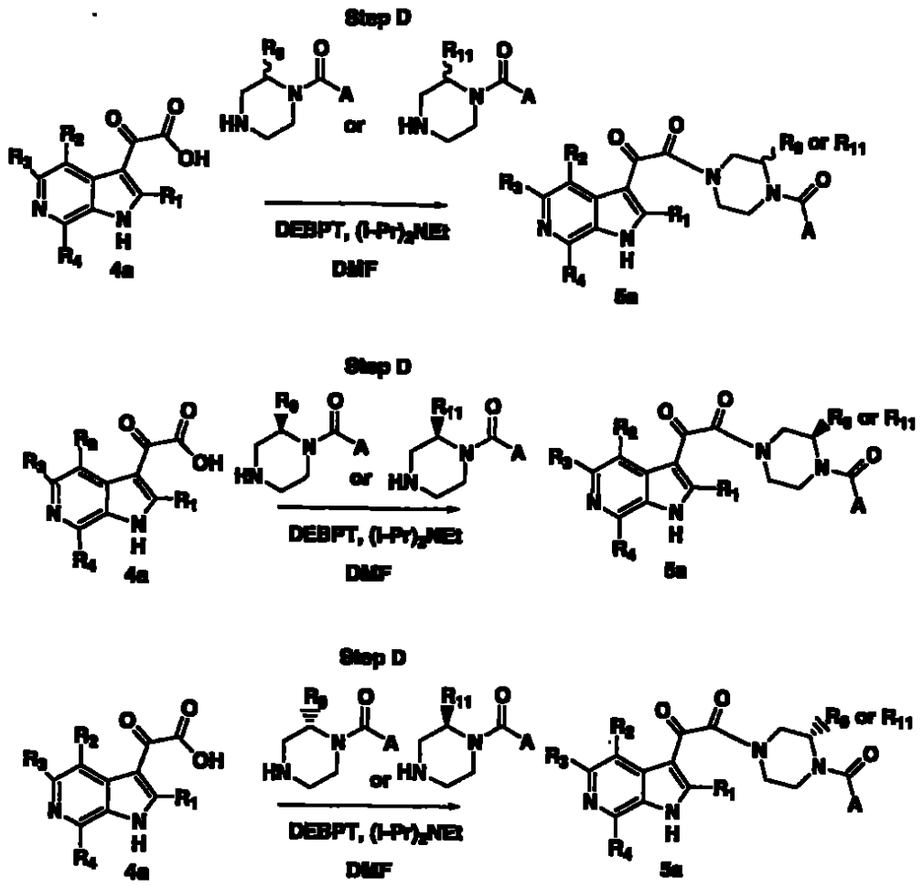


Throughout the chemistry discussion, chemical transformations which are well known in the art have been discussed. The average practioner in the art knows these transformations well and a comprehensive list of useful conditions for nearly all the transformations is available to organic chemists and this list is contained in reference

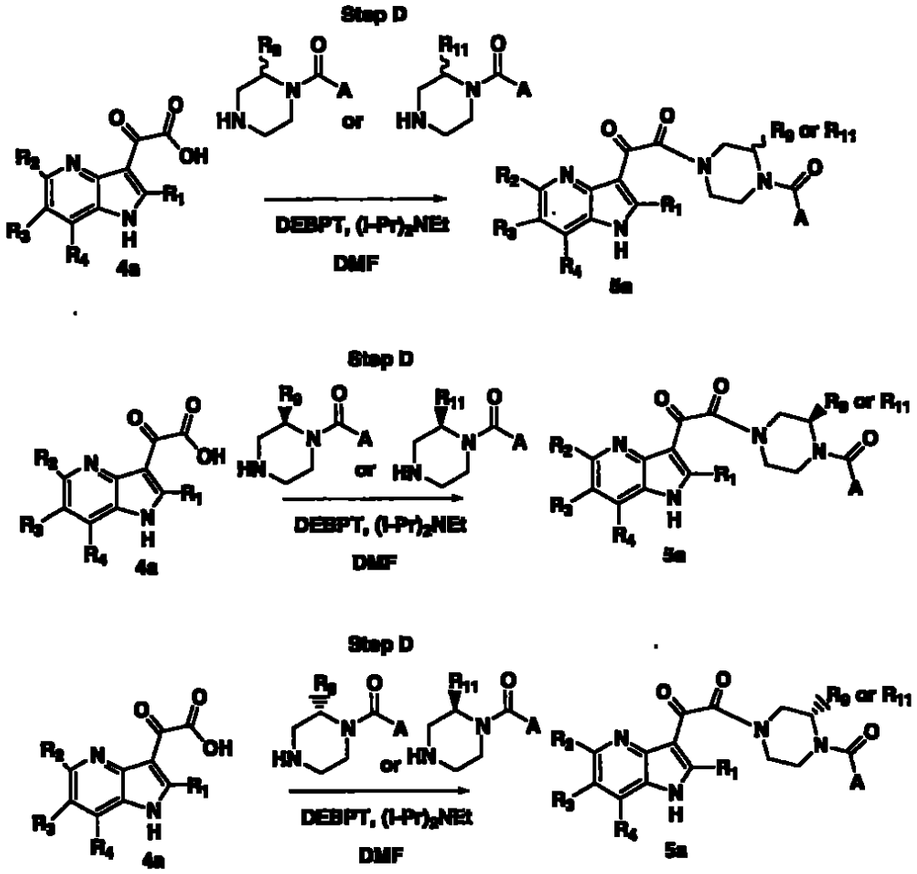
52 authored by Larock and is incorporated in its entirety for the synthesis of compounds of Formula I.

Schemes 75-78 provide more specific examples of the general synthesis described in Scheme 1. The examples describe the synthesis of compounds of the invention in which the piperazine of group W contains a substituent on the ring at a position next to the nitrogen which comprises part of the amide attached to group A. While other substitution patterns are important aspects of the invention, we have found that compounds with a single group adjacent to the amide attached to group A may have metabolic stability advantages in humans and yet retain exceptional antiviral properties. The specific substituted piperazines described in Schemes 75-78 may be prepared as described in reference 90(b) or as described for intermediates 17a-d in the experimental section. In schemes 75 and 76 the most preferred groups for R_9 and R_{11} are C1-C6 alkyl groups. As shown in schemes 77 and 78 the most preferred groups are methyl. As shown in schemes 75-78, the compounds may be single isomers or enantiomers or may be used as a racemic mixture or mixture of isomers. Preferred groups A as shown in the schems 75-78 are the same as those described for the invention. Most preferred groups A are 2-pyridyl or phenyl. In Schemes 75 and 77, the most preferred groups for R_2 are methoxy, halogen, or hydrogen. In schemes 75-76 the most preferred group for R1 and R3 is hydrogen. In scheme 76 the most preferred group for R2 is hydrogen. In schemes 75-78, the most preferred groups for R4 are phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, –C(O)NH2, -C(O)NHMe, or C(O)heteroaryl. Most preferred substituents on the substituted aryl or heteroaryl are methyl, amino, halogen, C(O)NHMe, COOH, COOMe, COOEt , or benzyl but this list should not be construed to be rate limiting as the R4 position is extremely tolerant of broad substitution. Particular groups at R4 of definite importance are triazole, oxadiazole, oxazole, pyrazole, pyrazine, pyrimidine, tetrazole, and phenyl but should not be construed as limiting.

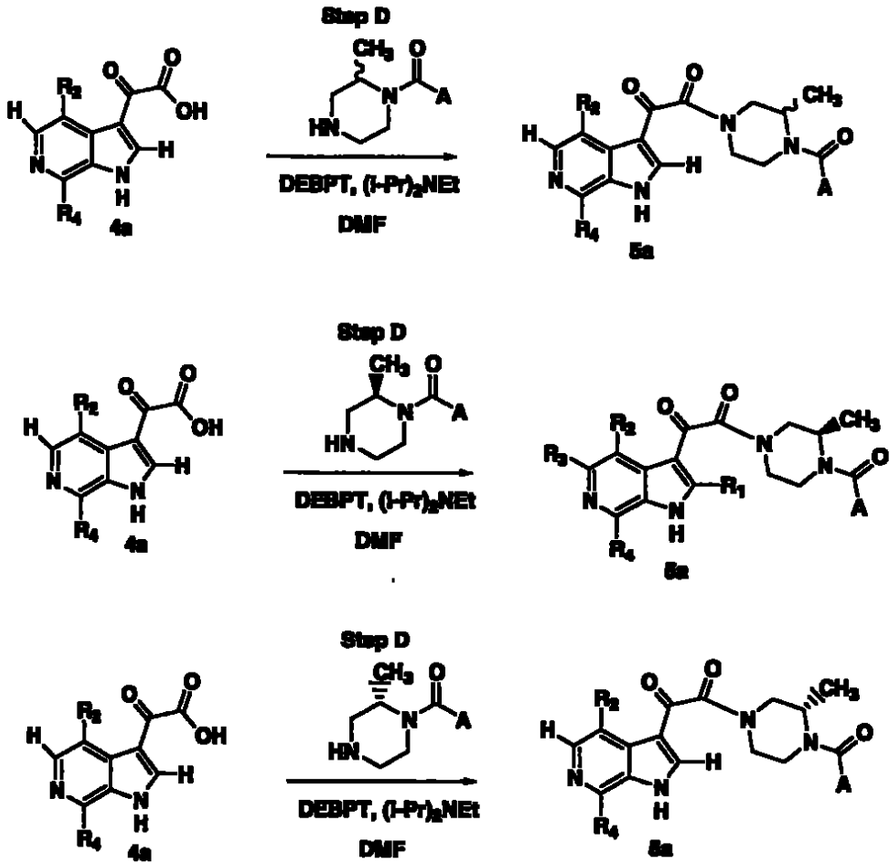
Scheme 75


Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a
or
Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a
or
Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a
or

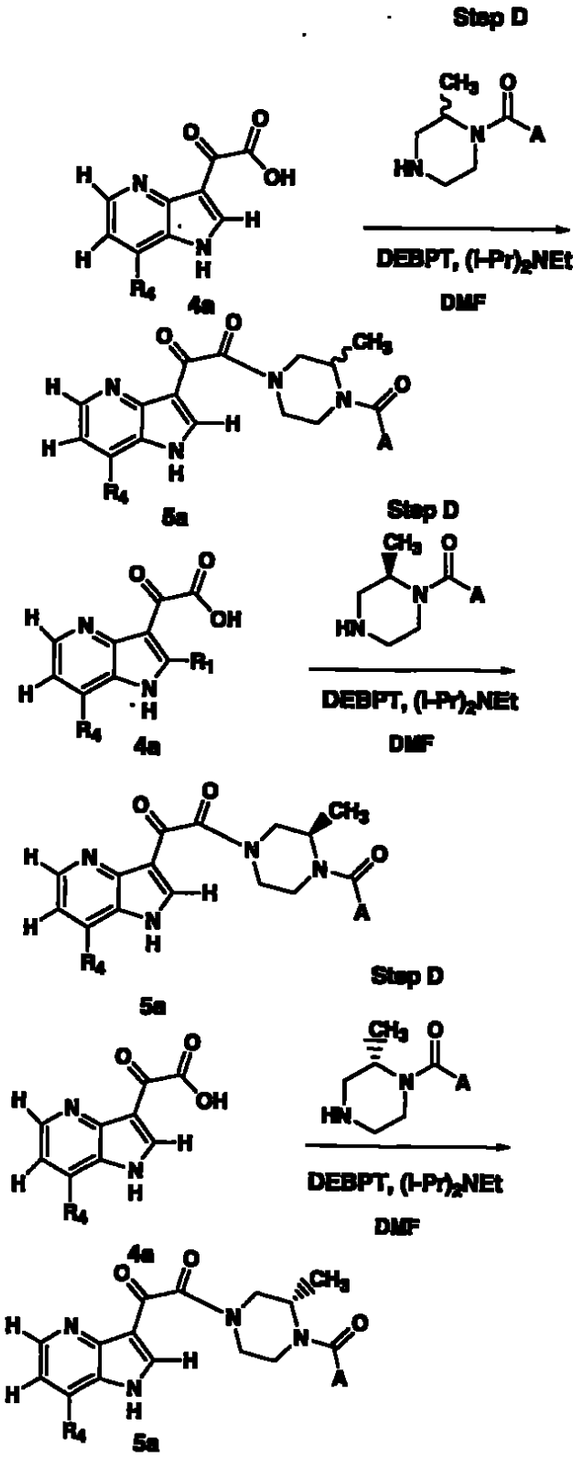
Scheme 76


Step D
or
DEBPT, (i-Pr)2NEt
DMF
4a
5a
Step D
or
DEBPT, (i-Pr)2NEt
DMF
4a
5a
Step D
or
DEBPT, (i-Pr)2NEt
DMF
4a
5a

Scheme 77

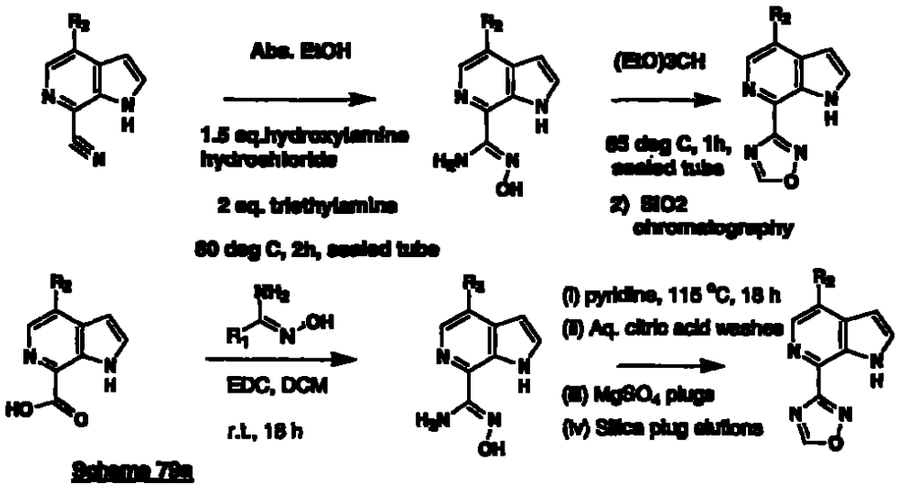

Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a
Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a
Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a

Scheme 78

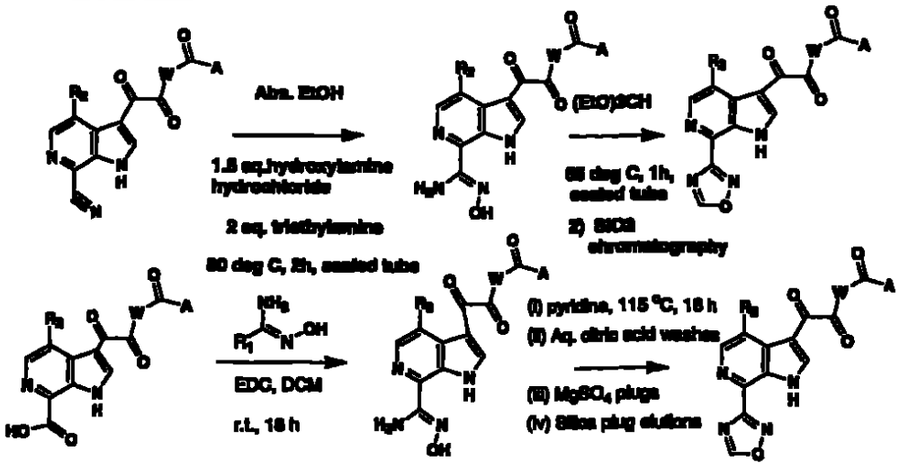

Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a
Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a
Step D
DEBPT, (i-Pr)2NEt
DMF
4a
5a

Schemes 79 provides examples and typical conditions for forming intermediates 2 which contain an oxadiazole or substituted oxadiazole. These intermediates can be converted to compounds of Claim 1 via the standard methodology described in Scheme 1 and the rest of the application. An alternate sequence is shown in Scheme 79a which utilizes cyano substituted intermediates 5 to generate the oxadiazoles of claim 1. Specific examples are given in the experimental section. Other oxadiazole isomers may be prepared via standard literature methodology.

Scheme 79



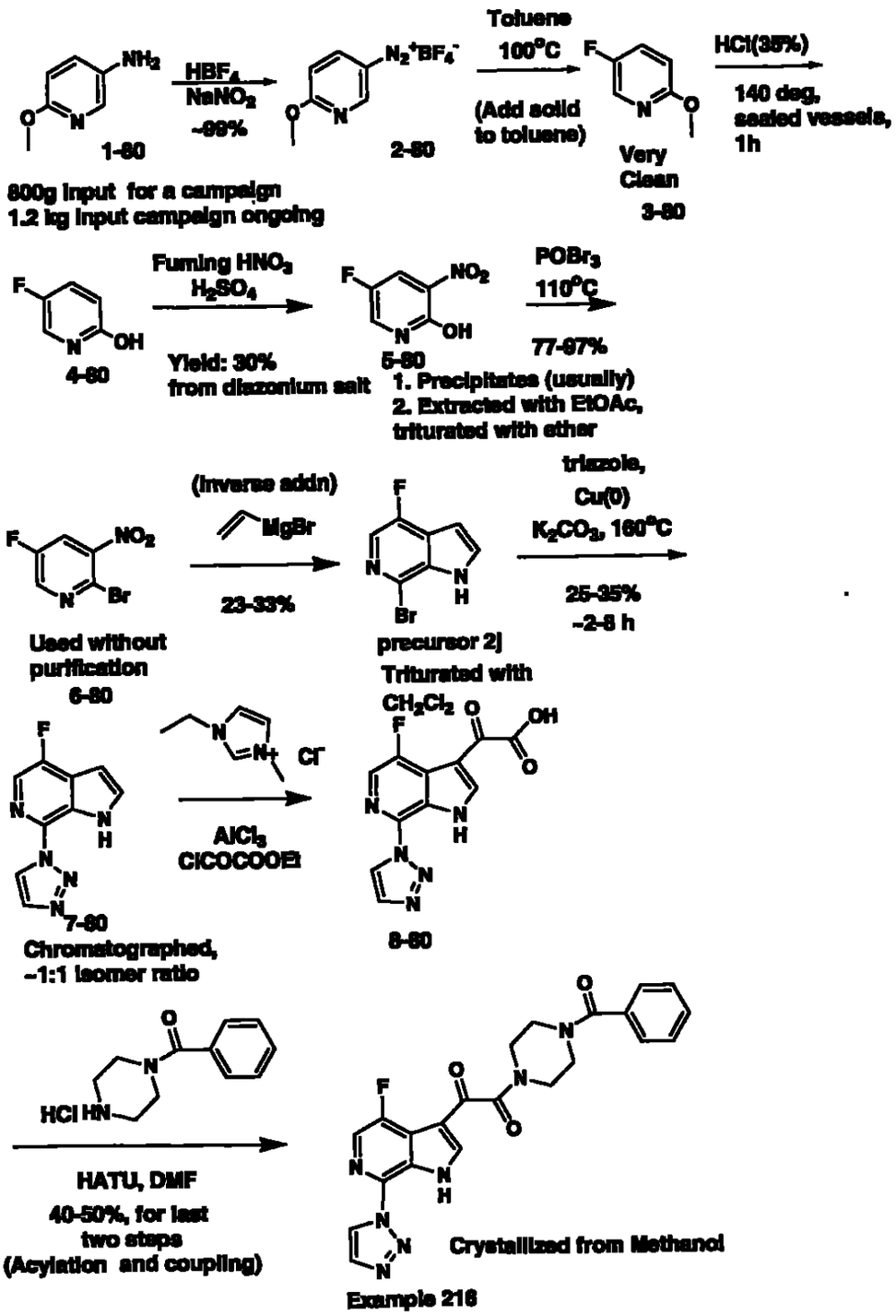
Scheme 79a



Scheme 80 is a preferred method for making compounds of Formula I and Ia where R^2 is fluoro. This is exemplified specifically in the preparation of compound Example 216. The synthesis of 2-hydroxy-3-nitro-5-fluoropyridine **5-80** as shown was carried out generally via the methods of A. Marfat and R.P. Robinson U.S. Patent 5,811,432 (column 25, example 5) and Nesnow and Heidleberger (*J. Heterocyclic Chem.* 1973, 10, pg 779) except that a number of procedural enhancements were incorporated as noted in the description of each step. 2-Hydroxy 5-fluoropyridine **4-80** is also commercially available. The formation of diazonium tetrafluoroborate salt **2-80** from 5-amino-2-methoxy pyridine **1-80** proceeded in essentially quantitative yield and was isolated via filtration. The Schiemann reaction provided poor yields of the desired 2-methoxy-fluoropyridine using the literature conditions due mainly to significant contamination with 3-fluoro 1-(N)-methyl pyridone and other byproducts. However, adoption of a procedure similar to that described in Sanchez, J. P.; Rogowski, J. W.; J Heterocycl Chem 1987, 24, 215 for a related compound provided very high yields of essentially clean but volatile 2-methoxy-5-fluoro pyridine **3-80** as a solution in toluene. In the interest of expediency, demethylation was achieved on large scale using aqueous HCl in pressure bottles at 140°C for 1hr. Prior to heating, the toluene solution was stirred with the aq HCl and then the toluene was removed by decantation. The literature method for carrying out this step using HBr at 100°C was also successful on small scale and had the advantage of avoiding the use of pressure bottles. Nitration of **4-80** as described by Marfat provided lower than expected yields so the procedure was modified slightly, using guidance from A.G. Burton, P.J.Hallis, and A.R. Katritzky (*Tetrahedron Letters* 1971, 24, 2211-2212) on the control of the regiochemistry of nitration of pyridones via modulation of the acidity of the medium. The chemical yields of 2-hydroxy-3-nitro-5-fluoro pyridine **5-80** were significantly improved using the procedure described in the experimental section. Occasionally the product failed to precipitate during workup and then considerable efforts were necessary to isolate this highly water soluble compound from the aqueous layer. Using neat excess $POBr_3$, compound **5-80** was converted to 2-bromo-3-nitro-5-fluoro pyridine **6** which could be used without further purification in the subsequent azaindole forming reaction. Addition of the pyridine **6** to excess vinyl magnesium bromide in THF at low temperature afforded the desired 4-fluoro-7-bromo-6-azaindol (precursor **5j**) in

yields of up to 35% following acidic work up and isolation via crystallization. A disadvantage of this method is the workup is difficult due to the large amounts of salts formed as co-products in the reaction and the low conversion to albeit clean product. The reaction is also exothermic and thus would require care on larger scales. Despite the moderate yields, as mentioned above the reaction proceeds cleanly and provides pure product precursor 5j without chromatography so it is anticipated that more detailed studies of this chemistry could result in yield enhancements. A selective copper/potassium carbonate mediated displacement of the 7-bromo group by commercially available 1,2,3-triazole provided an approximately 1:1 mixture of triazoles from which the desired 7-80 was isolated via chromatography in 25-35% yields. Copper-bronze rather than copper powder can also be used to carry out similar transformations. This reaction must not be allowed to overheat since concomitant displacement of the fluorine is possible and has been observed. Acylation occurred most efficiently under conditions that utilized excess acidic imidazolium chloro aluminate ionic liquid to provide highly activated glyoxylating reagent (K.S. Yeung et al. *Tetrahedron Lett.* 2002, *43*, 5793). The acylation of 7-80 usually does not proceed to completion and typically results in about 75% conversion as measured by LC/MS. An advantage to these conditions is that the typical next step, ester hydrolysis, proceeded *in situ* to provide the desired acid 8-80 which was isolated directly by precipitation during workup. Coupling of the piperazine benzamide was found to be cleaner and produced higher yields of the compound of Example 216 using the depicted HATU based coupling than with other standard coupling reagents such as EDC or DEPBT.

Scheme 80


HBF4
NaNO2
~99%
Toluene
100°C
(Add solid to toluene)
HCl(35%)
140 deg, sealed vessels, 1h
1-80
2-80
Very Clean
3-80
800g input for a campaign
1.2 kg input campaign ongoing
Fuming HNO3
H2SO4
Yield: 30% from diazonium salt
POBr3
110°C
77-97%
4-80
5-80
1. Precipitates (usually)
2. Extracted with EtOAc, triturated with ether
(Inverse addn)
MgBr
23-33%
triazole,
Cu(0)
K2CO3, 160°C
25-35%
~2-8 h
Used without purification
6-80
precursor 2]
Triturated with CH2Cl2
AlCl3
ClCOCOOEt
7-80
8-80
Chromatographed, ~1:1 isomer ratio
HCl HN
HATU, DMF
40-50%, for last two steps
(Acylation and coupling)
Crystallized from Methanol
Example 216

Chemistry

General:

Additional preparations of starting materials and precursors are contained in Wang et. al. U.S. Serial Number 09/912,710 filed July 25, 2001 (which is a continuation-in-part of U.S. Serial Number 09/765,189 filed January 18, 2001, abandoned, corresponding to PCT WO 01/62255) which is incorporated by reference.

Chemistry

All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

LC/MS Method (i.e., compound identification)

Column A: YMC ODS-A S7 3.0x50 mm column

Column B: PHX-LUNA C18 4.6x30 mm column

Column C: XTERRA ms C18 4.6x30 mm column

Column D: YMC ODS-A C18 4.6x30 mm column

Column E: YMC ODS-A C18 4.6x33 mm column

Column F: YMC C18 S5 4.6x50 mm column

Column G: XTERRA C18 S7 3.0x50 mm column

Column H: YMC C18 S5 4.6x33 mm column

Column I: YMC ODS-A C18 S7 3.0x50 mm column

Column J: XTERRA C-18 S5 4.6x50mm column

Column K: YMC ODS-A C18 4.6x33mm column

Column L: Xterra MS C18 5uM 4.6x30mm column

Column M: YMC ODS-A C18 S3 4.6x33mm column

Standard LC Run Conditions (used unless otherwise noted):

Gradient: 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B

Solvent A = 10% MeOH - 90% H_2O – 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O – 0.1% TFA; and R_t in min.

Gradient time: 2 minutes

Hold time 1 minute

Flow rate: 5 mL/min

Detector Wavelength: 220 nm

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

Alternate LC Run Conditions B:

Gradient: 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B

Solvent A = 10% MeOH - 90% H_2O – 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O – 0.1% TFA; and R_t in min.

Gradient time: 4 minutes

Hold time 1 minute

Flow rate: 4 mL/min

Detector Wavelength: 220 nm

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

Compounds purified by preparative HPLC were diluted in MeOH (1.2 mL) and purified using the following methods on a Shimadzu LC-10A automated preparative HPLC system or on a Shimadzu LC-8A automated preparative HPLC system with detector (SPD-10AV UV-VIS) wavelength and solvent systems (A and B) the same as above.

Preparative HPLC Method (i.e., compound purification)

Purification Method: Initial gradient (40% B, 60% A) ramp to final gradient (100% B, 0% A) over 20 minutes, hold for 3 minutes (100% B, 0% A)

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

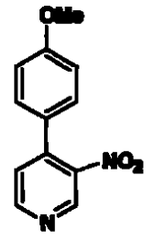
Column: YMC C18 S5 20x100 mm column

Detector Wavelength: 220 nm

Typical Procedures and Characterization of Selected Examples:

Preparation of Precursors:

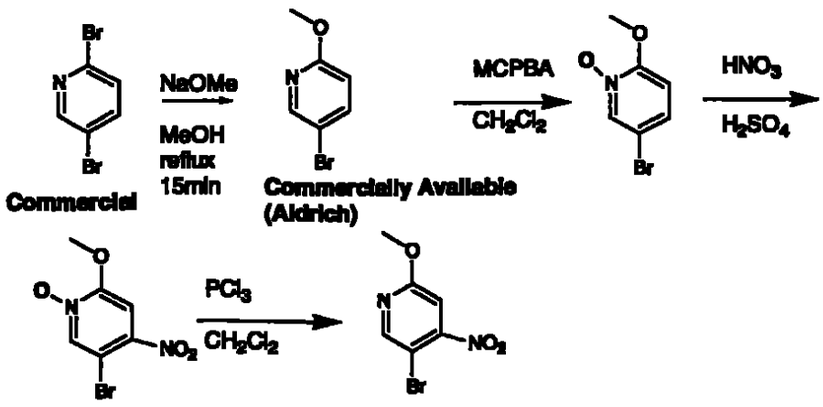
Precursor 1



4-Methoxyphenylboronic acid (24.54 g), 4-chloro-3-nitropyridine hydrochloride (26.24 g), $Pd(Ph_3P)_4$ (4 g) and K_2CO_3 (111 g) were combined in DME (500 mL). The reaction was heated to reflux for 10 hours. After the mixture cooled down to room temperature, it was poured into saturated aqueous NH_4OAc (500 mL)solution. The aqueous phase was extracted with EtOAc (3 x 200 mL). The combined extract was concentrated to give a residue which was purified using silica gel chromatography (10% to 30% EtOAc / PE) to afford 10.6 g of Precursor 1, 3-Nitro-4-(4-methoxyphenyl)pyridine. MS *m/z*: $(M+H)^+$ calcd for $C_{12}H_{11}N_2O_3$: 231.08; found 231.02. HPLC retention time: 1.07 minutes (column B).

Precursor 1a

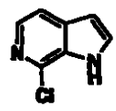
Alternate route to 6-azaindoles:



1a

2-methoxy-5-bromo pyridine can be purchased from Aldrich (or others) or prepared. Oxidation with 1.1eq of MCPBA in dichloromethane (20ml per 10.6 mmol bromide) in the presence of anhydrous MgSO4 (0.4g per mL dichloromethane) with stirring from 0° to ambient temperature for approximately 14 h provided the N-oxide after workup and flash chromatographic purification over silica gel using a 5% Etoac/Hexane gradient of increasing EtOAc. The N-oxide (1.6g) was dissolved in 10mL 98% sulfuric acid and cooled to 0°. 10 mL of 69% nitric acid was added and then allowed to warm to ambient temp with stirring. The reaction was then heated and stirred at 80° C for 14h and then poured over ice , extracted with dichloromethane, washed with water, and concentrated to give a yellow solid which was purified by flash chromatography over Silica gel using 1:1EtOAc/hexane and then a gradient to provide a yellow crystalline solid:). ^{1}H NMR (CDCl3) δ 8.50 (s,1H), 7.59 (s,1H), 4.12 (3H, s). LC MS showed desired M+H. The N-oxide was reduced by dissolving the startingmaterial in dichloromethane (0.147M substrate) and cooling to 0°. A solution of 1.2 eq PCl_3 (0.44M) in dicloromethane was added slowly to keep the reaction at 0°. Warm to ambient temp and stir for 72h. Aqueous workup and concentration provided a yellow solid which could be used in subsequent reactions or purified by chromatography. Note: a similar sequence could be used with 2-methoxy-5-chloro-pyridine as starting material.

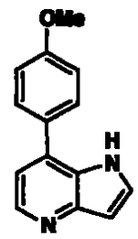
Precursor 2a



Typical procedure for preparing azaindole from nitropyridine: Preparation of 7-chloro-6-azaindole, Precursor 2a, is an example of Step A of Scheme 1. 2-chloro-3-nitropyridine (5.0g, 31.5mmol) was dissolved in dry THF (200 mL). After the solution was cooled to –78 °C, vinyl magnesium bromide (1.0M in THF, 100 mL) was added dropwise. The reaction temperature was maintained at –78°C for 1 h, and then at –20 °C for another 12 h before it was quenched by addition of 20% NH_4Cl aqueous solution (150 mL). The aqueous phase was extracted with EtOAc (3 x 150

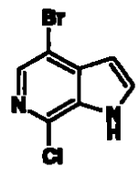
mL). The combined organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to give a residue which was purified by silica gel column chromatography (EtOAc / Hexane, 1 / 10) to afford 1.5g (31%) of 7-chloro-6-azaindole, Precursor 2a. ^1H NMR (500 MHz, CD_3OD) δ 7.84 (d, 1H, J = 10.7 Hz), 7.55 (dd, 1H, J = 10.9, 5.45 Hz), 6.62 (d, 1H, J = 5.54 Hz), 4.89 (s, 1H). MS *m/z*: $(M+H)^+$ calcd for $C_7H_6ClN_2$: 153.02; found 152.93. HPLC retention time: 0.43 minutes (column A).

Precursor 2b



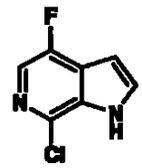
Precursor 2b, 7-(4-Methoxyphenyl)-4-azaindole, was prepared by the same method as Precursor 2a starting from 3-Nitro-4-(4-methoxyphenyl)pyridine, Precursor 1. MS *m/z*: $(M+H)^+$ calcd for $C_{14}H_{13}N_2O$: 225.10; found 225.02. HPLC retention time: 1.39 minutes (column B).

Precursor 2c

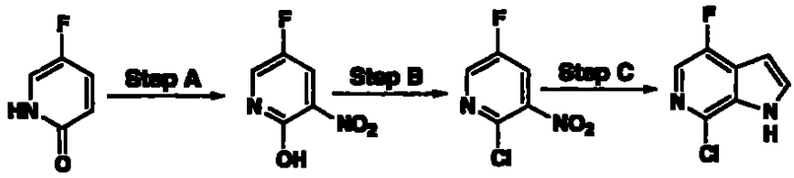


Precursor 2c, 4-bromo-7-chloro-6-azaindole, was prepared by the same method as Precursor 2a, starting from 2-Chloro-3-nitro-5-bromo-pyridine (available from Aldrich, Co.). MS m/z: $(M+H)^+$ calcd for $C_7H_5BrClN_2$: 230.93; found 231.15. HPLC retention time: 1.62 minutes (column B).

Precursor 2d



Precursor 2d, 4-fluoro-7-chloro-6-azaindole (above), was prepared according to the following scheme:



zz1' zz2' zz3' Precursor 2d

A) fuming HNO_3, H_2SO_4;
B) $POCl_3$/DMF, 110°C;
C) vinylmagnesium bromide, THF, -78°C ~ -20°C

It should be noted that 2-chloro-5-fluoro-3-nitro pyridine, zz3', may be prepared by the method in example 5B of the reference Marfat, A. ; and Robinson, R. P. ; "Azaoxindole Derivatives" *US. Patent* 5,811,432 1998. The preparation below provides some details which enhance the yields of this route.

In Step A, compound zz1' (1.2 g, 0.01 mol) was dissolved in sulfuric acid (2.7 mL) at room temperature. Premixed fuming nitric acid (1 mL) and sulfuric acid was added dropwise at 5-10 °C to the solution of compound zz1'. The reaction mixture was then heated at 85 °C for 1 hour, then was cooled to room temperature and poured into ice (20 g). The yellow solid precipitate was collected by filtration, washed with water and air dried to provide 1.01 g of compound zz2'.

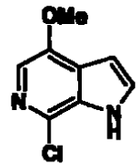
In Step B, compound zz2' (500 mg, 3.16 mmol) was dissolved in phosphorous oxychloride (1.7 mL, 18.9 mmol) and dimethoxyethane at room

temperature. The reaction was heated to 110 °C for 5 hours. The excess phosphorous oxychloride was then removed by concentrating the reaction mixture in vacuo. The residue was chromatographed on silica gel, eluted with chloroform (100%) to afford 176 mg of product zz3'.

In Step C, compound zz3' (140 mg, 0.79 mmol) was dissolved in THF (5 mL) and cooled to –78 °C under a nitrogen atmosphere. To this solution was added dropwise a solution of vinyl magnesium bromide (1.2 mmol, 1.0 M in diethyl ether, 1.2 mL). The reaction mixture was then kept at –20 °C for 15 hours. The reaction mixture was then quenched with saturated ammonium chloride, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica to provide 130 mg of precursor 2d ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (s, 1H), 7.60 (d, 1H, J = 3.0 Hz), 6.71 (d, 1H, J = 3.05 Hz). MS *m/z*: $(M+H)^+$ calcd for $C_7H_5ClFN_2$: 171.10; found 171.00. HPLC retention time: 1.22 minutes (column A).

Precursor 2d, 4-fluoro-7-chloro-6-azaindole, was prepared by the same method as Precursor 2a, starting from 2-Chloro-3-nitro-5-fluoro-pyridine which was prepared according to the procedure above. Experimental details for this preparation are contained in Wang et. al. PCT WO 01/62255. ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (s, 1H), 7.60 (d, 1H, J = 3.0 Hz), 6.71 (d, 1H, J = 3.05 Hz). MS *m/z*: $(M+H)^+$ calcd for $C_7H_5ClFN_2$: 171.10; found 171.00. HPLC retention time: 1.22 minutes (column A).

Precursor 2e

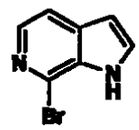


Precursor 2e was prepared by either Method A or Method B, below:

Method A: A mixture of 4-bromo-7-chloro-6-azaindole (1 g), CuI (0.65 g) and NaOMe (4 mL, 25% in methanol) in MeOH (16 mL) was heated at 110 – 120 °C for 16 hours in a sealed tube. After cooling to room temperature, the reaction mixture was neutralized with 1N HCl to pH 7. The aqueous solution was extracted with EtOAc (3 x 30 mL). Then the combined organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford a residue, which was purified by using silica gel chromotography to give 0.3 g of 4-methoxy-7-chloro-6-azaindole, Precursor 2e. MS *m/z*: $(M+H)^+$ calcd for $C_8H_8ClN_2O$: 183.03; found 183.09. HPLC retention time: 1.02 minutes (column B).

Method B :A mixture of 4-bromo-7-chloro-6-azaindole (6 g), CuBr (3.7 g) and NaOMe (30 mL, 5% in MeOH) was heated at 110°C for 24 hours in a sealed tube. After cooling to room temperature, the reaction mixture was added to saturated aqueous NH_4Cl. The resulting aqueous solution was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford a residue, which was purified by using silica gel chromotography to give 1.8 g of 4-methoxy-7-chloro-6-azaindole, Precursor 2e.

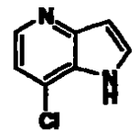
Precursor 2f



Precursor 2f, 7-bromo-6-azaindole was prepared by the same method as Precursor 2a, starting from 2-Bromo-3-nitro-pyridine (available from Aldrich, Co.). MS m/z: $(M+H)^+$ calcd for $C_7H_6BrN_2$: 197.97; found 197.01. HPLC retention time: 0.50 minutes (column A).

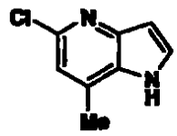
96

Precursor 2g



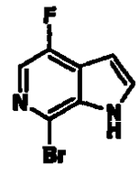
Precursor 2g, 7-chloro-4-azaindole was prepared by the same method as Precursor 2a, starting from 4-Chloro-3-nitro-pyridine (HCl salt, available from Austin Chemical Company, Inc.). MS *m/z*: $(M+H)^+$ calcd for $C_7H_6ClN_2$: 153.02; found 152.90. HPLC retention time: 0.45 minutes (column A).

Precursor 2h



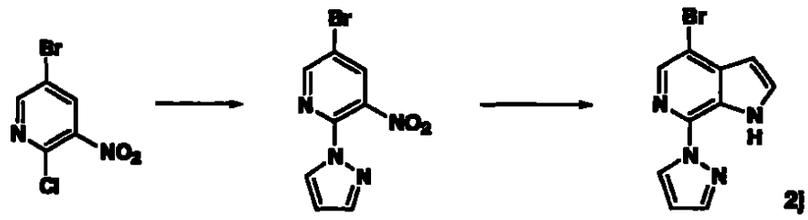
Precursor 2h, 5-chloro-7-methyl-4-azaindole was prepared by the same method as Precursor 2a, starting from 2-Chloro-4-methyl-5-nitro-pyridine (available from Aldrich, Co.). MS *m/z*: $(M+H)^+$ calcd for $C_8H_8ClN_2$: 167.04; found 166.99. HPLC retention time: 1.22 minutes (column B).

Precursor 2i



Precursor 2i, 4-fluoro-7-bromo-6-azaindole, was prepared by the same method as Precursor 2e, using $POBr_3$ in the step B instead of $POCl_3$. MS *m/z*: $(M+H)^+$ calcd for $C_7H_5BrFN_2$: 214.96; found 214.97. HPLC retention time: 1.28 minutes (column G).

Precursor 2j

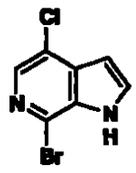


2j

To a mixture of 5-bromo-2-chloro-3-nitropyridine (10 g, 42 mmol) in 1,4-dioxane (100 ml) was added pyrazole (5.8 g, 85 mmol). The resulting mixture was stirred at 120°C for 26.5 h., and then evaporated after cooling to r.t. The crude material was purified by flash chromatography (0 to 5% EtOAc/Hexanes) to give the desired product 5-Bromo-3-nitro-2-pyrazol-1-yl-pyridine . ^{1}H NMR: (CD_3OD) δ 8.77 (s, 1H), 8.56 (s, 1H), 8.45 (s, 1H), 7.73 (s, 1H), 6.57 (s, 1H); LC/MS: (ES+) m/z $(M+H)^+$ = 269, 271, HPLC R_t = 1.223.

To a 250 mL round bottom flask was charged 5-Bromo-3-nitro-2-pyrazol-1-yl-pyridine (1.02 g, 3.8 mmol) and THF (30 ml). The mixture was then cooled to –78°C, and added a THF solution of vinylmagnesium bromide (23 mL, 18.4 mmol, 0.8 *M*). After three minutes, the reaction mixture was warmed to –45°C and remained stirring for 1 h. The reaction was then quenched with ammonium chloride, and the resulting mixture extracted with EtOAc. The combined extracts were evaporated *in vacuo*, and the residue purified by flash column chromatography (5% EtOAc/Hexanes) to give compound 2 (which by HPLC contained about 50% of a side product, presumably 3-vinylamino of compound 1) ; ^{1}H NMR: ($CDCl_3$) δ 10.75 (b s, 1H), 8.73 (s, 1H), 8.10 (s, 1H), 7.82 (s, 1H), 7.52 (s, 1H), 6.67 (s, 1H), 6.53 (s, 1H); LC/MS: (ES+) m/z (M+H) = 262, 264; HPLC R_t = 1.670.

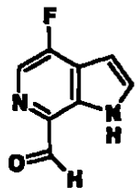
Precursor 2k



2k

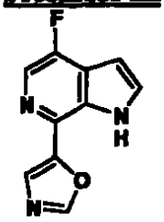
To a solution of 2-bromo-5-chloro-3-nitropyridine 5 (20 g, 84 mmol, prepared in 2 steps from 2-amino-5-chloropyridine as described in WO9622990) in THF (300 ml) at –78°C was charged a THF solution of vinylmagnesium bromide (280 ml, 252 mmol, 0.9 *M*). The resulting mixture was stirred at –78°C for one hour, followed by quenching with aqueous ammonium chloride (500 ml, *sat.*) and extracted with EtOAc (5 x 500 ml). The combined organic extracts were washed with aqueous ammonium chloride (2 x 500 ml, sat.) and water (3 x 500 ml), dried ($MgSO_4$) and evaporated to give a brownish residue. The crude material was triturated with CH_2Cl_2, and the solid formed filtered to give compound 6 as a yellow solid (8.0 g, 41%); ^1H NMR: (DMSO-d_6) 12.30 (b s, 1H), 7.99 (s, 1H), 7.80 (d, J = 3.0, 1H), 6.71 (d, J = 3.0, 1H); LC/MS: (ES+) m/z $(M+H)^+$ = 231, 233, 235; HPLC R_t = 1.833.

Precursor 2m



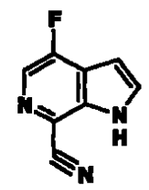
4-Fluoro-7-Bromo-6-azaindole (500 mg, 1.74 mmol) was dissolved in THF (5ml) and cooled to -78°C and *n*-BuLi (2.5 M, 2.1 ml) was added dropwise. The reaction mixture was stirred at -78°C for 15 min, then stirred at 0°C for 30 min. The reation was cooled to -78°C again, and DMF(0.7 ml, 8.7mmol) was added. After stirring for 30 min, water was added to quench the reaction. The reaction mixture was extracted with ethylacetate. The organic layer was dried over $MgSO_4$, filtered, concentrated and chromatographied to afford 208 mg of precursor 2m. LC/MS: (ES^+) m/z $(M+H)^+$ = 164.98. Rt = 0.44 min.

Precursor 2n



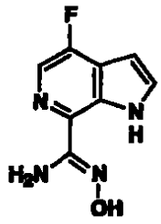
A mixture of precursor 2m (50 mg, 0.30 mmol), potassium carbonate (42 mg, 0.30 mmol) and tosylmethyl isocyanide (60 mg,0.30 mmol) in MeOH(3ml) was heated to reflux for about 2 hr. The solvent was removed in vacuum and the residue was treated with ice water and extracted with ether. The organic layer was washed with an aqueous solution of HCl (2%), water and dried over magnesium sulfate. After filtration and evaporation of the solvent, the residue was purified on silica to afford the title compound (60mg).LC/MS: (ES^+) m/z $(M+H)^+ = 204$. Rt = 0.77 min.

Precursor 2o



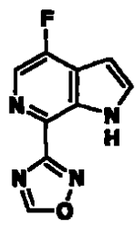
4-Fluoro-7-Bromo-6-azaindole (510 mg, 2.39 mmol) in anhydrous DMF (5 mL) was treated with copper cyanide (430 mg, 4.8 mmol) at 150°C in a seal tube for 1h. An aqueous solution of NH_4OH (10 mL) was added and the reaction was extracted with diethylether (2 x 50 mL) and ethylacetate (2 x 50 mL). The organic phases were combined and dried over sodium sulfate, filtered, concentrated in vacuum and chromatographied on silica gel (gradient elution AcOEt/Hexanes 0-30%) to afford the title compound as a brownish solid (255 mg, 66%) LC/MS: (ES^+) m/z $(M+H)^+ = 162$.

Precursor 2o



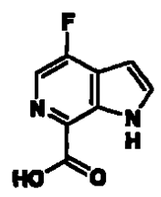
Precursor 2o (82 mg, 0.51 mmol) was dissolved in absolute ethanol (200% proof, 5 mL) and treated with hydroxylamine hydrochloride (53 mg, 0.76 mmol) and triethylamine (140 µL, 1.0 mmol) and the reaction mixture was heated up at 80°C in a seal tube for 2h. The solvent was removed in vacuum and the pale yellow solid residue was washed with water to afford the title compound. LC/MS: (ES$^+$) m/z $(M+H)^+$ = 195. This compound was taken to the next step without further purification.

Precursor 2q



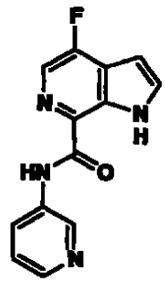
Precursor 2p was dissolved in trimethylorthoformate (1 mL) and heated at 85°C in a seal tube for 1h, then it was cooled to rt, the solvent was removed in vacuum and the residue was chromatographied on silica gel (AcOEt/Hexanes, gradient elution 10-60%) to afford the title compound (54 mg, LC/MS: (ES$^+$) m/z $(M+H)^+$ =205).

Precursor 2r



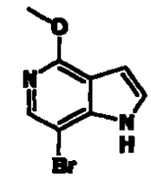
Precursor 2q (100 mg, 0.62 mmol, crude) in ethanol (5 mL) was treated with an aqueous solution of sodium hydroxide (50%, 2 mL) and the reaction mixture was heated at 110°C overnight in a seal tube. The pH was adjusted to 2 with HCl (6N) and a brown precipitate was filtered off. The solution was concentrated to dryness to afford the title compound as a pale yellow solid LC/MS: (ES^+) m/z $(M+H)^+$ =181. This compound was used without further purification.

Precursor 2s



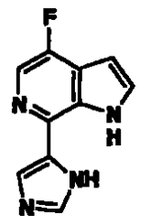
Precursor 2r (0.62 mmol) was dissolved in DMF (1 mL) and treated with 3-aminopyridine (58.3 mg, 0.62 mmol), DEBT (185 mg, 0.62) and Hunig's base (216 µL, 1.26 mmol) and the reaction mixture was stirred at room temperature for 18h. Water was added and the reaction was extracted with AcOEt (2 x 25 mL) and $CHCl_3$ (2 x 25 mL), dried over sodium sulfate, concentrated and chromatographied on silica gel (AcOEt/Hexanes gradient elution 0-50%) to afford the title compound as a brownish solid LC/MS: (ES^+) m/z $(M+H)^+$ =257.

Precursor 2s'



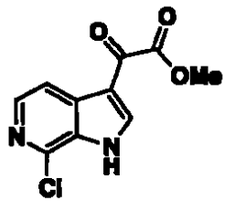
Precursor 2h, 4-methoxy-7-bromo-5-azaindole was prepared by the same method as Precursor 2a, starting from 2-methoxy-5-bromo-4-nitro-pyridine (precursor 1a). ^1H NMR (CDCl3) δ 8.52 (s,1H), 7.84 (s,1H), 7.12 (t, 1H), 6.68 (d, 1H), 3.99 (s, 3H). LC MS showed desired M+H.

Precursor 2t



A mixture of aldehyde precursor 2m (150 mg, 0.91 mmol), sodium cyanide (44mg, 0.091mmol) and tosylmethyl isocyanide (177 mg, 0.91 mmol) in EtOH(3ml) was stirred at room temperature for 30min, then filtered and the crystals were washed with ether-hexane (1:1) and dried. The obtained crystals, and a saturated solution of ammonia in dry methanol (8ml) were heated between 100-110°C for 16hr. The mixture was concentrated and chromatographed to provide 20mg of precursor 2. LC/MS: (ES^+) $m/z(m+H)^+ = 203$. Rt = 0.64 min.

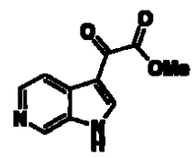
Precursor 3a



Typical procedure for acylation of azaindole: Preparation of Methyl (7-chloro-6-azaindol-3-yl)-oxoacetate, Precursor 3a is an example of Step B of Scheme 1. 7-Chloro-6-azaindole, Precursor 2a (0.5 g, 3.3 mmol) was added to a suspension of $AlCl_3$ (2.2 g, 16.3 mmol) in CH_2Cl_2 (100 mL). Stirring was continued at rt for 10 minutes before methyl chlorooxoacetate (2.0 g, 16.3 mmol) was added dropwise. The reaction was stirred for 8 h. The reaction was quenched with iced aqueous NH_4OAc solution (10%, 200 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100mL). The combined organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to give a residue which was carried to the next step without further purification. Precursor 2, Methyl (7-chloro-6-azaindol-3-yl)-

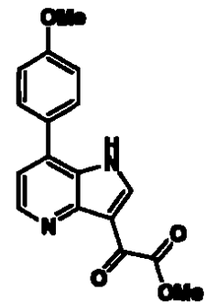
oxoacetate: MS *m/z*: $(M+H)^+$ calcd for $C_{10}H_8ClN_2O_3$: 239.02; found 238.97. HPLC retention time: 1.07 minutes (column A).

Precursor 3b



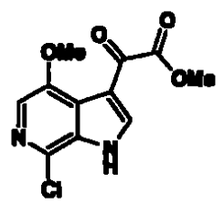
Precursor 3b, Methyl (6-azaindol-3-yl)-oxoacetate, was prepared by the same method as Precursor 3a, starting from 6-azaindole. MS *m/z*: $(M+H)^+$ calcd for $C_{10}H_9N_2O_3$: 205.06; found 205.14. HPLC retention time: 0.49 minutes (column A).

Precursor 3c



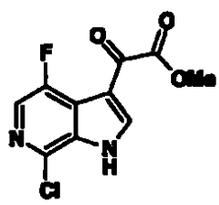
Precursor 3c, Methyl (7-(4-methoxyphenyl)-4-azaindol-3-yl)-oxoacetate, was prepared by the same method as Precursor 3a, starting from 7-(4-methoxyphenyl)-4-azaindole (Precursor 2b). MS *m/z*: $(M+H)^+$ calcd for $C_{17}H_{15}N_2O_4$: 311.10; found 311.04. HPLC retention time: 1.15 minutes (column A).

Precursor 3d



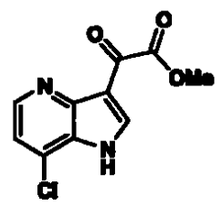
Precursor 3d, methyl (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 3a, starting from Precursor 2e, 4-methoxy-7-chloro-6-azaindole. MS *m/z*: $(M+H)^+$ calcd for $C_{12}H_{12}ClN_2O_4$: 283.05; found 283.22. HPLC retention time: 1.37 minutes (column B).

Precursor 3e



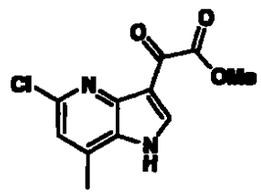
Precursor 3e, Methyl (7-chloro-4-fluoro-6-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 3a starting from Precursor 2d, 4-fluoro-7-chloro-6-azaindole. . ^1H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 8.00 (s, 1H), 3.95 (s, 3H). MS *m/z*: $(M+H)^+$ calcd for $C_{10}H_7ClFN_2O_3$: 257.01; found 257.00. HPLC retention time: 1.26 minutes (column A).

Precursor 3f



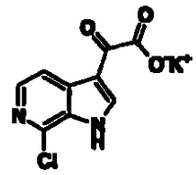
Precursor 3f, Methyl (7-chloro-4-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 3a, starting from Precursor 2g, 7-chloro-4-azaindole. MS *m/z*: $(M+H)^+$ calcd for $C_{10}H_8ClN_2O_3$: 239.02; found 238.97. HPLC retention time: 0.60 minutes (column A).

Precursor 3g



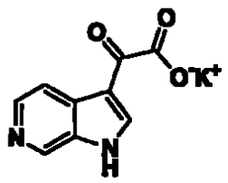
Precursor 3g, Methyl (5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 3a, starting from Precursor 2h, 5-chloro-7-methyl-4-azaindole. MS *m/z*: $(M+H)^+$ calcd for $C_{11}H_{10}ClN_2O_3$: 253.04; found 252.97. HPLC retention time: 1.48 minutes (column B).

Precursor 4a



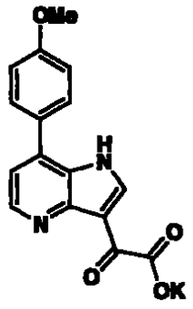
Typical procedure of hydrolysis of ester: Preparation of Potassium (7-chloro-6-azaindol-3-yl)-oxoacetate, Precursor 4a, is an example of Step C of Scheme 1. Crude methyl (7-chloro-6-azaindol-3-yl)-oxoacetate, Precursor 3a, and an excess of K_2CO_3 (2 g) were dissolved in MeOH (20 mL) and H_2O (20 mL). After 8 h, the solution was concentrated and the residue was purified by silica gel column chromatography to provide 200 mg of Potassium (7-chloro-6-azaindol-3-yl)-oxoacetate. MS *m/z*: $(M+H)^+$ of the corresponding acid was observed. Calc'd for $C_9H_6ClN_2O_3$: 225.01; found 225.05. HPLC retention time: 0.83 minutes (column A).

Precursor 4b



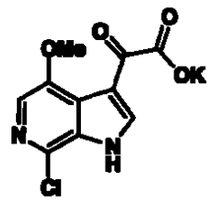
Potassium (6-azaindol-3-yl)oxoacetate, Precursor 4b, was prepared by the same method as Precursor 4a, starting from Methyl (6-azaindol-3-yl)oxoacetate, Precursor 3b. MS *m/z*: $(M+H)^+$ of the corresponding acid was observed. Calc'd for $C_9H_7N_2O_3$: 191.05; Found 190.99. HPLC retention time: 0.12 minutes (column A).

Precursor 4c



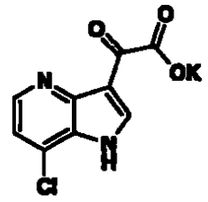
Precursor 4c, Potassium (7-(4-methoxyphenyl)-4-azaindol-3-yl)-oxoacetate, was prepared by the same method as Precursor 4a, starting from Methyl (7-(4-methoxyphenyl)-4-azaindol-3-yl)-oxoacetate, Precursor 3c. MS *m/z*: $(M-K+H)^+$ calcd for $C_{16}H_{13}N_2O_4$: 297.07; found 297.04. HPLC retention time: 1.00 minutes (column A).

Precursor 4d



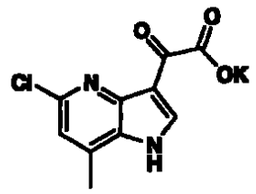
Precursor 4d, Potassium (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 4a starting from Methyl (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate, Precursor 3d. MS *m/z*: $(M+H)^+$ of the corresponding acid of compound 4d $(M-K+H)^+$ calcd for $C_{10}H_8ClN_2O_4$: 255.02; found 255.07. HPLC retention time: 0.74 minutes (column A).

Precursor 4e



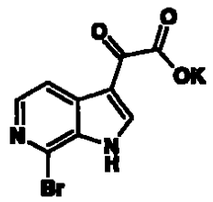
Precursor 4e, Potassium (7-chloro-4-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 4a, starting from Methyl (7-chloro-4-azaindol-3-yl)-oxoacetate, Precursor 3f . MS *m/z*: $(M+H)^+$ of the corresponding acid of compound 4e $(M-K+H)^+$ calcd for $C_9H_6ClN_2O_3$: 225.01; found 225.27. HPLC retention time: 0.33 minutes (column A).

Precursor 4f



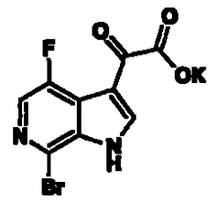
Precursor 4f, Potassium (5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 4a, starting from Methyl (5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetate, Precursor 3g. MS *m/z*: $(M+H)^+$ of the corresponding acid of compound 4f $(M-K+H)^+$ calcd for $C_{10}H_8ClN_2O_3$: 239.02; found 238.94. HPLC retention time: 1.24 minutes (column B).

Precursor 4g



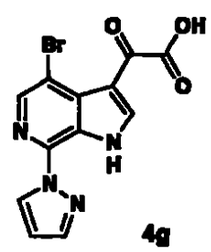
Precursor 4g, Potassium (7-bromo-6-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 4a, starting from Methyl (7-bromo-6-azaindol-3-yl)-oxoacetate (prepared according to the method of Precursor 3a from 7-Bromo-6-azaindole, Precursor 2f). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.16 (d, 1H, J = 5.3 Hz), 8.08 (d, 1H, J = 5.45 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.5, 164.0, 141.6, 140.4, 132.4, 125.3, 115.5, 113.0.

Precursor 4h



Precursor 4h, Potassium (7-bromo-4-fluoro-6-azaindol-3-yl)-oxoacetate was prepared by the same method as Precursor 4a, starting from Methyl (7-bromo-4-fluoro-6-azaindol-3-yl)-oxoacetate (prepared according to the method of Precursor 3a from 7-Bromo-4-fluoro-6-azaindole, Precursor 2i). MS *m/z*: $(M+H)^+$ of the corresponding acid of compound 4g $(M-K+H)^+$ calcd for $C_9H_5BrFN_2O_3$: 286.95; found 286.94. HPLC retention time: 0.94 minutes (column A).

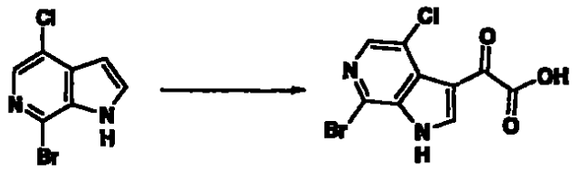
Precursor 4l



4g

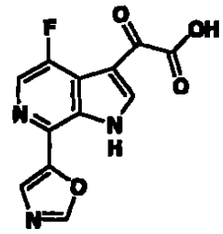
1-ethyl-3-methylimidazolium chloride (0.172 g, 1.1 mmol) was added to aluminum chloride (0.560 g, 4.2 mmol), and the mixture vigorously stirred. Upon formation of a liquid, precursor 2j was added, followed by ethyl chlorooxoacetate (0.12 ml, 1.1 mmol). The mixture was allowed to stir at r.t. for 16 h, after which additional chlorooxoacetate was added (0.12 ml, 1.1 mmol). Following this addition, the reaction was allowed to stir at r.t. for another 24 h. The flask was cooled to 0°C and water added, upon which precipitates were formed. The solid material was filtered, washed with water and methanol, and dried under high vacuum to give compound 3; LC/MS: (ES+) m/z (M+H) = 334, 336; HPLC R_t = 1.390.

Precursor 4j



To 1-ethyl-3-methylimidazolium chloride (2.54 g, 17.3 mmol) was added aluminum chloride (6.91 g, 51.8 mmol). The mixture was stirred vigorously at ambient temperature for ten minutes. To the resulting yellow liquid was added precursor 2k (2.0 g, 8.64 mmol) and ethyl chlorooxoacetate (2.0 ml, 17.3 mmol), and was stirred at ambient temperature for 16 h. The reaction mixture was then added ice/water (300 ml) to give precipitates, which were filtered and washed with water to give the title compound as a yellow solid (1.98 g). The aqueous solution was extracted with EtOAc (3 x 300 ml), and the extracts evaporated *in vacuo* to give a second batch of compound 8 as a yellow solid (439 mg, total yield 92%); ^{1}H NMR: (DMSO-d_6) 14.25 (b s, 1H), 13.37 (s, 1H), 8.56 (s, 1H), 8.18 (s, 1H); LC/MS: (ES+) m/z $(M+H)^+$ = 303, 305, 307; HPLC R_t = 1.360.

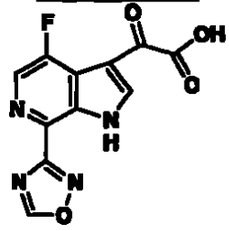
Precursor 4k



1-Ethyl-3-methylimidazolium chloride (82mg, 0.56 mmol) was added to a flask which contained precursor 2n (56 mg, 0.28 mmol) and the mixture was cooled to 0°C. Aluminum chloride (336 mg, 2.52 mmol) was added in one portion followed by ClCOCOOEt (58 µL, 0.56 mmol) and the reaction mixture was stirred at room temperature for 2 days. Ice water was added to quench the reaction. The reaction mixture was filtered. The solid was washed with water and diethylether and dried in

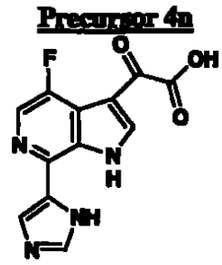
air to afford the title compound (58mg). LC/MS: (ES$^+$) m/z $(M+H)^+ = 276$. Rt = 0.85 min.

Precursor 4m



1-Ethyl-3-methylimidazolium chloride (73mg, 0.52 mmol) and aluminum chloride (198 mg, 1.56 mmol) were stirred together under nitrogen for 1h. To this solution was added intemediate 2q (54 mg, 0.26 mmol) and ethyloxalylchloride (58 µL, 0.52 mmol) and the reaction mixture was stirred at rt for 18h. The reaction was quenched with water and the mixture was stirred for 15 min. The solid was collected by filtration and washed with water and diethylether. LC/MS (ES$^+$) m/z $(M+H)^+$ =276. This compound was used without further purification.

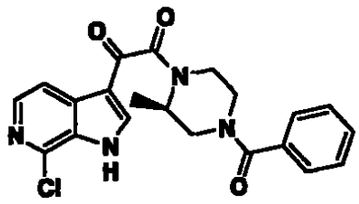
Precursor 4n



1-Ethyl-3-methylimidazolium chloride (26mg, 0.18 mmol) was added to a flask which contained precursor 2t (18 mg, 0.09 mmol) and the mixture was cooled to 0°C. Aluminum chloride (92 mg, 0.54mmol) was added in one portion followed by ClCOCOOEt (20µL, 0.18 mmol) and the reaction mixture was stirred at room temperature for 2 days. Ice water was added to quench the reaction. The reaction mixture was filtered. The solid was washed with water and diethylether and dried in air to afford compound D (18mg). LC/MS: (ES$^+$) m/z$(m+H)^+ = 275$. Rt = 0.49 min.

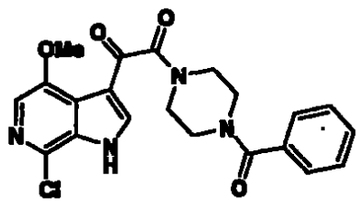
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Precursor 5a



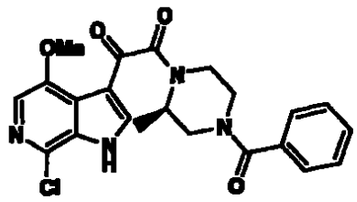
Typical procedure for coupling piperazine derivative and azaindole acid: Preparation of 1-benzoyl-3-(R)-methyl-4-[(7-chloro-6-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 5, is an example of Step D of Scheme 1. Potassium 7-chloro-6-azaindole 3-glyoxylate, Precursor 4a, (100 mg, 0.44 mmol), 3-*(R)*-methyl-1-benzoylpiperazine (107 mg, 0.44 mol), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) (101 mg, 0.44 mol) and Hunig's Base (diisopropylethylamine, 0.5 mL) were combined in 5 mL of DMF. The mixture was stirred at rt for 8 h. DMF was removed *via* evaporation at reduced pressure and the residue was purified using a Shimadzu automated preparative HPLC System to give 1-(benzoyl)-3-(R)-methyl-4-[(7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine (70 mg, 39%). MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{20}ClN_4O_3$: 411.12; Found 411.06. HPLC retention time: 1.32 minutes (column A).

Precursor 5b



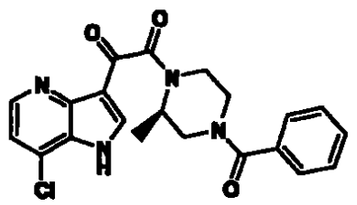
Precursor 5b, 1-benzoyl-4-[(7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate, Precursor 4d, and 1-benzoylpiperazine. MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_4$: 427.12; found 427.12. HPLC retention time: 1.28 minutes (column A).

Precursor 5c



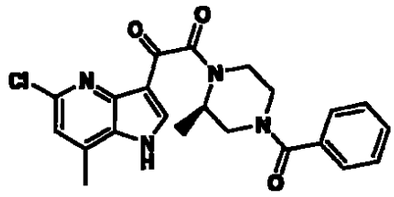
Precursor 5c, 1-benzoyl-3-(R)-methyl-4-[(7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetate, Precursor 4d, and 1-benzoylpiperazine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.72 (s, 1H), 7.40 (s, 5H), 3.89 (s, 3H), 3.71 – 3.40 (m, 8H). MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{22}ClN_4O_4$: 441.13; found 441.17. HPLC retention time: 1.33 minutes (column A).

Precursor 5d



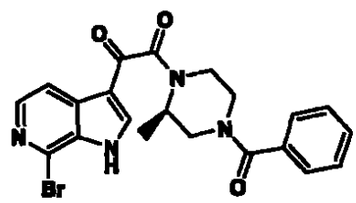
Precursor 5d, 1-benzoyl-3-(R)-methyl-4-[(7-chloro-4-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a, starting from Potassium (7-chloro-4-azaindol-3-yl)-oxoacetate, Precursor 4e, and 1-benzoyl-3-(R)-methyl piperazine. MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{20}ClN_4O_3$ 411.12, found 411.04. HPLC retention time: 1.10 minutes (column A).

Precursor 5e



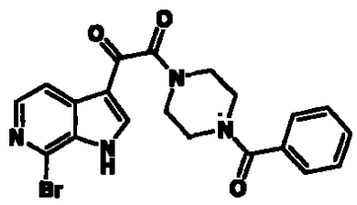
Precursor 5e, 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a, starting from Potassium (5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetate, Precursor 4f, and 1-benzoyl-3-(R)-methyl piperazine. MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{22}ClN_4O_3$ 425.24, found 425.04. HPLC retention time: 1.72 minutes (column B).

Precursor 5f



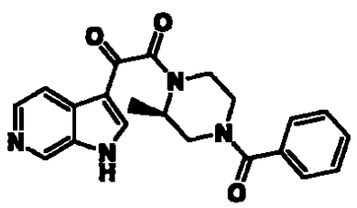
Precursor 5f, 1-benzoyl-3-(R)-methyl-4-[(7-bromo-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a, starting from (7-bromo-6-azaindol-3-yl)-oxoacetic acid potassium salt, Precursor 4g, and 1-benzoyl-3-(R)-methylpiperazine. MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{20}BrN_4O_3$: 455.07; found 455.14. HPLC retention time: 1.45 minutes (column B).

Precursor 5g



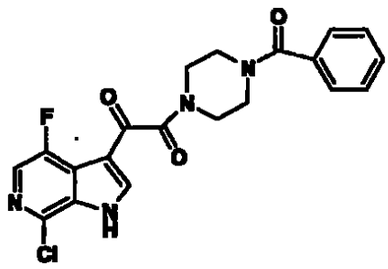
Precursor 5g, 1-benzoyl-4-[(7-bromo-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a, starting from (7-bromo-6-azaindol-3-yl)-oxoacetic acid potassium salt, Precursor 4g, and 1-benzoylpiperazine. MS *m/z*: $(M+H)^+$ calcd for $C_{20}H_{18}BrN_4O_3$: 441.06; found 441.07. HPLC retention time: 1.43 minutes (column B).

Precursor 5h



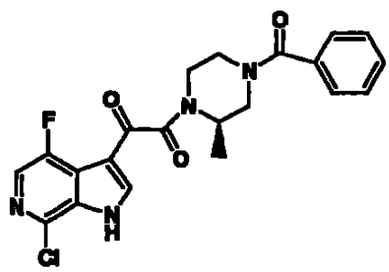
Precursor 5h, 1-benzoyl-3-(R)-methyl-4-[(6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (6-azaindol-3-yl)oxoacetate, Precursor 4b, and 1-benzoyl-3-(R)-methylpiperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{21}N_4O_3$: 377.16; Found 377.10. HPLC retention time: 0.88 minutes (column A).

Precursor 5i



Addition of precursor 2d to a solution of aluminum trichloride in dichloromethane stirring at ambient temperature followed 30 minutes later with chloromethyl or chloroethyl oxalate (according to the method described for precursor 3a) provides either the methyl or ethyl ester, respectively. Hydrolysis with KOH (as in the standard hydrolysis procedure described for precursor 4a) provided potassium (7-chloro-4-fluoro-6-azaindol-3-yl)oxoacetate. Potassium (7-chloro-4-fluoro-6-azaindol-3-yl)oxoacetate was then reacted with 1-benzoyl piperazine in the presence of DEPBT under the standard conditions (as described for precursor 5a) to provide 1-benzoyl-4-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]piperazine, precursor 5i. ^{1}H NMR (500 MHz, CD_3OD) δ 8.40 (s, 1H), 8.04 (s, 1H), 7.46 (bs, 5H), 3.80-3.50 (m, 8H); *LC/MS* (ES^+) m/z $(M+H)^+$ 415 observed; retention time 1.247 minutes; *LC/MS* method: YMC ODS-A C18 S7 3.0 x 50 mm column; Start %B = 0, Final %B = 100, Gradient time = 2 minutes; Flow rate = 5 mL/min; detector wavelength = 220 nm.

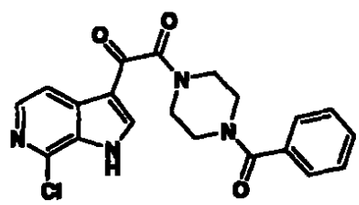
Precursor 5j



1-benzoyl-3-(R)-methyl-4-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl]-piperazine was prepared by coupling potassium (7-chloro-4-fluoro-6-azaindol-3-

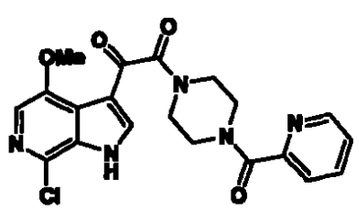
yl)oxoacetate, prepared as described above for precursor 5i, with 1-benzoyl-3-(R)-methylpiperazine in the presence of DEPBT under the standard conditions (as described for precursor 5a) to provide 1-benzoyl-3-(R)-methyl-4-[(4-fluoro-7-chloro-6-azaindol-3-yl)-oxoacetyl] piperazine, precursor 5j. ^{1}H NMR (500 MHz, CD_3OD) δ 8.42, 8.37 (s, s, 1H), 8.03 (s, 1H), 7.71-7.45 (m, 5H), 4.72-3.05 (m, 7H), 1.45-1.28 (m, 3H); LC/MS (ES$^+$) m/z $(M+H)^+$ 429 observed; retention time 1.297 minutes; LC/MS method: YMC ODS-A C18 S7 3.0 x 50 mm column; Start %B = 0, Final %B = 100, Gradient time = 2 minutes; Flow rate = 5 mL/min; detector wavelength = 220 nm.

Precursor 5k



Precursor 5k, 1-benzoyl-4-[(7-chloro-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a, starting from (7-chloro-6-azaindol-3-yl)-oxoacetic acid potassium salt, Precursor 4a, and 1-benzoylpiperazine. MS *m/z*: $(M+H)^+$ calcd for $C_{20}H_{18}ClN_4O_3$: 397.11; found 396.97. HPLC retention time: 2.37 minutes (column F, gradient time = 3 min, flow rate = 4 ml/min).

Precursor 5l

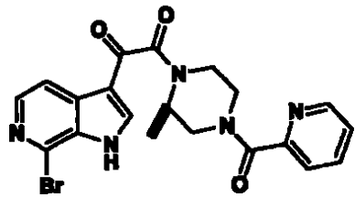


Precursor 5l, 1-picolinoyl-4-[(4-methoxy-7-chloro-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (4-methoxy-7-chloro-6-azaindol-3-yl)oxoacetate, Precursor 4d, and

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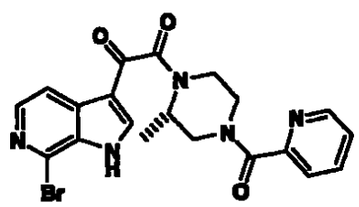
picolinoyl-piperazine. ^{1}H NMR (500 MHz, DMSO-d_6) δ8.63 – 7.45 (m, 7 H), 3.94 (s, 3H), 3.82 – 2.50 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{20}H_{19}ClN_5O_4$: 428.11; Found 428.11. HPLC retention time: 1.09 minutes (column A).

Precursor 5m



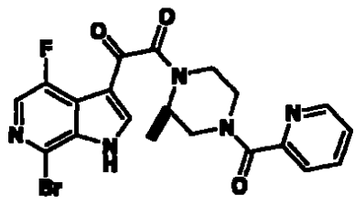
Precursor 5m, (R)-1-picolinoyl-3- methyl-4-[(7-bromo-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (7-bromo-6-azaindol-3-yl)oxoacetate, Precursor 4g, and (R)-3-methyl-1-picolinoyl-piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{20}H_{19}BrN_5O_3$: 456.07; Found 456.11. HPLC retention time: 1.12 minutes (column A).

Precursor 5n



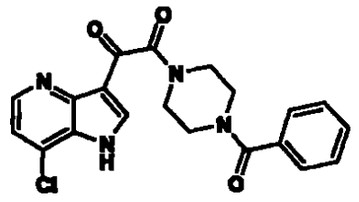
Precursor 5n, (S)-1-picolinoyl-3- methyl-4-[(7-bromo-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (7-bromo-6-azaindol-3-yl)oxoacetate, Precursor 4g, and (S)-3-methyl-1-picolinoyl-piperazine. ^{1}H NMR (500 MHz, $CDCl_3$) δ8.63 – 7.36 (m, 7H), 5.02 – 3.06 (m, 7H), 1.42 – 1.26 (m, 3H).

Precursor 5o



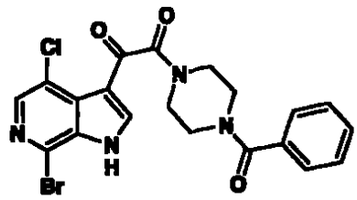
Precursor 5o, (R)-1-picolinoyl-3- methyl-4-[(7-bromo-4-fluoro-6-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (7-bromo-4-fluoro-6-azaindol-3-yl)oxoacetate, Precursor 4h, and (R)-3-methyl-1-picolinoyl-piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.68 – 7.52 (m, 6H), 4.94 – 2.69 (m, 7H), 1.48 – 1.24 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{20}H_{18}BrFN_5O_3$: 474.06; Found 474.23. HPLC retention time: 1.20 minutes (column A).

Precursor 5p



Precursor 5p, 1-benzoyl-4-[(7-chloro-4-azaindol-3-yl)-oxoacetyl]piperazine was prepared by the same method as Precursor 5a starting from Potassium (7-chloro-4-fluoro-4-azaindol-3-yl)oxoacetate, Precursor 4e, and 1-benzoyl-piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.83 (s, 1H), 8.63 (d, 1H, J = 5.35 Hz), 7.91 (d, 1H, J = 5.75 Hz), 7.47 (m, 5H), 3.80 – 3.30 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{20}H_{18}ClN_4O_3$: 397.11; Found 397.02. HPLC retention time: 1.20 minutes (column A).

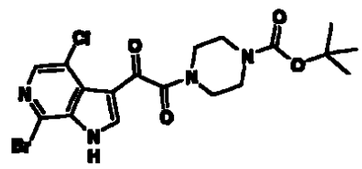
Precursor 5q



Precursor 5q, 1-(4-Benzoyl-piperazin-1-yl)-2-(7-bromo-1H-pyrrolo[2,3-c]pyridin-3-yl)-ethane-1,2-dione

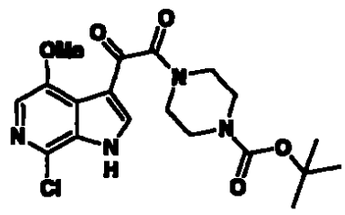
To a solution of acid precursor 4j (2.4 g, 7.9 mmol) in DMF (40 ml) was added 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT, 5.96 g, 19.9 mmol), benzoylpiperazine hydrochloride (2.71 g, 11.9 mmol), and *N,N*-diisopropylethylamine (14 ml, 80.4 mmol). The mixture was stirred at ambient temperature for 16 h. The reaction mixture was then added water (400 ml) and extracted with EtOAc (4 x 300 ml). The combined extracts were evaporated *in vacuo* to give a brownish residue, which was triturated with MeOH to provide the title compound as a white solid (2.8 g, 74%); ^{1}H NMR: (DMSO-d_6) 13.41 (s, 1H), 8.48 (s, 1H), 8.19 (s, 1H), 7.45 (b s, 5H), 3.80 – 3.35 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 475, 477, 479; HPLC (alternate conditions B, column G) R_t = 1.953.

Precursor 5r



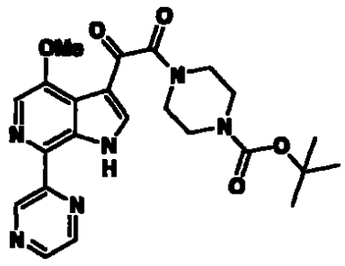
Precursor 5r was prepared by procedure used for 5q using mono N-Boc piperazine . ^{1}H NMR: ($CDCl_3$) δ 8.26 (s, 1H), 8.19 (s, 1H), 3.71 (b s, 2H), 3.53 (b m, 6H), 1.48 (s, 9H); LC/MS: (ES+) m/z $(M+H)^+$ = 471, 473, 475; HPLC (alternate conditions B, column G) R_t = 1.543.

Precursor 5s



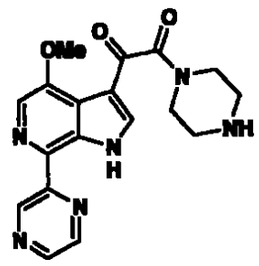
Precursor 5s was prepared by procedure used for 5b using mono N-Boc piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{19}H_{24}ClN_4O_5$: 423.14; Found 423.07 HPLC retention time: 1.44 minutes (column L).

Precursor 5t



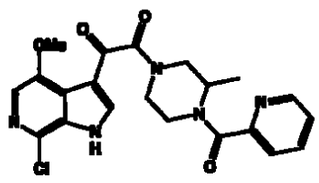
Precursor 5t, was prepared from Precursor 5s and the pyrazin-2-yl stannane, via the procedure described in the later section Preparation of Compounds of Formula I. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{27}N_6O_5$: 467.20; found 467.47. HPLC retention time: 1.57 minutes (column C).

Precursor 5u



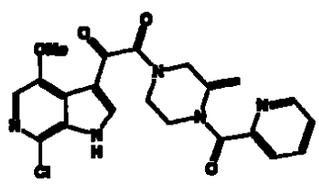
Preparation of precursor 5u: Precursor 5t (30 mg) was dissolved in TFA (0.5 g). After the reaction was stirred for 30 minutes, the mixture was concentrated *in vacuo* to give the desired intermediae 5u which was used in further reactions without any purification. MS *m/z*: $(M+H)^+$ Calc'd for $C_{18}H_{19}N_6O_5$: 367.15; found 367.06. HPLC retention time: 0.91 minutes (column M).

Precursor 5v



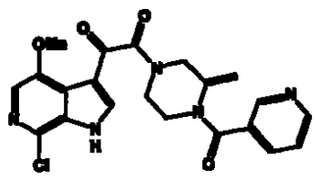
Precursor 5v was prepared by procedure used for 5b using 2-methyl-1-picolinoylpiperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{21}ClN_5O_4$: 442.13; Found 442.11. HPLC retention time: 1.01 minutes (column G).

Precursor 5xx



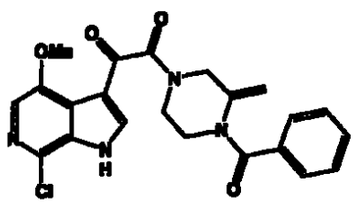
Precursor 5xx was prepared by procedure used for 5b using (R)-2-methyl-1-picolinoylpiperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{21}ClN_5O_4$: 442.13; Found 442.23. HPLC retention time: 1.12 minutes (column L).

Precursor 5y



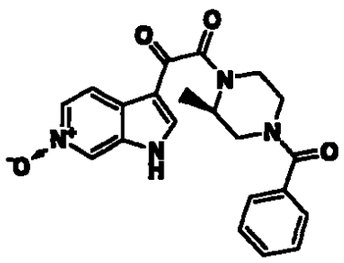
Precursor 5y was prepared by procedure used for 5b using (R)-2-methyl-1-nicotinoylpiperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{21}ClN_5O_4$: 442.13; Found 442.15. HPLC retention time: 0.87 minutes (column C).

Precursor 5z



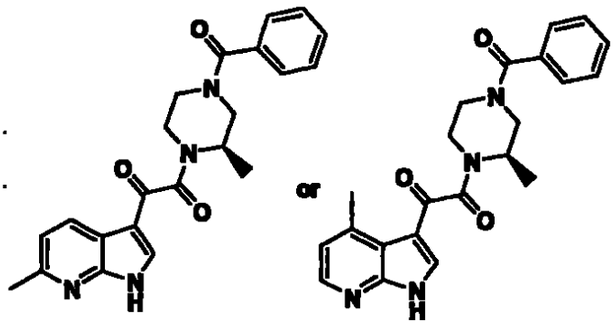
Precursor 5z was prepared by procedure used for 5b using (R)-2-methyl-1-benzoylpiperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{22}H_{22}ClN_4O_4$: 441.13; Found 441.46. HPLC retention time: 1.27 minutes (column C).

Precursor 6



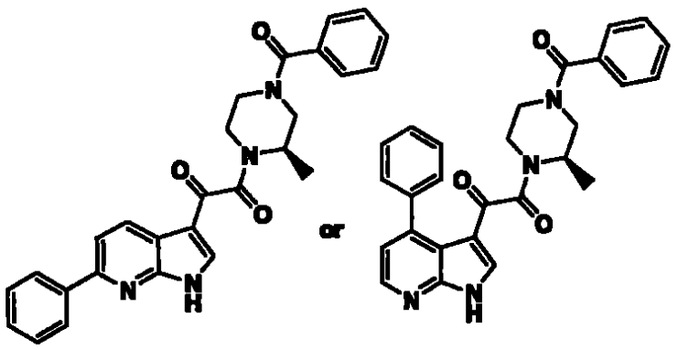
Typical procedure for N-Oxide formation: Preparation of 1-benzoyl-3-(R)-methyl-4-[(6-oxide-6-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 6. 20 mg of 1-benzoyl-3-(R)-methyl-4-[(6-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 5h, (0.053 mmol) was dissolved in CH_2Cl_2 (2 mL). 18 mg of mCPBA (0.11 mmol) was then added into the solution and the reaction was stirred for 12 h at rt. CH_2Cl_2 was removed *via* evaporation at reduced pressure and the residue was purified using a Shimadzu automated preparative HPLC System to give the compound shown above (5.4 mg, 26%). MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{21}N_4O_4$: 393.16; Found 393.11. HPLC retention time: 0.90 minutes (column A).

Precursor 7



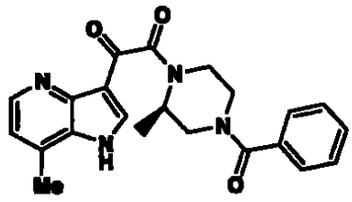
Preparation of 1-benzoyl-3-(R)-methyl-4-[(6-methyl-7-azaindol-3-yl)-oxoacetyl]-piperazine or 1-benzoyl-3-(R)-methyl-4-[(4-methyl-7-azaindol-3-yl)-oxoacetyl]-piperazine. An excess of MeMgI (3M in THF, 0.21 ml, 0.63 mmol) was added into a solution of 1-benzoyl-3-(R)-methyl-4-[(6-oxide-6-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 6, (25 mg, 0.064 mmol). The reaction mixture was stirred at rt and then quenched with MeOH. The solvents were removed under vacuum, the residue was diluted with MeOH and purified using a Shimadzu automated preparative HPLC System to give a compound shown above which was a single isomer but regiochemistry was not definitively assigned. (6.7 mg, 27%). MS *m/z*: $(M+H)^+$ Calc'd for $C_{22}H_{23}N_4O_3$: 391.18; Found 391.17. HPLC retention time: 1.35 minutes (column B).

Precursor 8



1-benzoyl-3-(R)-methyl-4-[(6-phenyl-7-azaindol-3-yl)-oxoacetyl]piperazine or 1-benzoyl-3-(R)-methyl-4-[(4-phenyl-7-azaindol-3-yl)-oxoacetyl]piperazine (regiochemistry was not definitively assigned) were prepared by the method described for Example 7 starting with 1-benzoyl-3-(R)-methyl-4-[(6-oxide-6-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 6, and phenyl magnesium bromide (phenyl Grignard reagent). MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{25}N_4O_3$: 453.19; Found 454.20. HPLC retention time: 1.46 minutes (column B).

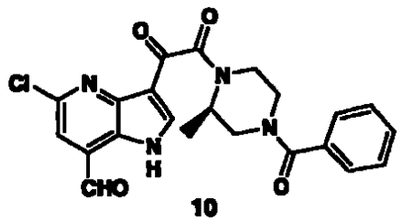
Precursor 9



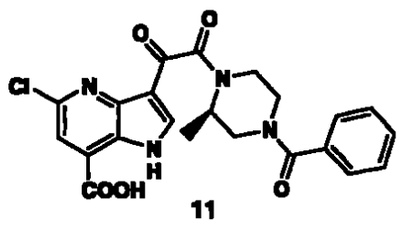
A mixture of Pd (10% on carbon, 100 mg), trifluoroacetic acid (1 mL) and 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 5e (1.5 g) in MeOH (50 mL) and EtOAc (50 mL) was shaken in a Parr reactor under a hydrogen atmosphere (45 psi) for 48 hours. After solids were removed via filtration, the filtrate was concentrated *in vacuo* to afford precursor 9 (1

g) which was used without further purification. MS *m/z*: $(M+H)^+$ calcd for $C_{21}H_{21}N_4O_3$ 391.18, found 391.15. HPLC retention time: 1.15 minutes (column A).

Precursors 10 and 11



10

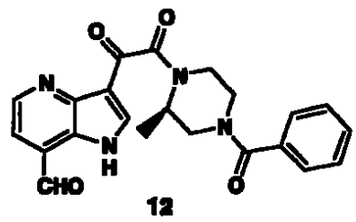


11

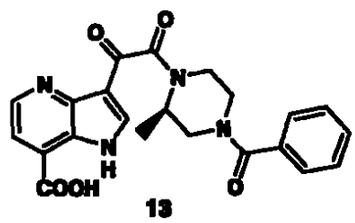
Preparation of Precursor 10, 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-carbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine and Precursor 11, 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-hydroxycarbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine: A mixture of 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-methyl-4-azaindol-3-yl)-oxoacetyl]piperazine (1.78 g) and SeO_2 (4.7 g) in dioxane/water (100 : 1) was refluxed for 10 hours. After cooling to room temperature, the mixture was concentrated *in vacuo* to provide a residue. The residue was purified by using silica gel chromatography with EtOAc and MeOH as eluting solvents to afford precursor 10 (350 mg) and precursor 11 (410 mg).

Precursor 10, 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-carbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{20}ClN_4O_4$: 439.12, found 439.01. HPLC retention time: 1.37 minutes (column A); Precursor 11, 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-hydroxycarbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{20}ClN_4O_5$: 455.11, found 455.10. HPLC retention time: 1.44 minutes (column A).

Precursors 12 and 13



12



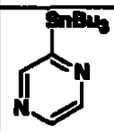
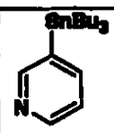
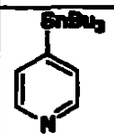
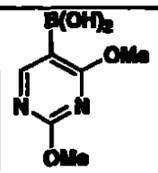
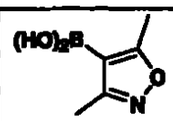
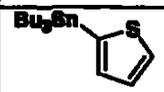
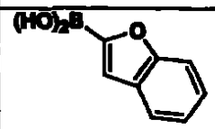
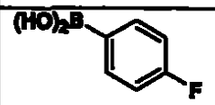
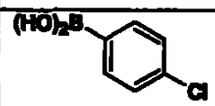
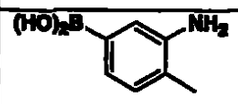
13

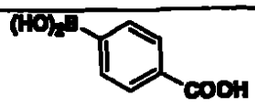
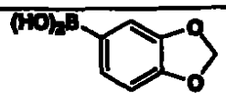
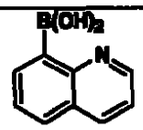
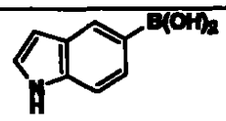
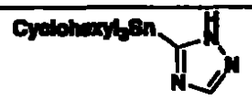
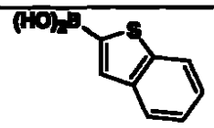
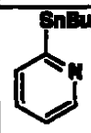
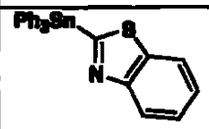
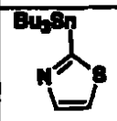
Precursor 12, 1-benzoyl-3-(R)-methyl-4-[(7-carbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine and Precursor 13, 1-benzoyl-3-(R)-methyl-4-[(7-hydroxycarbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine were made according to the same procedure of preparing Precursors 10 and 11, by using Precursor 9 as a starting material. Precursor 12, 1-benzoyl-3-(R)-methyl-4-[(7-carbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{21}N_4O_4$: 405.16, found 405.14. HPLC retention time: 0.91 minutes (column A); Precursor 13, 1-benzoyl-3-(R)-methyl-4-[(7-hydroxycarbonyl-4-azaindol-3-yl)-oxoacetyl]-piperazine: MS *m/z*: $(M+H)^+$ calcd for $C_{22}H_{21}N_4O_5$: 421.15, found 421.09. HPLC retention time: 1.02 minutes (column A).

Precursors 14a-1 - 14a-21

The following tin agents and boron agents can be purchased from commercial resources and used without any further treatment (Table I-1).

Table I-1

Precursor Number	Structure	Company
14a-1		Frontier Scientific, Inc.
14a-2		Maybridge Chem. Co.
14a-3		Frontier Scientific, Inc.
14a-4		Matrix Scientific
14a-5		Matrix Scientific
14a-6		Aldrich, Co.
14a-7		Aldrich, Co.
14a-8		Aldrich, Co.
14a-9		Aldrich, Co.
14a-10		Aldrich, Co.
14a-11		Lancaster

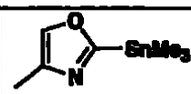
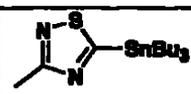
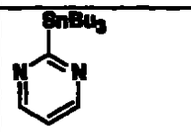
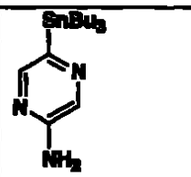
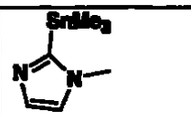
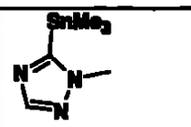
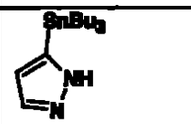
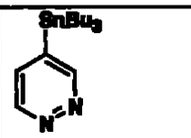
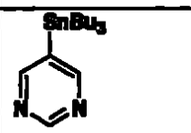
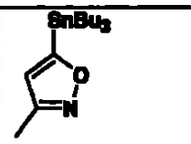
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14a-13		Aldrich, Co.
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14a-15		Matrix Scientific
14a-16		Frontier Scientific, Inc.
14a-17		Riedel-de Haen AG
14a-18		Lancaster
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14a-20		Aldrich, Co.
14a-21		Frontier Scientific, Inc.

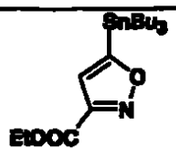
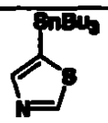
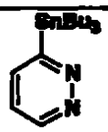
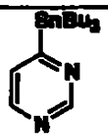
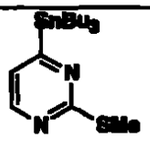
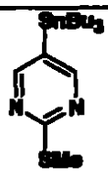
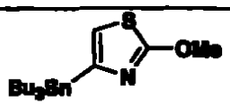
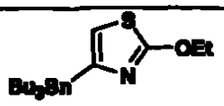
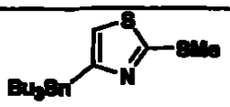
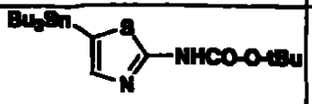
Preparation of Tin Agents:

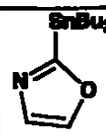
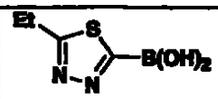
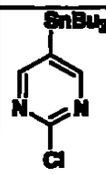
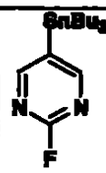
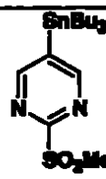
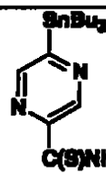
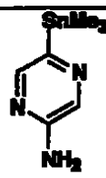
Precursors 14-1 – 14-65

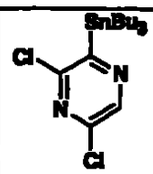
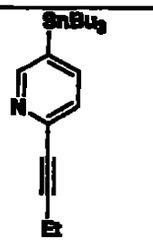
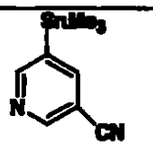
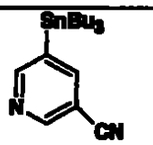
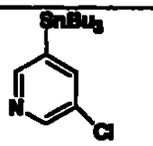
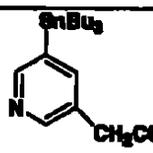
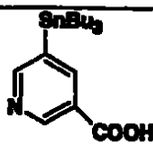
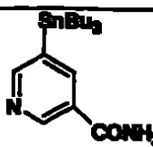
The following known tin agents and boron agents could be prepared according to the documented procedures indicated without any modification (Table I-2):

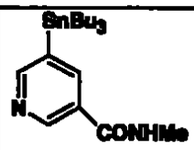
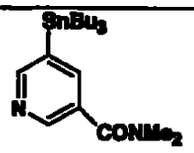
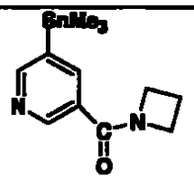
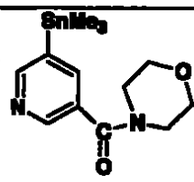
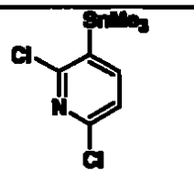
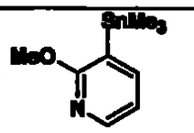
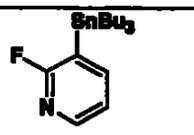
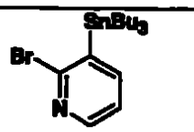
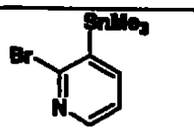
Table I-2

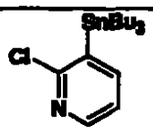
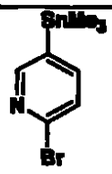
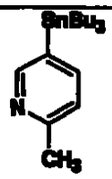
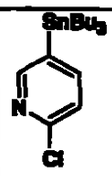
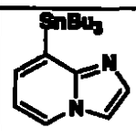
Precursor Number	Structure	Reference
14-1		Dondoni, A., et al Synthesis, 1987, 693
14-2		Aldous, D. J., et al US – 5,453,433
14-3		Sandosham, J., et al Tetrahedron 1994, 50, 275.
14-4		Lehn, L. M., et al. Chem. Eur. J. 2000, 6, 4133.
14-5		Jutzi, P., et al J. Organometallic Chem. 1983, 246, 163.
14-6		Jutzi, P., et al J. Organometallic Chem. 1983, 246, 163.
14-7		Graybill, T. L., et al Bioorg. Med. Chem. Lett. 1995, 5 (4), 387.
14-8		Heldmann, D. K., et al Tetrahedron Lett. 1997, 38, 5791.
14-9		Kennedy, G., et al Tetrahedron Lett. 1996, 37, 7611.
14-10		Kondo, Y., et al Tetrahedron Lett. 1989,30, 4249

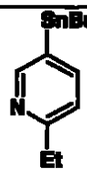
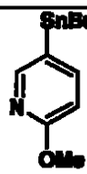
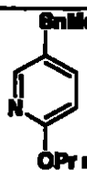
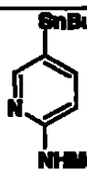
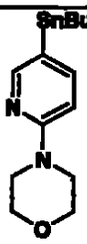
14-11		Kondo, Y., et al Tetrahedron Lett. 1989,30, 4249
14-12		Or, Y. S., et al US-6,054,435
14-13		Or, Y. S., et al US-6,054,435
14-14		Okada, T., et al WO-0123383
14-15		Okada, T., et al WO-0123383
14-16		Sandosham, J., et al Tetrahedron 1994, 50, 275
14-17		Sandosham, J., et al Acta Chem. Scand. 1989, 43, 684.
14-18		Nicolaou, K. C., et al WO-9967252
14-19		Nicolaou, K. C., et al WO-9967252
14-20		Nicolaou, K. C., et al WO-9967252
14-21		Benhedia, R., et al Tetrahedron Lett. 1999, 40, 5701.

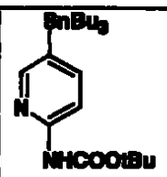
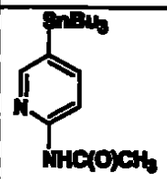
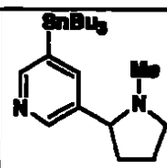
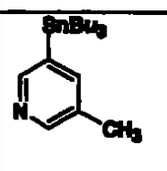
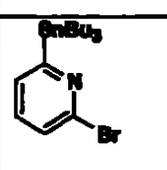
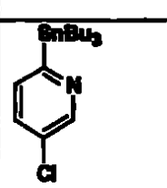
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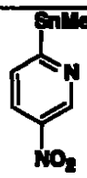
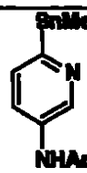
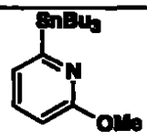
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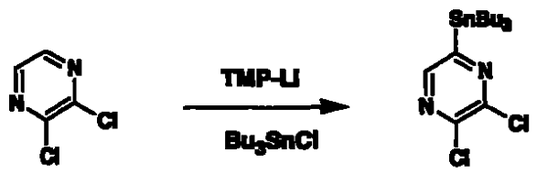
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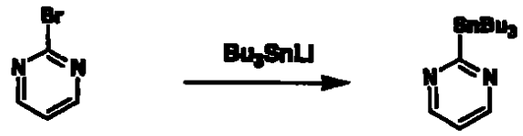
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Precursor 14-66



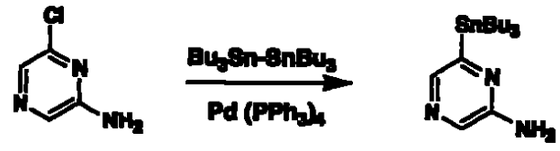
Preparation of 2,3-dicloro-5-(tri-n-butylstannyl)pyrazine (An example of general procedure Tin-01, below): TMP-Li (2,2,6,6-tetramethylpiperidinyl lithium) was prepared by addition of n-butyl lithium (1.6 M, 6.25 mL) to a solution of 2,2,4,4-tetramethylpiperidine (1.4 g) in dry THF (180 mL) at –78 °C. The solution was then allowed to warm to 0 °C, was stirred at 0 °C for 15 minutes, then was cooled to –78 °C. To the solution was added 2,3-dichloropyrazine (1.35 g), and followed by an addition of tri-n-butyltin chloride (3.25 g) in another 2 hours. The reaction was quenched with aqueous ammonium chloride solution. The organic layer was separated, and aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extract was dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 2,3-dicloro-5-(tri-n-butylstannyl)pyrazine (1 g).

Precursor 14-67



Preparation of 2-(tri-n-butylstannyl)-pyrimidine: (Example of the general procedure Tin-03, below) Tri-n-butylstannyl lithium was prepared at 0 °C in dry THF (20 mL) from tri-butyltin hydride (2.2 mL) and LDA (lithium diisopropylamide, 2M, 4.09 mL). The tri-n-butylstannyl lithium solution was then cooled to –78 °C and to it was added 2-bromopyrimidine (1 g). The reaction mixture was then allowed to warm up to room temperature over 8 hours. The reaction was then quenched with aqueous ammonium chloride solution. The organic layer was separated, and aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 2-(tri-n-butylstannyl)-pyrimidine (190 mg).

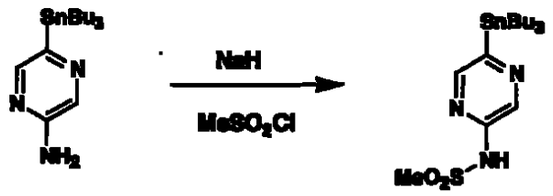
Precursor 14-68



Preparation of 2-amino-6-(tri-n-butylstannyl)pyrazine (Example of the general procedure Tin-04, below): To a sealed tube, 2-amino-6-chloro-pyrazine (1 g), bis(tri-butyltin) (3.92 mL) and tetrakis-triphenylphosphine palladium, $Pd(Ph_3P)_4$ (100 mg) were combined in dioxane (10 mL). The reaction was heated at 110-120 °C for 10 h. After the mixture cooled down to room temperature, it was poured into 20 mL of water. The solution was extracted with EtOAc (4 x 20 mL). The combined extract

was concentrated *in vacuo* to give a residue which was purified by silica gel chromatography to afford 2-amino-6-(tri-n-butylstannyl)pyrazine (0.5 g)

Precursor 14-69

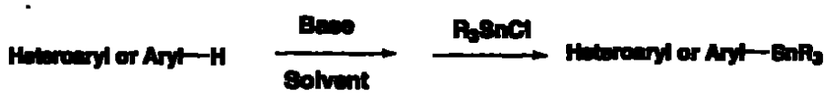


Preparation of 2-methylsulfonylamino-5-(tri-n-butylstannyl)pyrazine (Example of general procedure Tin-05, below): NaH (60%, 20 mg) was added into a solution of 2-amino-5-(tri-n-butylstannyl)pyrazine (0.2 g) in THF (30 mL) at room temperature. After the mixture stirred at room temperature for 30 minutes, to it was added methylsulfonyl chloride (63 mg). The reaction mixture was stirred at room temperature over 8 hours. The reaction was quenched with aqueous ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extract was dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography to afford 2-methylsulfonylamino-5-(tri-n-butylstannyl)pyrazine (20 mg).

Precursors 14-70 – 14-129

The precursors 14-70 – 14-129 were prepared according to the following general procedures designated Tin-01 through Tin-05 (Table I-3).

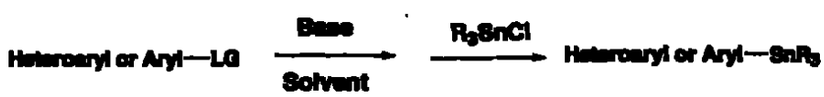
General Procedure Tin-01:



Base = LDA, TMP-Li, n-BuLi, S-BuLi or t-BuLi;
Solvent = THF, diethyl ether or DME;
R = methyl or butyl

To a solution of a base (1.1 equivalents) selected from lithium diisopropylamide, 2,2,6,6-tetramethylpiperidinyl lithium, n-butyl lithium, sec-butyl lithium or tert-butyl lithium in a solvent selected from tetrahydrofuran, diethyl ether or dimethoxyethane (concentration of approximately 0.05 mmol base/mL of solvent) at –78 °C was added an appropriate aryl or heteroaryl substrate (1.0 equivalents) followed by an addition of tri-n-butyltin chloride or trimethyltin chloride (1.1 equivalents) in another 2 hours. The reaction was quenched with aqueous ammonium chloride solution. The organic layer was separated, and aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired stannane.

General Procedure Tin-02:

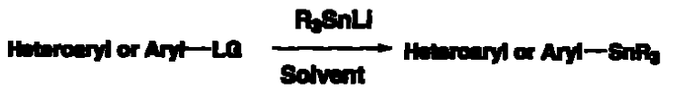


LG = Br or I; Base = n-BuLi, S-BuLi, or t-BuLi;
Solvent = THF, ether or DME;
R = methyl or butyl

To a solution of a base (1.1 equivalents) selected from n-butyl lithium, sec-butyl lithium or tert-butyl lithium in a solvent selected from tetrahydrofuran, diethyl ether or dimethoxyethane (concentration of approximately 0.05 mmol base/mL of solvent) at –78 °C was added an appropriate aryl or heteroaryl bromide or aryl or heteroaryl iodide substrate (1.0 equivalents). The reaction mixture was stirred at –78 °C for a period suitable to generate the anion via metal-halogen exchange then to it

was added tri-n-butyltin chloride or trimethyltin chloride (1.1 equivalents). The reaction was quenched with aqueous ammonium chloride solution. The organic layer was separated, and aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired stannane.

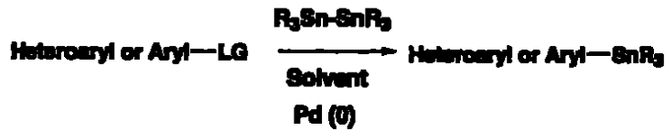
General Procedure Tin-03:



LG = F, Cl, Br, I; Solvent = THF, diethyl ether or DME; R = methyl or butyl

Tri-n-butylstannyl lithium or trimethylstannyl lithium (1.3 equivalents) was prepared at 0 °C in dry solvent selected from THF, diethyl ether or dimethoxyethane (20 mL) from tri-n-butyltin hydride or trimethyltin hydride, respectively (1.3 equivalents) and LDA (lithium diisopropylamide, 1.3 equivalents) at a concentration of approximately 0.4 mmol of alkylstannyl lithium/mL of solvent. The tri-n-butylstannyl lithium or trimethylstannyl lithium solution was then cooled to –78 °C and to it was added an appropriate haloaryl or haloheteroaryl substrate (1.0 equivalent). The reaction mixture was then allowed to warm up to room temperature over 8 hours. The reaction was then quenched with aqueous ammonium chloride solution. The organic layer was separated, and aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired stannane precursor.

General Procedure Tin-04:

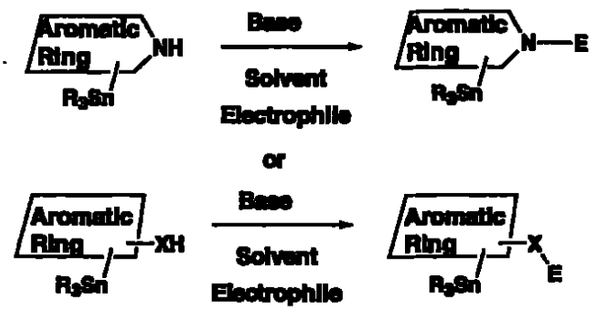


LG = Cl, Br, I or OTf;Solvent= Dioxane or Toluene; R = methyl or butyl

To a sealed tube, an appropriate aryl or heteroaryl substrate (1.0 equivalent), bis(tri-butyltin) or hexamethylditin (1.0 equivalent) and tetrakis-triphenylphosphine palladium, $Pd(Ph_3P)_4$ (1.0 mol%) were combined in dioxane or toluene (10 mL). The reaction was heated at 110-120 °C for 10 h. After the mixture cooled down to room temperature, it was poured into water. The solution was extracted with ethyl acetate and the combined extracts were concentrated *in vacuo* to give a residue which was purified by silica gel chromatography to afford the desired stannane product.

General Procedure Tin-05:

The following general reaction scheme depicts the derivatization of stannane precursors in which the stannane has a reactive ring NH group or reactive exocyclic amino, hydroxy or thiol group. The starting stannane is treated with base in an appropriate solvent then is reacted with suitable electrophiles such as alkyl halides, acid chlorides, sulfonyl chlorides, isocyanates and the like.



Electrophile = R'-halide, R'C(O)Cl, R'OC(O)Cl, R'R''NCOCl, $R'SO_2Cl$, R'NCO, R'NSO, R'NCNR''

E = R'-, R'C(O)-, R'OC(O)-, R'R''NC(O)-, $R'SO_2$-, R'NC(O)-, R'NS(O)-, R'NCNR''

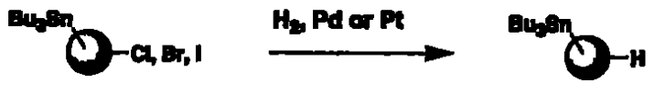
Solvent = CH_2Cl_2, THF, diethyl ether, DMF

R = methyl or butyl; X = NH, O or S

Base = NaH, BuLi, LDA, K_2CO_3, Et_3N, DBU, DMAP, NaHMDS

An appropriate base selected from sodium hydride, n-butyl lithium, lithium diisopropylamide, potassium carbonate, triethylamine, DBU, DMAP or sodium hexamethyldisilazide (1.0 equivalent) was added into a solution of an appropriate stannane substrate (as depicted above, 1.0 equivalent) in an appropriate solvent selected from dichloromethane, THF, diethyl ether or N,N-dimethylformamide at a temperature between –78 °C and room temperature. After the mixture stirred for a period sufficient to allow deprotonation, typically for 5 to 30 minutes, then to it was added an appropriate electrophile such as an alkyl halide, acid chloride, sulfonyl (1.0 equivalent). The reaction mixture was stirred, typically at room temperature, over a period of 2 to 8 hours. The reaction was quenched with aqueous ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extract was dried over magnesium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography to afford the desired stannane precursor.

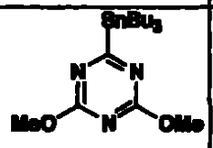
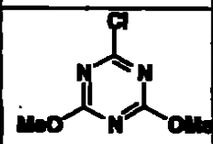
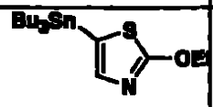
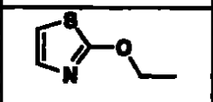
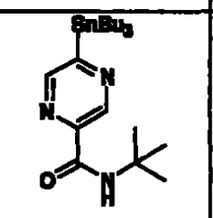
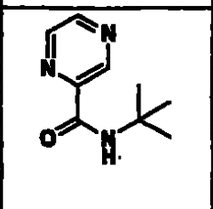
General procedure Tin-06

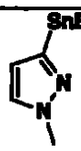
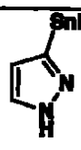
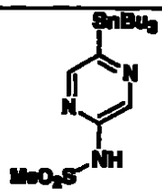
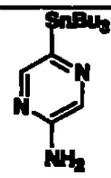
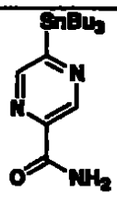
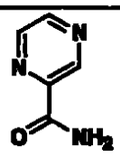
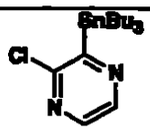
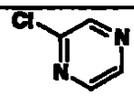
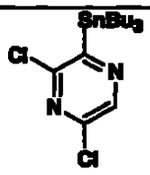
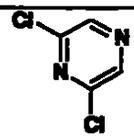
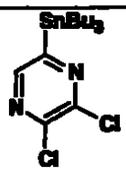
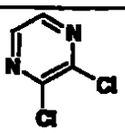


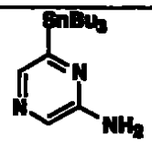
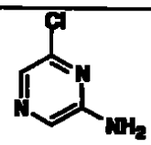
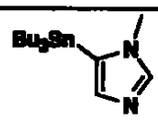
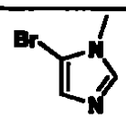
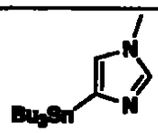
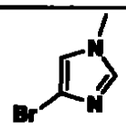
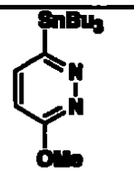
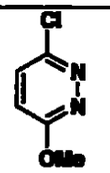
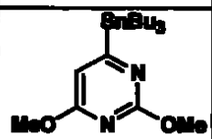
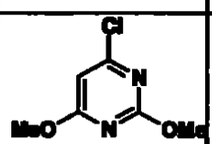
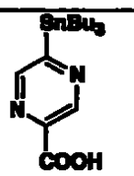
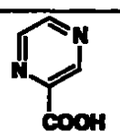
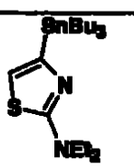
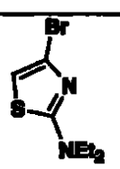
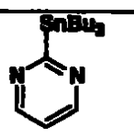
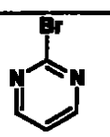
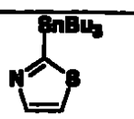
An aryl hilide stannane agent was dissolved in appropriate alcohol, either methanol or ethanol. After a catayist (pt or pd) was added into the solvent, the reaction mixture is placed in an environment of hydrogen under normal or raised pressure. After reaction finishes, the catalyst is filtered, and, concentration of the mother solution provides a residue which is used in the further reactions without any purification.

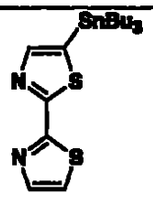
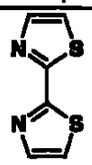
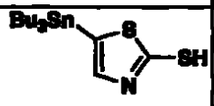
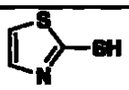
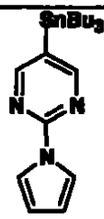
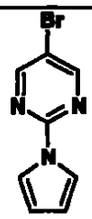
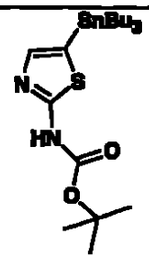
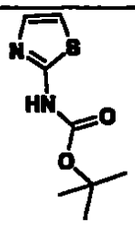
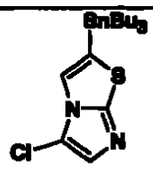
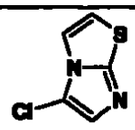
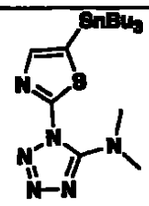
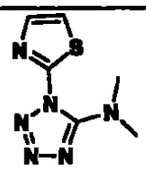
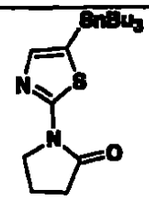
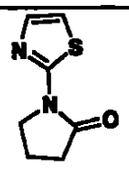
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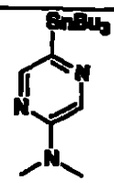
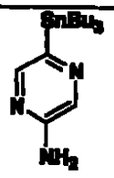
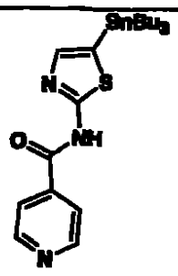
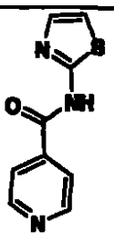
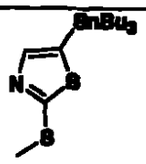
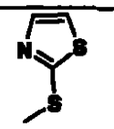
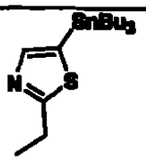
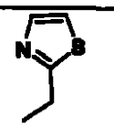
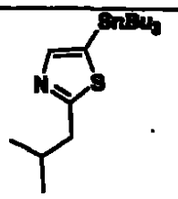
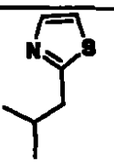
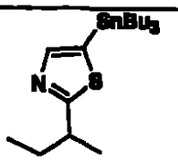
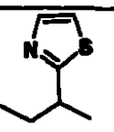
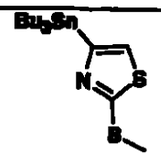
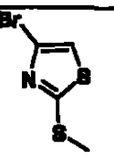
Rf = retention time

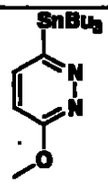
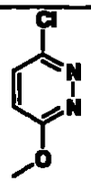
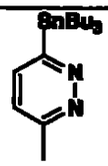
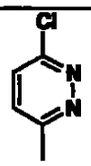
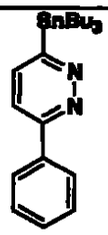
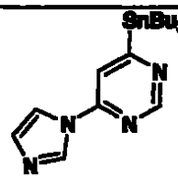
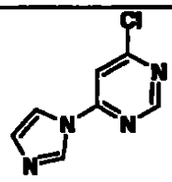
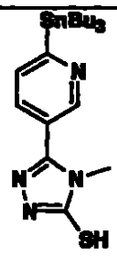
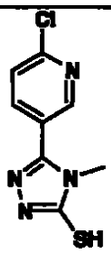
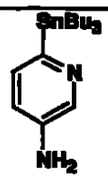
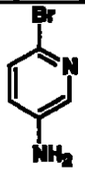
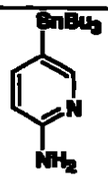
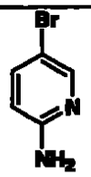
Intermed. Number	Structure	Starting Material	Method Applied	Identification
14-70			Tin-04	R_f = 2.33 min (Column A) ^{1}H NMR (500 MHz, CDCl3) δ 4.00 (s, 6H), 1.63 – 0.85 (m, 27H)
14-71			Tin-01	R_f = 2.52 min (Column A) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 4.44 (q, 2H, *J* = 7.02 Hz), 1.63 – 0.85 (m, 30H)
14-72			Tin-01	R_f = 2.84 min (Column B) ^{1}H NMR (500 MHz, CDCl3) δ 9.48 (s, 1H), 8.45 (s, 1H), 2.03 – 0.88 (m, 36H)

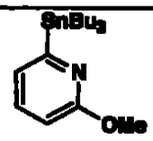
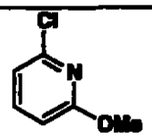
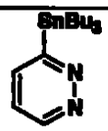
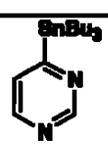
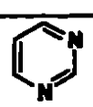
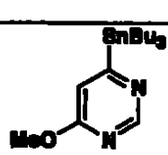
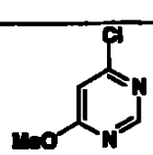
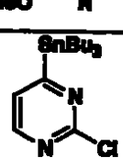
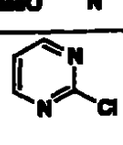
14-73			Tin-05	R_f = 2.27 min (Column A) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 1H), 6.29 (m, 1H), 3.94 (s, 3H), 1.56 – 0.87 (m, 27H)
14-74			Tin-05	R_f = 2.22 min (Column A)
14-75			Tin-01	R_f = 2.44 min (Column B) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.34 (s, 1H), 1.61 – 0.85 (m, 27H)
14-76			Tin-01	R_f = 3.41 min (Column A, flow rate = 4 ml/min) ^{1}H NMR (300 MHz, CDCl3) δ 8.58 (d, 1H, *J* = 2.52 Hz), 8.13 (d, 1H, *J* = 2.52 Hz), 1.63 – 0.85 (m, 27H)
14-77			Tin-01	R_f = 3.89 min (Column A, flow rate = 4 ml/min) ^{1}H NMR (300 MHz, CDCl3) δ 8.63 (s, 1H), 1.61 – 0.85 (m, 27H)
14-78			Tin-01	R_f = 3.86 min (Column A, flow rate = 4 ml/min) ^{1}H NMR (300 MHz, CDCl3) δ 8.24 (s, 1H), 1.61 – 0.85 (m,

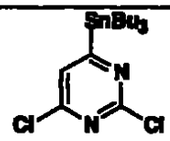
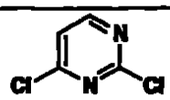
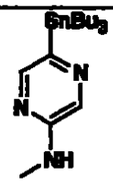
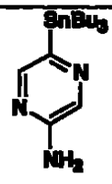
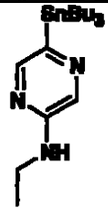
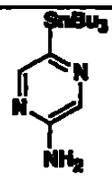
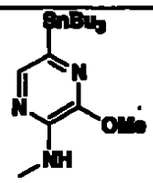
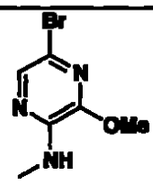
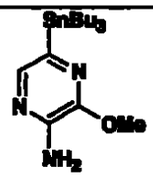
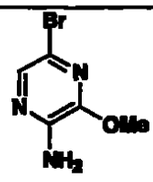
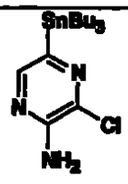
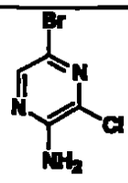
				27H)
14-79			Tin-04	R_t = 2.10 min (Column B) ^{1}H NMR (500 MHz, CDCl3) δ 7.90 (s, 1H), 7.26 (s, 1H), 1.58 – 0.87 (m, 27H)
14-80			Tin-04	R_t = 1.83 min (Column A)
14-81			Tin-04	R_t = 1.84 min (Column A)
14-82			Tin-04	R_t = 1.84 min (Column A)
14-83			Tin-04	R_t = 1.90 min (Column A)
14-84			Tin-01	R_t = 2.23 min (Column A)
14-85			Tin-04	R_t = 1.92 min (Column A)
14-86			Tin-03	R_t = 2.01 min (Column A)
14-87			Tin-01	R_t = 2.45 min (Column A)

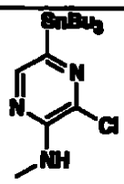
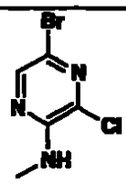
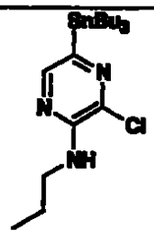
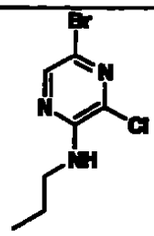
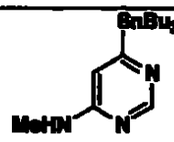
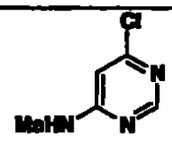
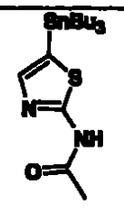
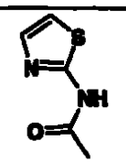
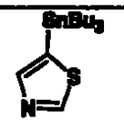
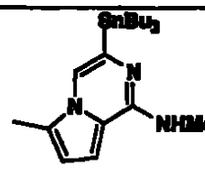
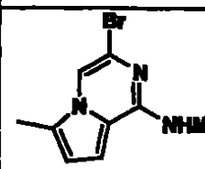
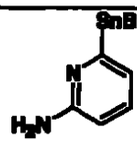
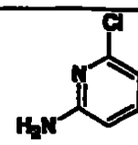
14-88			Tin-01	R_t = 2.67 min (Column C)
14-89			Tin-01	R_t = 2.31 min (Column C)
14-90			Tin-04	R_t = 2.71 min (Column D)
14-91			Tin-01	R_t = 2.49 min (Column C)
14-92			Tin-01	R_t = 2.42 min (Column C)
14-93			Tin-01	R_t = 3.49 min (Column C) Flow Rate = 4 ml/min
14-94			Tin-01	R_t = 2.46 min (Column C)

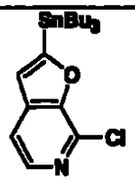
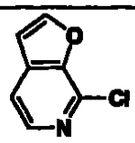
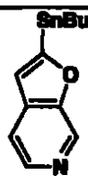
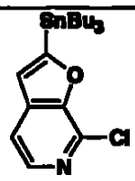
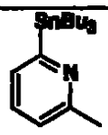
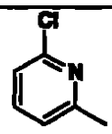
14-95			Tin-05	Rf = 2.15 min (Column A)
14-96			Tin-01	R_t = 2.28 min (Column C)
14-97			Tin-01	R_t = 2.60 min (Column C)
14-98			Tin-01	R_t = 2.37 min (Column A)
14-99			Tin-01	R_t = 2.59 min (Column A)
14-100			Tin-01	R_t = 2.49 min (Column C)
14-101			Tin-04	R_t = 2.41 min (Column A)

14-102			Tin-04	R_f = 1.88 min (Column E)
14-103			Tin-04	R_f = 1.92 min (Column E)
14-104			Tin-04	R_f = 2.01 min (Column E)
14-105			Tin-04	R_f = 2.15 min (Column E)
14-106			Tin-04	R_f = 1.91 min (Column E)
14-107			Tin-04	Rf = 1.95 min (Column A)
14-108			Tin-04	Rf = 1.93 min (Column A)

12-109			Tin-01	Rf = 1.95 min (Column A)
14-110			Tin-01	Rf = 1.83 min (Column A) ^{1}H NMR (500 MHz, CDCl3) δ 9.03 (d, 1H, J = 5.15 Hz), 7.49 (d, 1H, J = 7.95 Hz), 7.26 (m, 1H), 1.61 – 0.86 (m, 27H); ^{13}C NMR (125 MHz, CDCl3) δ 175.3, 149.8, 133.2, 123.7, 29.0, 27.3, 13.6, 10.1.
14-111			Tin-01	Rf = 2.18 min (Column B) ^{1}H NMR (500 MHz, CDCl3) δ 9.22 (s, 1H), 8.46 (d, 1H, J = 4.80 Hz), 7.42 (d, 1H, J = 4.75 Hz), 1.56 – 0.86 (m, 27H); ^{13}C NMR (125 MHz, CDCl3) δ 185.4, 158.0, 153.2, 130.6, 28.9, 27.2, 13.5, 9.9.
14-112			Tin-04	Rf = 1,96 min (Column A)
14-113			Tin-01	Rf = 2.61 min (Column A)

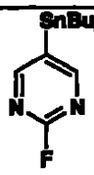
14-114			Tin-01	Rf = 2.85 min (Column A)
14-115			Tin-05	Rf = 2.09 min (Column A) ^{1}H NMR (500 MHz, CDCl3) δ 8.12 (s, 1H), 7.95 (s, 1H), 4.11 (s, 1H), 2.95 (s, 3H), 2.03 – 0.85 (m, 27H)
14-116			Tin-05	Rf = 2.16 min (Column A) ^{1}H NMR (500 MHz, CDCl3) δ 8.08 (s, 1H), 7.92 (s, 1H), 4.49 (s, 1H), 3.35 (m, 2H), 1.63 – 0.85 (m, 30H)
14-117			Tin-04	Rf = 2.19 min (Column A)
14-118			Tin-04	Rf = 2.18 min (Column A)
14-119			Tin-04	Rf = 2.47 min (Column A) ^{1}H NMR (500 MHz, CDCl3) δ 7.85 (s, 1H), 4.91 (s, 2H), 2.16 – 0.87 (m, 27H)

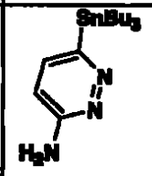
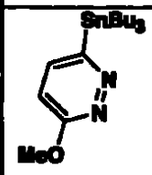
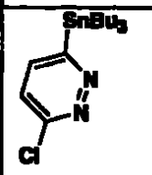
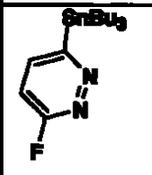
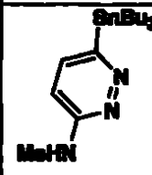
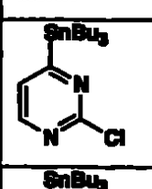
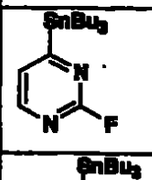
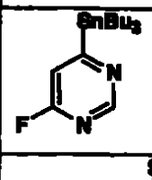
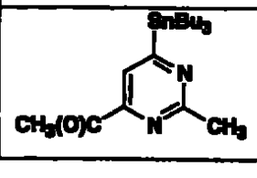
14-120			Tin-04	Rf = 2.61 min (Column A)
14-121			Tin-04	Rf = 2.92 min (Column A)
14-122			Tin-04	Rf = 1.93 min (Column A)
14-123			Tin-01	Rf = 2.20 min (Column A)
14-124			Tin-01	Rf = 2.50 min (Column A) ^{1}H NMR (500 MHz, CDCl3) δ 9.07 (s, 1H), 7.87 (s, 1H), 1.59 – 0.85 (m, 27H)
12-125			Tin-04	Rf = 1.97 min (Column A)
14-126			Tin-04	Rf = 1.97 min (Column A)

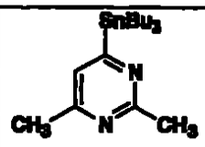
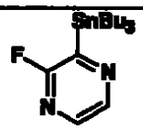
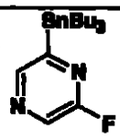
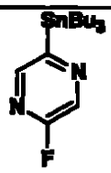
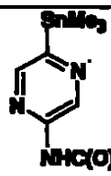
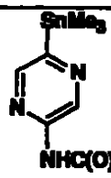
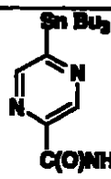
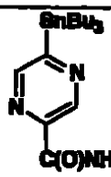
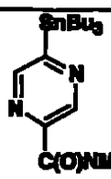
14-127			Tin-01	Rf = 2.70 min (Column E) ^{1}H NMR (500 MHz, CDCl3) δ 8.11 (d, 1H, J = 5.2 Hz), 7.41 (d, 1H, J = 5.2 Hz), 6.94 (s, 1H), 1.62 – 0.89 (m, 27H)
14-128			Tin-06	^{1}H NMR (500 MHz, CDCl3) δ 8.12 (d, 1H, J = 5.2 Hz), 7.78 (s, 1H), 7.46 (d, 1H, J = 5.2 Hz), 6.84 (s, 1H), 1.98 – 0.85 (m, 27H)
14-129			Tin-01	Rf = 1.86 min (Column A)

The following Table I-4 contains novel stannane reagents which can be prepared by the methodology described above and then could be used to prepare compounds of formula I.

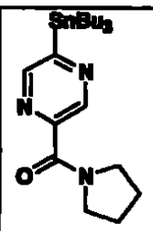
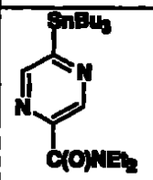
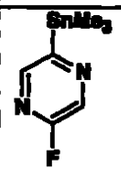
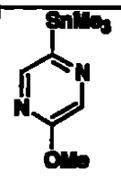
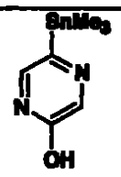
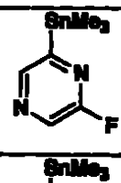
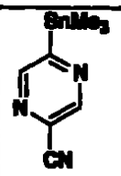
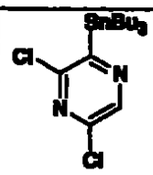
Table I-4

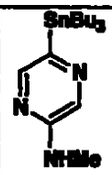
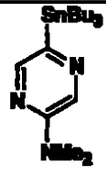
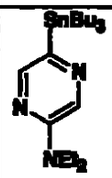
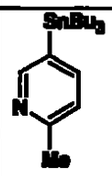
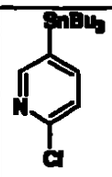
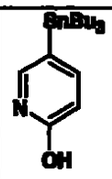
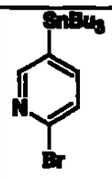
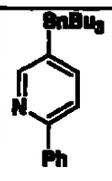
Precursor Number	Structure	Reference
		From 5-iodo2-chloro-1,3 pyrimidine. Fluoropyrimidines are obtained by fluorination of chloropyrimidines with CsF in N-methyl-2-pyrrolidinone or DMF 2.5-63 h at 80-150°C. The iodo is then converted to the lithium reagent with tBuLi and trapped with

		Bu3SnCl. See Sandosham above.
		
		
		
		
		
		
		
		
		

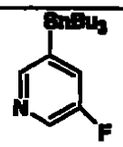
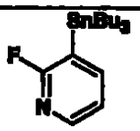
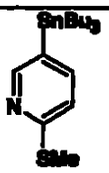
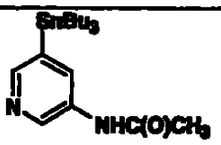
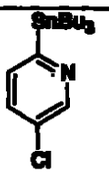
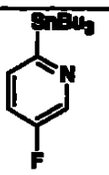
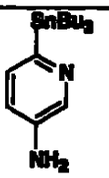
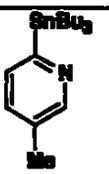
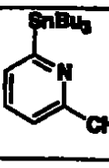
		
		
		
		
		
		
		
		
		

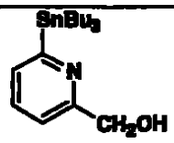
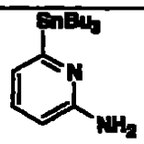
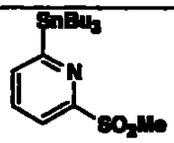
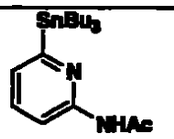
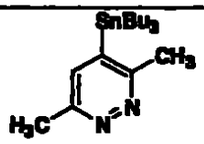
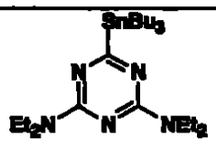
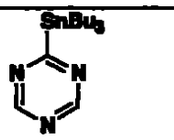
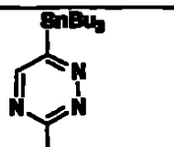
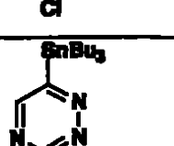
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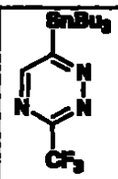
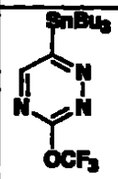
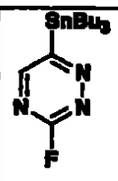
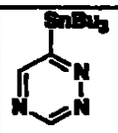
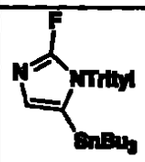
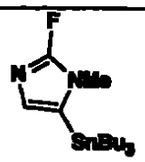
		
		
		
		
		
		
		
		Turck, A.; et.al Lab.. J. Organomet. Chem. (1991), 412(3), 301-10. Metallation of 2,6-dicloropyrazine and quench with Bu3SnCl

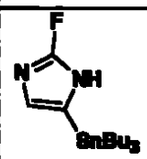
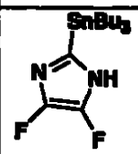
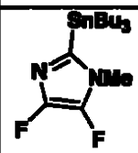
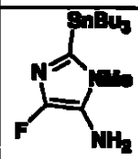
		Analogous to Lehn, L. M., et al. Chem. Eur. J. 2000, 6, 4133.
		
		
		
		
		
		
		

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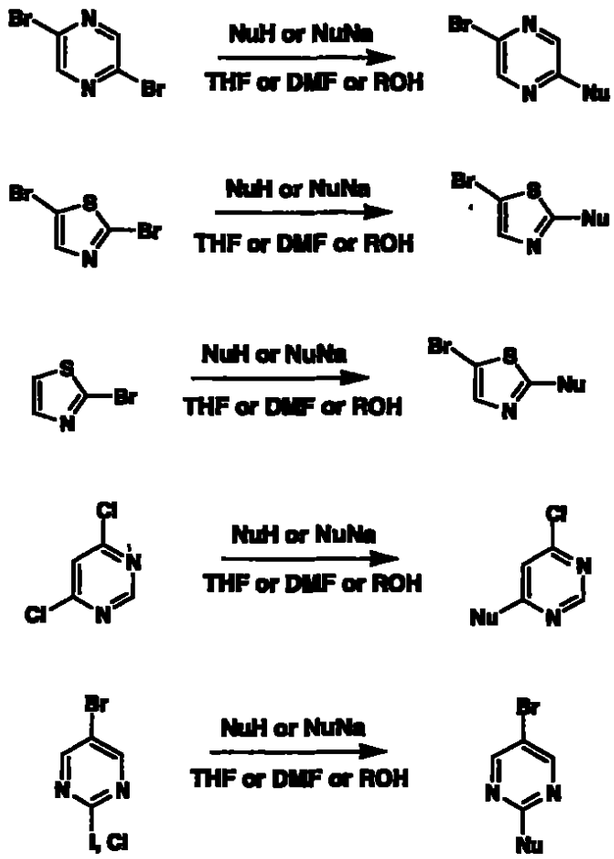
		
		
		
		
		
		
		
		
		

		
		
		
		
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		Metallation of 1-methyl-4-iodo imidazole (prepared in Takahashi, Kazuyuki; Kirk, Kenneth L.; Cohen, Louis A. Lab. Chem., Natl. Inst. Arthritis Diabetes Dig. Kidney Dis., Bethesda,

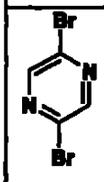
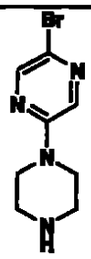
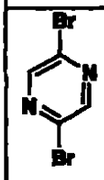
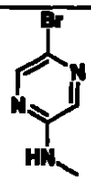
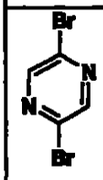
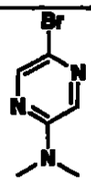
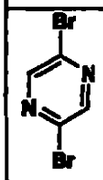
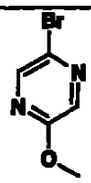
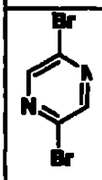
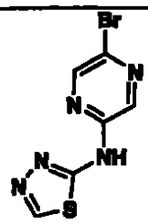
		MD, USA. J. Labelled Compd. Radiopharm. (1986), 23(1), 1-8) using tBuLi in THF at –78 and quenching with Bu_3SnCl. El Borai, M.; Moustafa, A. H.; Anwar, M.; Abdel Hay, F. I. The bromo derivative is described in Pol. J. Chem. (1981), 55(7-8), 1659-65 and can be used to generate the tin reagent via transmetallation.
		
		4,5difluoroimidazole prepared as in Dolensky, Bohumil;et.al, USA. J. Fluorine Chem. (2001), 107(1), 147-148.
		Dolensky, Bohumil;et.al, USA. J. Fluorine Chem. (2001), 107(1), 147-148.
		

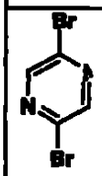
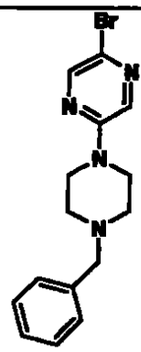
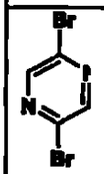
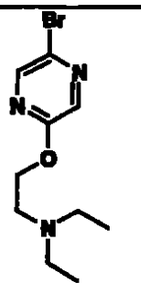
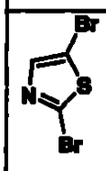
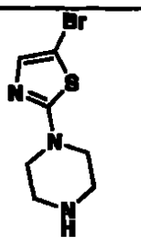
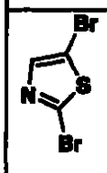
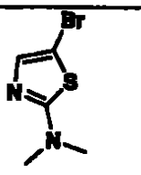
Select general procedures, *via* S_NAr reactions, for the preparation of starting materials for Tin agents

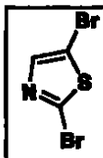
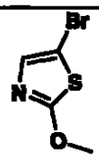
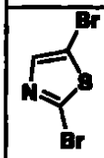
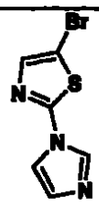
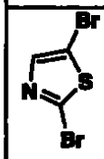
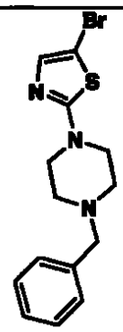
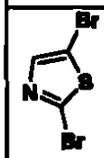
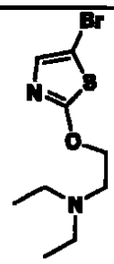
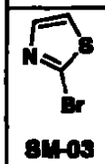
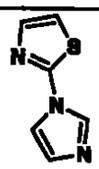
a. Preparation of 2-bromo-5-substituted-pyrazine, 5-bromo-2-subsituted-thiazole, 2-substituted-thiazaole, 4-chloro-6-substituted-pyrimidine and 5-bromo-2-substituted-pyrimidine



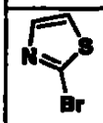
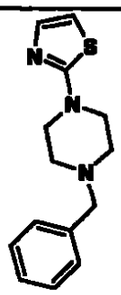
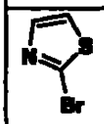
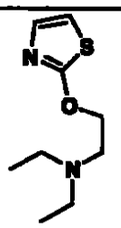
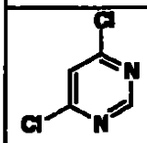
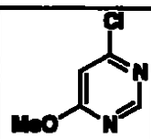
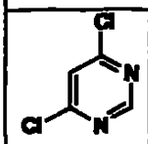
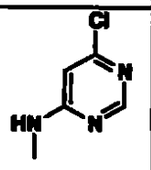
To a flask, an appropriate pyrazine, pyrimidine or thiazole (1.0 equivalent) and a nucleophile (Nu), such as amine, alcohol or thio-derivatives in one equivalence or an excess amount were combined in a solvent such as THF, DMF or alcohol, with or without an addition of NaH. The reaction was either stirred at room temperature or under heating for one to three days. After all the solvents were removed, the residue was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with ethyl acetate and the combined extracts were concentrated *in vacuo* to give a residue, which was purified by silica gel chromatography to afford the desired product.

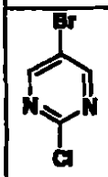
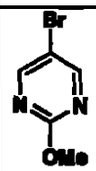
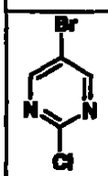
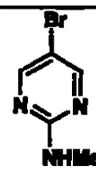
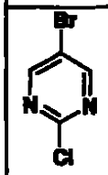
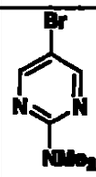
Starting Material	Product	Reaction Condition	Rf (minutes)	MS (M+H)+ Cald.	MS (M+H)+ Obsv.
 SM-01		SM-01 (2g) Piperazine (10 g), THF (50 ml), r.t.	0.56 (column G)	243.02	243.03
 SM-01		SM-01 (1 g), $MeNH_2$ (2M in THF, 100 ml), r.t.	0.89 (column E)	187.93	187.98
 SM-01		SM-01 (1g), Me_2NH (2M in THF, 100 ml), r.t.	1.19 (column E)	201.92	202.00
 SM-01		SM-01 (1 g), MeONa (0.5M in MeOH, 100 ml), r.t.	1.05 (column E)	188.91	188.97
 SM-01		SM-01 (50 mg), NaH (17 mg), 2-amino-1,3,4-thiadiazole (25 mg),	1.21 (column E)	257.94	257.89

		DMF 5 ml) r.t.			
 SM-01		SM-01 (50 mg), NaH (17 mg), N-benzylpiperazine (25 mg), DMF 5 ml) r.t.	1.04 (column E)	333.07	332.99
 SM-01		SM-01 (50 mg), NaH (17 mg), N,N-diethylamino-ethanol (0.033 ml), DMF 5 ml) r.t.	0.72 (column E)	274.06	273.97
 SM-02		SM-02 (2 g) Piperazine (10 g), THF (50 ml), r.t.	0.89 (column E)	247.99	247.97
 SM-02		SM-05 (1 g), Me_2NH (2M in THF, 100 ml), r.t.	0.65 (column E)	206.89	206.96

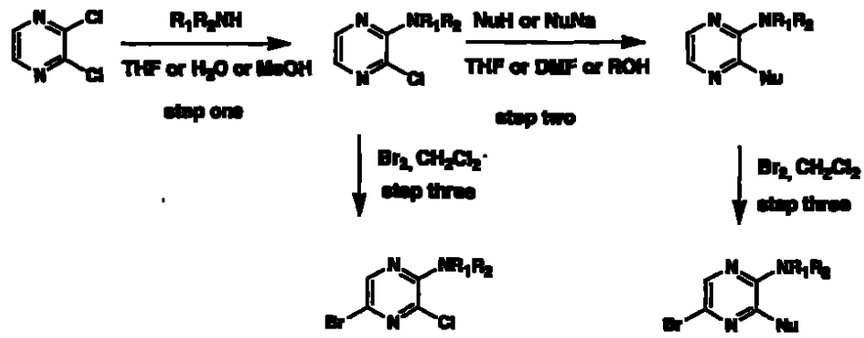
 SM-02		SM-02 (1 g), MeONa (0.5M in MeOH, 100 ml), r.t.	1.35 (column E)	193.93	193.84
 SM-02		SM-03 (50 mg), NaH (16 mg), imidazole (77 mg), DMF 5 ml) r.t.	0.89 (column E)	229.94	229.83
 SM-02		SM-02 (50 mg), NaH (16 mg), N-benzylpiperazine (30 mg), DMF 5 ml) r.t.	1.02 (column E)	338.03	337.98
 SM-02		SM-02 (50 mg), NaH (16 mg), N,N-diethylamino-ethanol (0.033 ml), DMF 5 ml) r.t.	0.83 (column E)	279.02	278.95
 SM-03		SM-03 (50 mg), NaH (25 mg),	0.31 (column E)	151.91	152.03

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		imidazole (25 mg), DMF 5 ml) r.t.			
 SM-03		SM-03 (50 mg), NaH (25 mg), N-benzylpiperazine (37 mg), DMF 5 ml) r.t.	0.66 (column E)	260.07	260.12
 SM-03		SM-03 (50 mg), NaH (25 mg), N,N-diethylamino-ethanol (0.05 ml), DMF 5 ml) r.t.	0.46 (column E)	201.11	201.02
 SM-04		SM-04 (1g), MeONa (0.5M in MeOH, 13.52 ml), r.t.	0.86 (column E)	145.02	144.99
 SM-04		SM-04 (1g), $MeNH_2$ (2M in THF,	0.46 (column E),	144.03	143.96

		100ml), r.t.			
 SM-05		SM-05 (1g), MeONa (0.5M in MeOH, 100ml), 1 day, r.t.	0.91 (column E)	188.97	188.91
 SM-05		SM-05 (1g), $MeNH_2$ (2M in THF, 100 ml), r.t.	0.84 (column E)	187.99	187.94
 SM-05		SM-05 (1g), Me_2NH (2M in THF, 100 ml), r.t.	1.24 (column E)	202.00	201.98

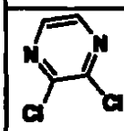
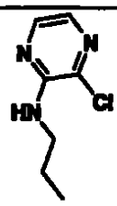
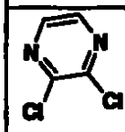
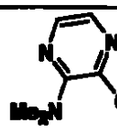
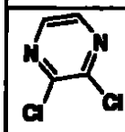
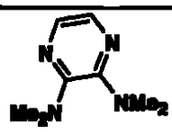
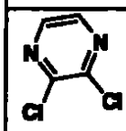
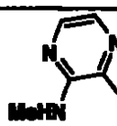
b. Preparation of 2-bromo-5,6-disubstituted-pyrazine

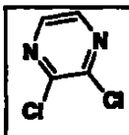
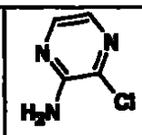


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Step one

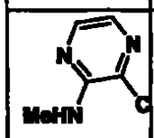
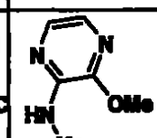
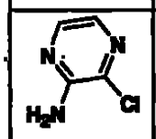
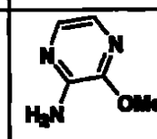
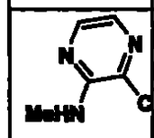
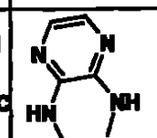
To a flask, an appropriate pyrazine (1.0 equivalent) and a nucleophile, such as amine or sodium alkoxide in an excess amount were combined in a solvent such as water or THF or without solvent. The reaction was either stirred at room temperature or under heating for one to three days. After all the solvents were removed, a residue was collected and used in the further steps without any purification.

Starting Material	Product	Reaction Condition	Rf (minutes)	MS (M+H) + Cald.	MS (M+H)+ Obsv.
 SM-06		SM-06 (100 mg), propylamine (2 ml), r.t.	1.28 (column C)	172.06	172.09
 SM-06		SM-06 (100 mg), Me_2NH (2M in THF, 10 ml) or Me_2NH (40% in water, 10 ml), r.t.	1.21 (column C)	158.05	158.07
 SM-06		SM-06 (100 mg), Me2NH (40% in water, 10 ml), 100°C	0.49 (column C)	167.13	167.19
 SM-06		SM-06 (100 mg), $MeNH_2$ (2M in THF, 10 ml), r.t.	0.72 (column C)	144.03	144.07

 SM-06		SM-06 (100 mg), NH_4OH (10 ml), 100°C	0.41 (column C)	162.04 (M+MeOH+H)+	162.06 (M+MeOH+H)+

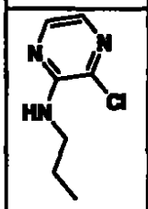
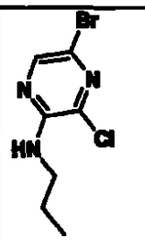
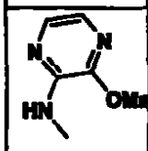
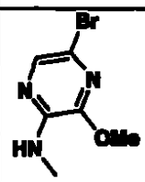
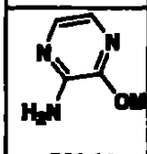
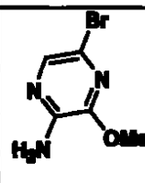
Step two

To a flask, the crude pyrazine derivative obtained from the step one (1.0 equivalent) and a nucleophile, such as amine or sodium alkoxide in an excess amount were combined in a solvent such as water or THF or without solvent. The reaction was either stirred at room temperature or under heating for one to three days. After all the solvents were removed, a residue was collected and used in the further steps without any purification.

Starting Material	Product	Reaction Condition	Rf (minutes)	MS (M+H)+ Cald.	MS (M+H)+ Obsv.
 SM-07		SM-07 (2 g), MeONa (12.5 wt%, 100ml, 100°C	0.28 (column C)	140.08	140.14
 SM-08		SM-08 (2 g), MeONa (12.5 wt%, 20ml), 100°C	0.28 (column C)	158.13	158.09
 SM-07		SM-07 (2 g), $MeNH_2$ (40% in water, 100 ml), 110°C	0.34 (column C)	139.10	139.13

Step three

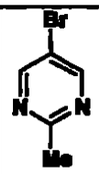
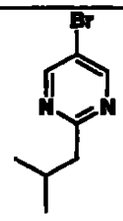
To a flask, the crude pyrazine derivative obtained from the step two (1.0 equivalent) was dissolved in methylene chloride. A slightly excess of bromine was then added into the mixed solution. The reaction was stirred at room temperature for ten hours. After all the solvents were removed, a residue was collected and purified by silica gel chromatography to afford the desired product.

Starting Material	Product	Reaction Condition	Rf (minutes)	MS (M+H)+ Cald.	MS (M+H)+ Obsv.
 SM-09		SM-09 (5 g), bromine (1.34 ml), CH_2Cl_2 (100 ml)	1.77 (column C)	249.97	250.02
 SM-10		SM-10 (2 g), bromine (0.72 ml), CH_2Cl_2 (20 ml)	1.13 (column C)	217.99	217.98
 SM-11		SM-11 (2 g), bromine (0.72 ml), CH_2Cl_2 (20 ml)	0.98 (column C)	203.98	203.99

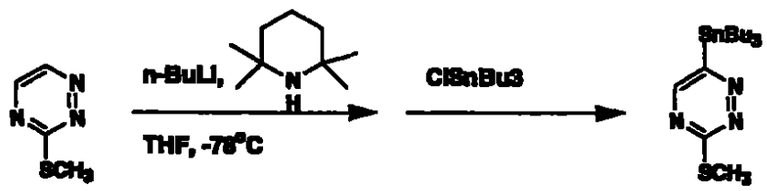
General procedure of the preparation of 2-alkyl-5-bromo-pyrimide:



To a sealed tube, 5-bromo-2-iodopyrimidine (1.0 equivalent), tri-alkylaluminum (1.5 equivalent) and tetrakis-triphenylphosphine palladium, $Pd(Ph_3P)_4$ (1.0 mol%) were combined in dioxane(10 mL). The reaction was heated at 110-120 °C for 10 h. After the mixture cooled down to room temperature, it was poured into water. The solution was extracted with ethyl acetate and the combined extracts were concentrated *in vacuo* to give a residue which was purified by silica gel chromatography to afford the desired 2-alkyl-5-bromopyrimidine product.

R3Al	Product	Rf (minutes)	MS (M+H)+ Cald.	MS (M+H)+ Obsv.
Me_3Al		0.90 (column E)	172.94	172.97
$(i\text{-}Bu)_3Al$		1.45 (column E)	215.02	214.99

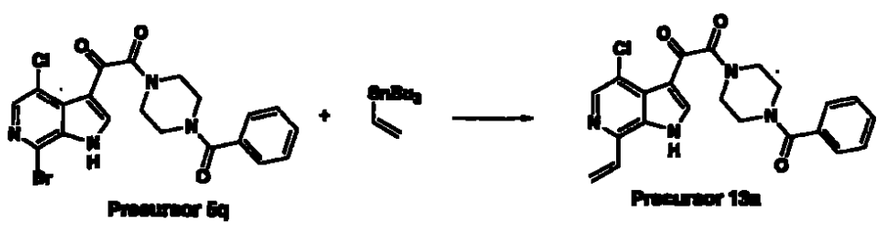
Prep of triazine stannane for Stille coupling to prepare examples of claim 1. (the sulfur can thenbe removed with Raney Nickel to give additional desulfurized triazines).



2,2,6,6-tetramethylpiperidine (2.0ml, 11.81mmol) in 30ml of THF was cooled to -78oC and treated with n-butyllithium (4.7ml, 11.81mmol, 2.5M in hexane). After stirring 30min at 0oC, the reaction was cooled to -78oC again and 3-methylthio-1,2,4-triazine (1.0g, 7.87mmol) was added. The resulting solution was stirred at -78oC for 30min before tributyltin chloride (2.1ml, 7.87mmol) was added. The reaction was kept at -78oC for 1hr, then quenched with water. The THF solvent was removed on rotarory evaporator and the remaining solution was extracted with ethylacetate. The organic layer was dried over MgSO4, filtered and the filtrate was concentrated. The residue was chromatographed to afford 96mg of 3-methylthio-6-tributyltin-1,2,4-triazine.

1H NMR (300Hz, CHCl3): 8.83 (s, 1H); 2.62 (s, 3H); 2.04 - 0.79 (m, 27H).
LC/MS: (ES+) M/Z (M+H)+ = 418, RT = 2.29min.

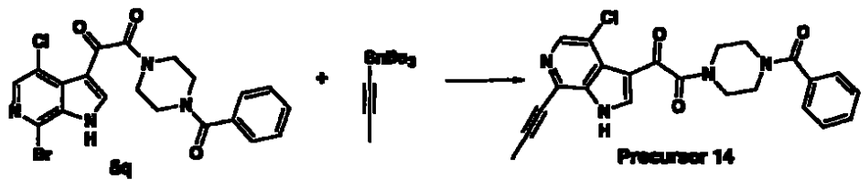
Precursor 13a



To a mixture of 5q (50 mg, 105 µmol) and $Pd(PPh_3)_4$ (25 mg, 21 µmol) was added 1,4-dioxane (1 ml) and vinyl tributylstannane (50 mg, 158 µmol). The reaction mixture was heated in a sealed tube at 145°C for 3 hours. After cooling to ambient temperature, the reaction mixture was added MeOH (4 ml) and then filtered. The filtrate was purified by preparative reverse phase HPLC to give the TFA salt of Precursor 13a using the method: Start %B = 30, Final %B = 75, Gradient time = 20

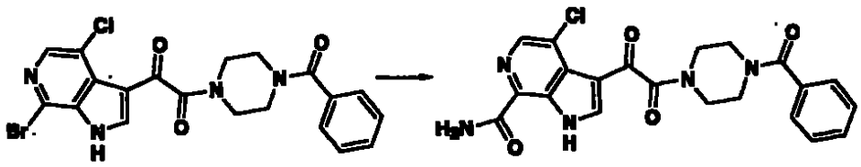
min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 7.92 – 8.58 min. ^{1}H NMR: (CD_3OD) δ 8.61 (s, 1H), 8.37 (s, 1H), 7.47 (b s, 5H), 7.31 (dd, J = 17.3, 11.3, 1H), 6.50 (d, J = 17.3, 1H), 5.97 (d, J = 11.3, 1H), 3.97 – 3.38 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 423, 425; HPLC R_t = 1.887.

Precursor 14



To a mixture of precursor 5q (30 mg, 63 μmol) and $Pd(PPh_3)_4$ (20 mg, 17 μmol) was added 1,4-dioxane (1 ml) and 1-tributylstannyl propyne (40 mg, 122 μmol). The reaction mixture was heated in a sealed tube at 145°C for 2 hours. After cooling to ambient temperature, the reaction mixture was added MeOH (4 ml) and then filtered. The filtrate was purified by preparative reverse phase HPLC to give the TFA salt of precursor 14 (1-(4-Benzoyl-piperazin-1-yl)-2-(4-chloro-7-prop-1-ynyl-1H-pyrrolo[2,3-c]pyridin-3-yl)-ethane-1,2-dione) using the method: Start %B = 20, Final %B = 80, Gradient time = 20 min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 8.74 – 9.00 min. ^{1}H NMR: (CD_3OD) δ 8.47 (s, 1H), 8.27 (s, 1H), 7.46 (b s, 5H), 3.82 – 3.34 (b m, 8H), 2.26 (s, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 435, 437; HPLC (alternate conditions B, column G) R_t = 2.123.

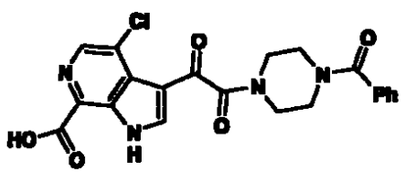
Precursor 15



To a solution of precursor 5q (50 mg, 0.11 mmol) in DMF (1 ml) was added CuCN (30 mg, 0.335 mmol). The reaction mixture was heated at 170°C for 30 min. After cooling to ambient temperature, the reaction mixture was diluted with MeOH (15

ml), filtered under gravity, and the filtrate evaporated *in vacuo* to afforded a brownish residue. To the residue in EtOH (3 ml) at ambient temperature was bubbled hydrogen chloride gas for 10 minutes to give a yellow solution, which was purified by preparative reverse phase HPLC using the method: Start %B = 15, Final %B = 85, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : XTERRA C18 5 um 30 x 100 mm, Fraction Collection: 10.40 – 10.85 min; ^{1}H NMR: (CD_3OD) 8.35 (s, 1H), 8.33 (s, 1H), 7.42 (b s, 5H), 3.95 – 3.41 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 440, 442; HPLC (alternate conditions B, column G) R_t = 1.820.

Precursor 16



Preparation of precursor 16:

To a suspension of precursor 15 (6 mg, 13 μmol) in a mixture of AcOH (0.5 ml) and Ac_2O (1.0 ml) at 0°C was charged with sodium nitrite (17 mg, 246 μmol). The reaction mixture was stirred at 0°C for 30 min. and then at ambient temperature for 1 hour. After addition of MeOH (4 ml), the reaction mixture was purified by preparative reverse phase HPLC to give the TFA solvate of the title compound using the method: Start %B = 15, Final %B = 80, Gradient time = 15 min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 9.48 – 10.03 min. ^{1}H NMR: (DMSO-d_6) δ 12.76 (s, 1H), 8.48 (s, 1H), 8.32 (d, J = 3.0, 1H), 7.44 (b s, 5H), 3.97 – 3.47 (b m, overlapping with water peak, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 441, 443; HPLC (alternate conditions B, column G) R_t = 1.530. Ref: Amide hydrolysis: Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* 1997, *38*, 4535 and references cited therein.

Additional Piperazine Precursors

***N*-(Benzoyl)-2-methylpiperazine, Precursor 17a,** was prepared according to the procedure described in Ref. 90(b). ^{1}H NMR (300 MHz, CD_3OD) δ7.47 (m, 5H), 3.30-2.70 (m, 7H), 1.36 (d, 3H, J = 6.90 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ171.0, 135.4, 129.7, 128.5, 126.3, 48.5, 44.3,14.5;[2] HRMS *m/z*: $(M+H)^+$ calcd for $C_{12}H_{17}N_2O$ 205.1341, found 205.1341.

(R)-*N*-(Benzoyl)-2-methylpiperazine, Precursor 17b, was prepared according to the procedure described in Ref. 90(b). ^{1}H NMR (300 MHz, CD_3OD) δ7.41 (m, 5H), 3.31-2.70 (m, 7H), 1.35 (d, 3H, J = 6.90 Hz). MS *m/z*: $(M+H)^+$ Calc'd for $C_{12}H_{17}N_2O$: 205.13; Found 205.16. HPLC retention time: 0.51 minutes (column L).

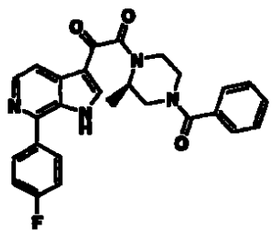
(S)-*N*-(Benzoyl)-2-methylpiperazine, Precursor 17c, was prepared according to the procedure described in Ref. 90(b). ^{1}H NMR (300 MHz, CD_3OD) δ7.41 (m, 5H), 3.31-2.72 (m, 7H), 1.35 (d, 3H, J = 6.90 Hz). MS *m/z*: $(M+H)^+$ Calc'd for $C_{12}H_{17}N_2O$: 205.13; Found 205.16. HPLC retention time: 0.50 minutes (column L).

[2]Some carbon peaks are missing due to the overlap of signals.

***N*-(Benzoyl)-2-ethylpiperazine, Precursor 17d,** was prepared according to the procedure described in Ref. 90(b).. ^{1}H NMR (300 MHz, CD_3OD) δ7.49 (m, 5H), 3.34-2.80 (m, 7H), 2.10-1.70 (m, 2H), 0.85 (b, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ171.5, 135.1, 129.8, 128.5, 126.5, 48.5, 46.0, 43.9, 21.8, 9.6;[2] HRMS *m/z*: $(M+H)^+$ calcd for $C_{13}H_{19}N_2O$ 219.1497, found 219.1501.

Preparation of Compounds of Formula I

EXAMPLE 1



Typical procedure for coupling azaindole with aromatic boron reagent (An example of the general procedure described below for examples 2-14): Preparation of 1-benzoyl-3-(R)-methyl-4-[(7-(4-fluorophenyl)-6-azaindol-3-yl)-oxoacetyl]-piperazine is an example of Step E as described in Scheme 15. To a sealed tube, 1-(benzoyl)-3-(R)-methyl-4-[(7-chloro-6-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 5a, (20 mg, 0.049 mmol), 4-fluorophenylboronic acid, Precursor 14a-9, (8.2 mg, 0.059 mmol), $Pd(Ph_3P)_4$ (5 mg) and K_2CO_3 (20 mg, 0.14 mmol) were combined in 1.5 mL of DMF and 1.5 mL of water. The reaction was heated at 110-120 °C for 10 h. After the mixture cooled down to rt, it was poured into 20 mL of water. The solution was extracted with EtOAc (4 x 20 mL). The combined extract was concentrated to give a residue which was purified using a Shimadzu automated preparative HPLC System to give compound 1-benzoyl-3-(R)-methyl-4-[(7-(4-fluorophenyl)-6-azaindol-3-yl)-oxoacetyl]piperazine (1.8 mg, 7.9%). MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{24}FN_4O_3$: 471.18; found 471.08. HPLC retention time: 1.12 minutes (column A).

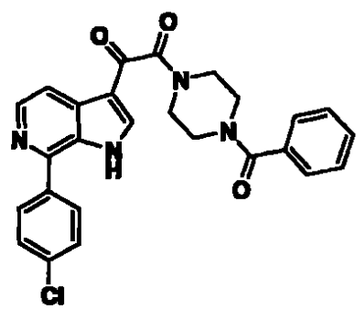
EXAMPLES 2-14

Examples 2-14 were prepared according to the following general method in a manner analogous to the preparation of Example 1.

Typical procedure for coupling azaindole with aromatic boron reagent: To a sealed tube, an appropriately substituted azaindole precursor (0.049 mmol), an appropriate boronic acid derivative (0.059 mmol), $Pd(Ph_3P)_4$ (5 mg) and K_2CO_3 (20

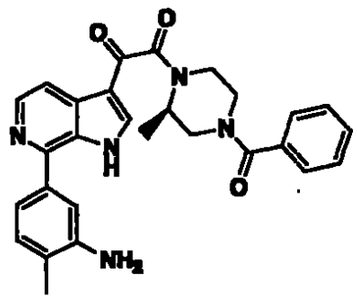
mg, 0.14 mmol) were combined in 1.5 mL of DMF and 1.5 mL of water. The reaction was heated at 110-120 °C for 10 h. After the mixture cooled down to rt, it was poured into 20 mL of water. The solution was extracted with EtOAc (4 x 20 mL). The combined extract was concentrated *in vacuo* to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide the desired compound.

EXAMPLE 2



Example 2, was prepared according to the general method described above starting from Precursor 5g and 4-chlorophenyl boronic acid, Precursor 14a-10, to provide 1-benzoyl-4-[(7-(4-chlorophenyl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{24}FN_4O_3$: 473.14; found 473.13. HPLC retention time: 1.43 minutes (column B).

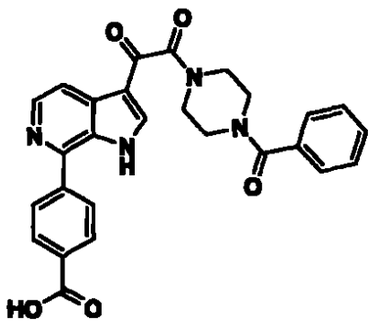
EXAMPLE 3



Example 3, was prepared according to the general method described above starting from Precursor 5a and 3-amino-4-methylphenyl boronic acid, Precursor 14a-

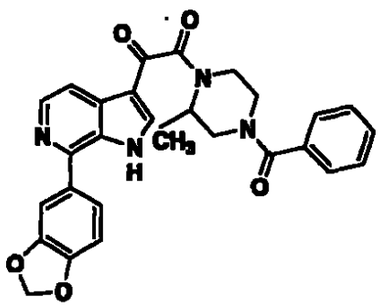
11, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(3-amino-4-methylphenyl)-6-azaindol-3-yl)-oxoacetyl] piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{24}ClN_4O_3$: 482.22; found 482.25. HPLC retention time: 1.35 minutes (column B).

EXAMPLE 4



Example 4, was prepared according to the general method described above starting from Precursor 5g and 4-hydroxycarbonylphenyl boronic acid, Precursor 14a-12, to provide 1-benzoyl-4-[(7-(4-carboxy-phenyl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{24}ClN_4O_3$: 483.17; found 483.10. HPLC retention time: 1.00 minutes (column A).

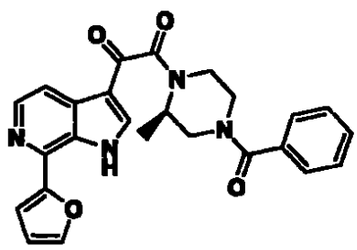
EXAMPLE 5



Example 5, was prepared according to the general method described above from 1-benzoyl-3-methyl-4-[(7-chloro-6-azaindol-3-yl)-oxoacetyl]piperazine and 3,4-methylenedioxyphenyl boronic acid, Precursor 14a-13, to provide 1-benzoyl-3-methyl-4-[(7-(3,4-methylenedioxyphenyl)-6-azaindol-3-yl)-oxoacetyl]piperazine.

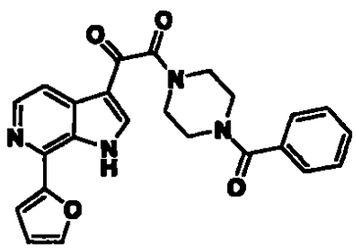
MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{25}N_4O_5$: 497.18; found 497.03. HPLC retention time: 1.41 minutes (column B).

EXAMPLE 6



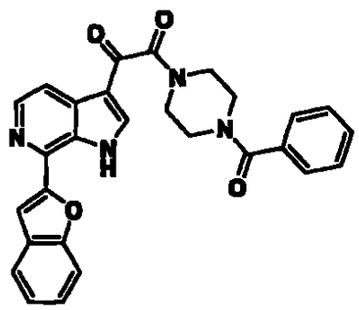
Example 6, was prepared according to the general method described above starting from Precursor 5a and furan-2-yl boronic acid to provide 1-benzoyl-3-(R)-methyl-4-[(7-(furan-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_4$: 443.17; found 443.12. HPLC retention time: 1.20 minutes (column A).

EXAMPLE 7



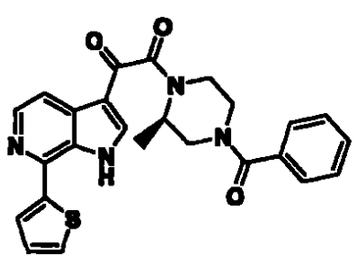
Example 7, was prepared according to the general method described above starting from Precursor 5g and furan-2-yl boronic acid to provide 1-benzoyl-4-[(7-(furan-2-yl)-6-azaindol-3-yl)-oxoacetyl] piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{21}N_4O_4$: 429.16; found 428.98. HPLC retention time: 1.36 minutes (column A).

EXAMPLE 8



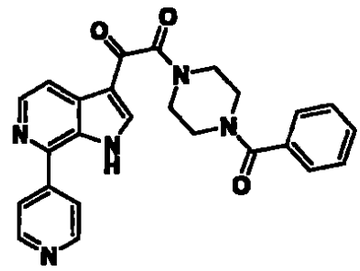
Example 8, was prepared according to the general method described above starting from Precursor 5g and benzofuran-2-yl boronic acid to provide 1-benzoyl-4-[(7-(benzofuran-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{23}N_4O_4$: 479.17; found 479.09. HPLC retention time: 1.67 minutes (column B).

EXAMPLE 9



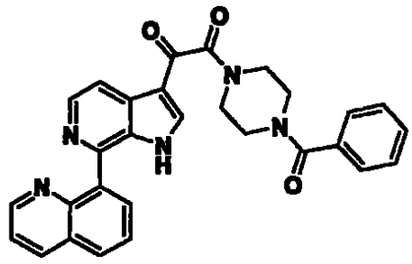
Example 9, was prepared according to the general method described above starting from Precursor 5a and thien-2-yl boronic acid to provide 1-(benzoyl)-3-(*R*)-methyl-4-[(7-(thien-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_3S$: 459.15; found 459.10. HPLC retention time: 1.20 minutes (column A).

EXAMPLE 10



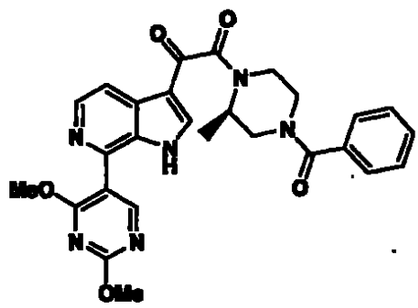
Example 10, was prepared according to the general method described above starting from Precursor 5g and pyridin-4-yl boronic acid to provide 1-(benzoyl)-4-[(7-(pyridin-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{22}N_5O_3$: 440.17; found 440.10. HPLC retention time: 0.97 minutes (column A).

EXAMPLE 11



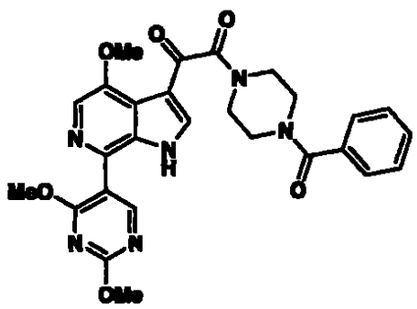
Example 11, was prepared according to the general method described above starting from Precursor 5g and quinolin-8-yl boronic acid, Precursor 14a-14, to provide 1-benzoyl-4-[(7-(quinolin-8-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{22}N_5O_3$: 490.19; found 490.09. HPLC retention time: 1.34 minutes (column B).

EXAMPLE 12



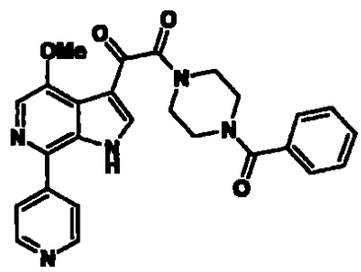
Example 12, was prepared according to the general method described above starting from Precursor 5a and 2,4-dimethoxypyrimidin-5-yl boronic acid, Precursor 14a-4, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(2,4-dimethoxy-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{27}N_6O_5$: 515.20; found 515.28. HPLC retention time: 1.17 minutes (column B).

EXAMPLE 13



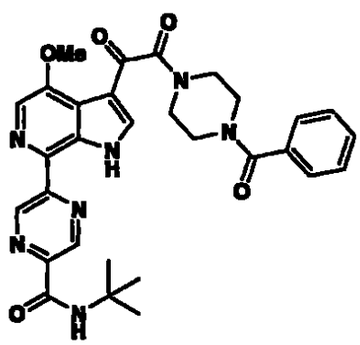
Example 13, was prepared according to the general method described above starting from Precursor 5b and 2,4-dimethoxypyrimidin-5-yl boronic acid, Precursor 14a-4, to provide 1-benzoyl-4-[(4-methoxy-7-(2,4-dimethoxy-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine ^1H NMR (500 MHz, CD_3OD) δ 8.71 (s, 1H), 8.64 (s, 1H), 8.21 (s, 1H), 7.48 (s, 5H), 4.15 (s, 3H), 4.13 (s, 3H), 3.84 (s, 3H), 3.64 – 3.34 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{29}N_6O_6$: 531.20; found 531.26. HPLC retention time: 1.09 minutes (column A).

EXAMPLE 14



Example 14, was prepared according to the general method described above starting from Precursor 5b and pyridin-4-yl boronic acid to provide 1-benzoyl-4-[(4-methoxy-7-(pyridin-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_5O_4$: 470.18; found 470.32. HPLC retention time: 1.02 minutes (column A).

EXAMPLE 15



Typical procedure for coupling azaindole with aromatic tin reagent (An example of the general procedure described below for examples 16-53):

Preparation of Example 15, 1-benzoyl-4-[(4-methoxy-7-(2-(1,1-dimethylethylaminocarbonyl)-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine is an example of Step E as described in Scheme 15. To a sealed tube, 1-benzoyl-4-[(7-chloro-4-methoxy-6-azaindol-3-yl)-oxoacetyl]piperazine, Precursor 5b, (20 mg), 2-

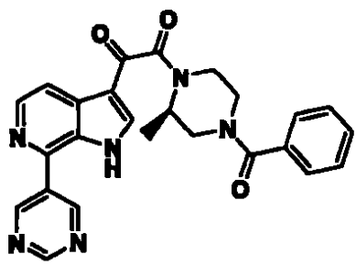
(1,1-dimethylethylaminocarbonyl)-5-tributylstannyl-pyrazine (1.2 equivalents, 27 mg.) and $Pd(Ph_3P)_4$ (1 mg) were combined in 1.5 mL of dioxane. The reaction was heated at 110-120 °C for 10 h. After the mixture cooled down to room temperature, it was poured into 5 mL of water. The solution was extracted with EtOAc (4 x 5 mL). The combined extract was concentrated *in vacuo* to give a residue which was purified using a Shimadzu automated preparative HPLC System to give compound 1-benzoyl-4-[(4-methoxy-7-(2-(1,1-dimethylethylaminocarbonyl)-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine (1 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{32}N_7O_5$: 570.25; found 570.43. HPLC retention time: 1.83 minutes (column B).

EXAMPLES 16-54

Examples 16-54 were prepared according to the following general procedure by a method analogous to the method described for the preparation of Example 15.

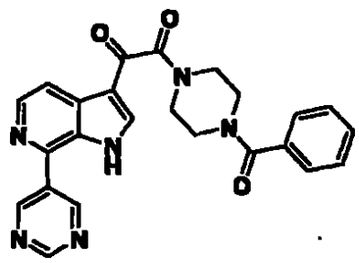
Typical procedure for coupling azaindole with aromatic tin reagent: To a sealed tube, an appropriate azaindole (0.049 mmol), an appropriate stannane (0.059 mmol) and $Pd(Ph_3P)_4$ (1 mg) were combined in 1.5 mL of dioxane. The reaction was heated at 110-120 °C for 10 h. After the mixture cooled down to rt, it was poured into 5 mL of water. The solution was extracted with EtOAc (4 x 5 mL). The combined extract was concentrated to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide the desired compound.

EXAMPLE 16



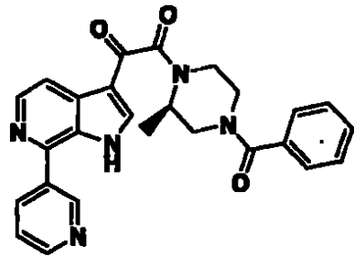
Example 16, was prepared according to the general method described above starting from Precursor 5a and pyrimidin-5-yl tributyltin, Precursor 14-9, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_3$: 455.18; found 455.17. HPLC retention time: 1.33 minutes (column B).

EXAMPLE 17



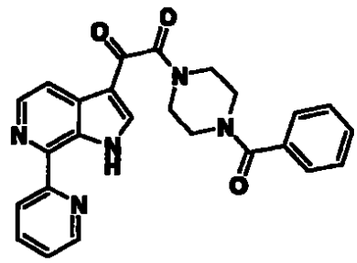
Example 17, was prepared according to the general method described above starting from Precursor 5g and pyrimidin-5-yl tributyltin, Precursor 14-9, to provide 1-benzoyl-4-[(7-(pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_3$: 441.17; found 441.07. HPLC retention time: 1.30 minutes (column B).

EXAMPLE 18



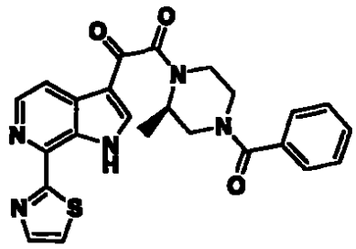
Example 18, was prepared according to the general method described above starting from Precursor 5a and pyridin-3-yl tributyltin, Precursor 14a-2, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(pyridin-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_5O_3$: 454.19; found 454.17. HPLC retention time: 1.11 minutes (column A).

EXAMPLE 19



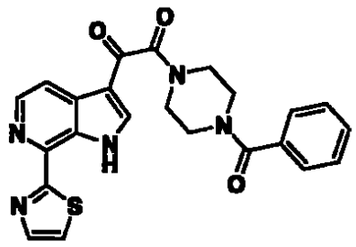
Example 19, was prepared according to the general method described above starting from Precursor 5g and pyridin-2-yl tributyltin, Precursor 14a-19, to provide 1-benzoyl-4-[(7-(pyridin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{22}N_5O_3$: 440.17; found 440.07. HPLC retention time: 1.40 minutes (column B).

EXAMPLE 20



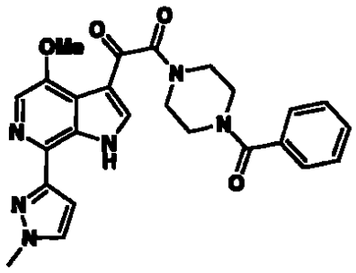
Example 20, was prepared according to the general method described above starting from Precursor 5a and thiazol-2-yl tributyltin, Precursor 14a-21, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(thiazol-2-yl)-6-azaindol-3-yl)oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_5O_3S$: 460.14; found 460.15. HPLC retention time: 1.48 minutes (column B).

EXAMPLE 21



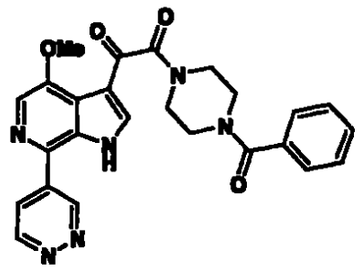
Example 21, was prepared according to the general method described above starting from Precursor 5g and thiazol-2-yl tributyltin, Precursor 14a-21, to provide 1-benzoyl-4-[(7-(thiazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{20}N_5O_3S$: 446.13; found 446.03. HPLC retention time: 1.44 minutes (column B).

EXAMPLE 22



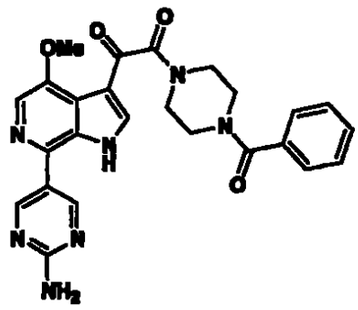
Example 22, was prepared according to the general method described above starting from Precursor 5b and 1-methylpyrazol-3-yl tributyltin, to provide 1-benzoyl-4-[(4-methoxy-7-(1-methyl-pyrazol-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_6O_4$: 473.19; found 473.28. HPLC retention time: 1.18 minutes (column B).

EXAMPLE 23



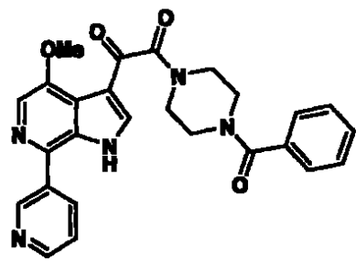
Example 23, was prepared according to the general method described above starting from Precursor 5b and Intermediate 14-9 to provide 1-benzoyl-4-[(4-methoxy-7-(pyridazin-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.26. HPLC retention time: 1.20 minutes (column B).

EXAMPLE 24



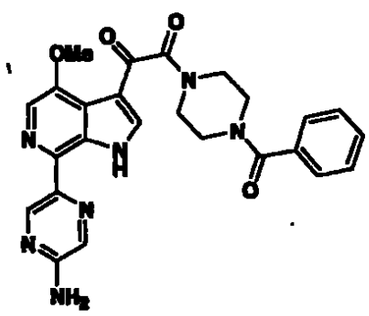
Example 24, was prepared according to the general method described above starting from Precursor 5b and 2-aminopyrimidin-5-yl tributyltin, to provide 1-benzoyl-4-[(4-methoxy-7-(2-amino-pyrimidin-5-yl))-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for for $C_{25}H_{24}N_7O_4$: 486.19: found 486.24. HPLC retention time: 1.19 minutes (column A).

EXAMPLE 25



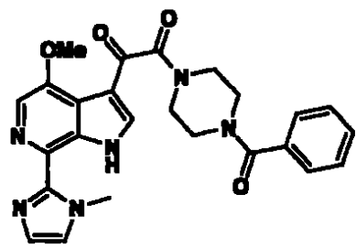
Example 25, was prepared according to the general method described above starting from Precursor 5b and pyridin-3-yl tributyltin, Precursor 14a-2, to provide 1-benzoyl-4-[(4-methoxy-7-(pyridin-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_5O_4$: 470.18; found 470.19. HPLC retention time: 1.04 minutes (column A).

EXAMPLE 26



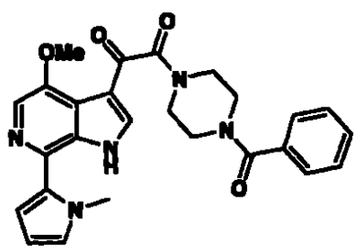
Example 26, was prepared according to the general method described above starting from Precursor 5b and 2-aminopyrazin-5-yl trimethyltin, Precursor 14-28, to provide 1-benzoyl-4-[(4-methoxy-7-(2-amino-pyrazin-5-yl))-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 470.19. HPLC retention time: 1.13 minutes (column B).

EXAMPLE 27



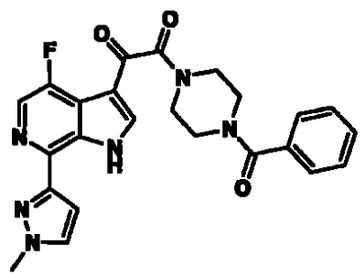
Example 27, was prepared according to the general method described above starting from Precursor 5b and 1-methylimidazol-2-yl trimethyltin, Precursor 14-5, to provide 1-benzoyl-4-[(4-methoxy-7-(1-methyl-imidazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_6O_4$: 473.18; found 473.27. HPLC retention time: 1.07 minutes (column B).

EXAMPLE 28



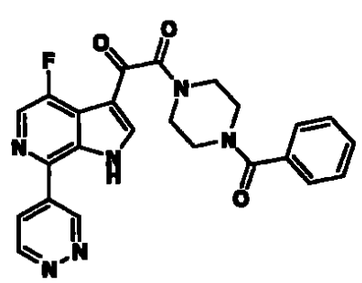
Example 28, was prepared according to the general method described above starting from Precursor 5b and 1-methylpyrrol-2-yl tributyltin, Precursor 14a-15, to provide 1-benzoyl-4-[(4-methoxy-7-(1-methyl-pyrrol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_5O_4$: 472.20; found 470.26. HPLC retention time: 1.11 minutes (column A).

EXAMPLE 29



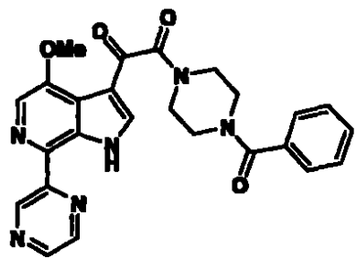
Example 29, was prepared according to the general method described above starting from Precursor 5i and 1-methylpyrazol-3-yl tributyltin, to provide 1-benzoyl-4-[(4-fluoro-7-(1-methyl-pyrazol-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}FN_6O_3$: 461.17; found 461.24. HPLC retention time: 1.36 minutes (column A).

EXAMPLE 30



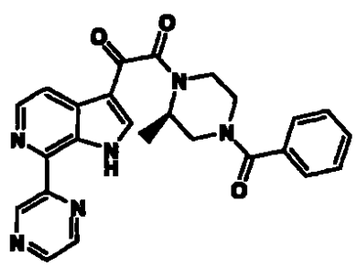
Example 30, was prepared according to the general method described above starting from Precursor 5i and pyridazin-4-yl tributyltin, Precursor 14-8, to provide 1-benzoyl-4-[(4-fluoro-7-(pyridazin-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine ^{1}H NMR (500 MHz, CD_3OD) δ 9.72 (s, 1H), 9.39 (s, 1H), 8.42 (m, 2H), 8.22 (s, 1H), 7.47 (s, 5H), 3.84 – 3.38 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{20}FN_6O_3$: 459.16; found 459.25. HPLC retention time: 1.26 minutes (column A).

EXAMPLE 32



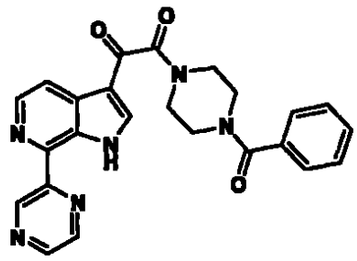
Example 32, was prepared according to the general method described above starting from Precursor 5b and pyrazin-2-yl tributyltin, Precursor 14a-1, to provide 1-benzoyl-4-[(4-methoxy-7-(pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_3$: 471.18; found 471.17. HPLC retention time: 1.35 minutes (column A).

EXAMPLE 33



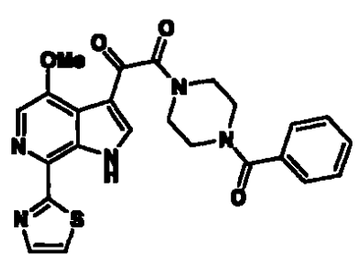
Example 33, was prepared according to the general method described above starting from Precursor 5a and pyrazin-2-yl tributyltin, Precursor 14a-1, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_3$: 455.18; found 455.26. HPLC retention time: 1.46 minutes (column A).

EXAMPLE 34



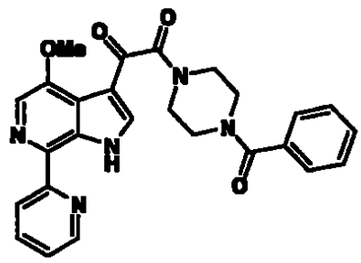
Example 34, was prepared according to the general method described above starting from Precursor 5g and pyrazin-2-yl tributyltin, Precursor 14a-1, to provide 1-benzoyl-4-[(7-(pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{21}N_6O_3$: 441.17; found 441.22. HPLC retention time: 1.22 minutes (column A).

EXAMPLE 35



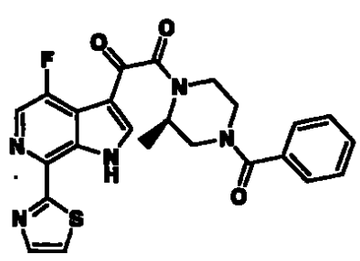
Example 35, was prepared according to the general method described above starting from Precursor 5b and thiazol-2-yl tributyltin, Precursor 14a-21, to provide 1-(benzoyl)-4-[(4-methoxy-7-(thiazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_5O_3S$: 476.14; found 476.20. HPLC retention time: 1.25 minutes (column B).

EXAMPLE 36



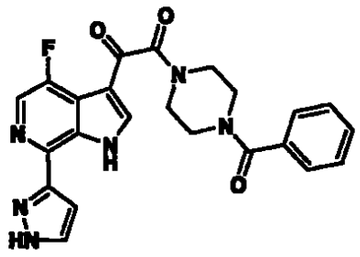
Example 36, was prepared according to the general method described above starting from Precursor 5b and pyridin-2-yl tributyltin, Precursor 14a-19, to provide 1-benzoyl-4-[(4-methoxy-7-(pyridin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_5O_4$: 470.18; found 470.17. HPLC retention time: 1.04 minutes (column A).

EXAMPLE 37



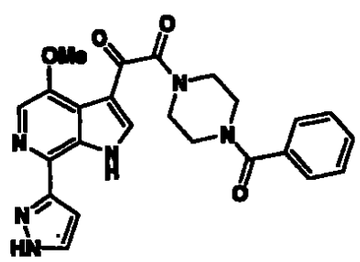
Example 37, was prepared according to the general method described above starting from Precursor 5j and thiazol-2-yl tributyltin, Precursor 14a-21, to provide 1-benzoyl-3-(R)-methyl-4-[(4-fluoro-7-(thiazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{21}FN_5O_3S$: 478.13; found 478.13. HPLC retention time: 1.34 minutes (column A).

EXAMPLE 38



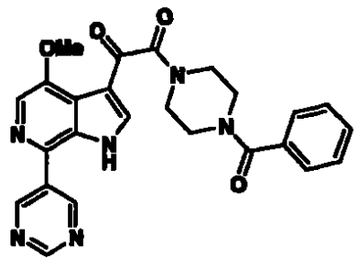
Example 38, was prepared according to the general method described above starting from Precursor 5i and pyrazol-3-yl tributyltin, to provide 1-benzoyl-4-[(4-fluoro-7-(pyrazol-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{20}FN_6O_3$: 447.16; found 447.15. HPLC retention time: 1.26 minutes (column A).

EXAMPLE 39



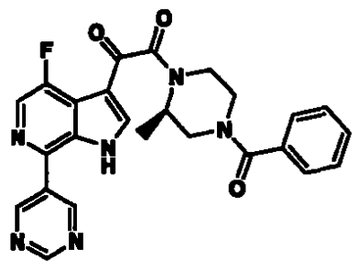
Example 39, was prepared according to the general method described above starting from Precursor 5b and pyrazol-3-yl tributyltin, to provide 1-benzoyl-4-[(4-methoxy-7-(pyrazol-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{23}N_6O_4$: 459.18; found 459.21. HPLC retention time: 1.11 minutes (column A).

EXAMPLE 40



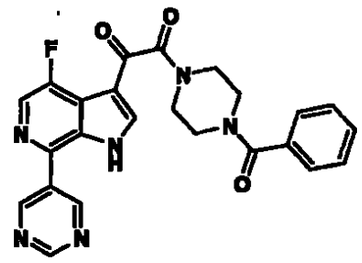
Example 40, was prepared according to the general method described above starting from Precursor 5b and pyrimidin-5-yl tributyltin, Precursor 14-9, to provide 1-benzoyl-4-[(4-methoxy-7-(pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.20. HPLC retention time: 1.61 minutes (column A).

EXAMPLE 41



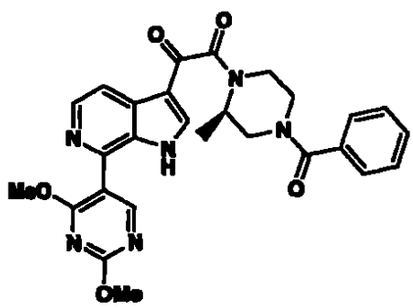
Example 41, was prepared according to the general method described above starting from Precursor 5j and pyrimidin-5-yl tributyltin, Precursor 14-9, to provide 1-benzoyl-3-(R)-methyl-4-[(4-fluoro-7-(pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; ^{1}H NMR (500 MHz, CD_3OD) δ 9.26 (m, 3H), 8.39 (m, 2H), 7.56 (m, 5H), 4.72 – 3.12 (m, 7H), 1.40 – 0.91 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{22}FN_6O_3$: 473.17; found 473.17. HPLC retention time: 1.34 minutes (column A).

EXAMPLE 42



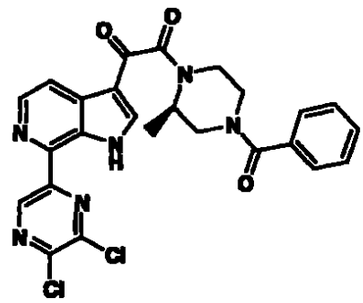
Example 42, was prepared according to the general method described above starting from Precursor 5i and pyrimidin-5-yl tributyltin, Precursor 14-9, to provide 1-benzoyl-4-[(4-fluoro-7-(pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{20}FN_6O_3$: 459.16; found 459.14. HPLC retention time: 1.28 minutes (column A).

Example 43



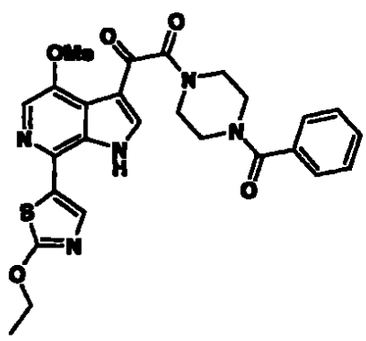
Example 43, (R)-1-(benzoyl)-3-methyl-4-[(7-(2,4-dimethoxy-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{27}N_6O_5$: 515.20; found 515.28. HPLC retention time: 1.17 minutes (column B).

EXAMPLE 44



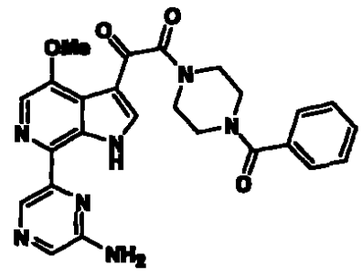
Example 44, was prepared according to the general method described above starting from Precursor 5a and 2,3-dichloropyrazin-5-yl tributyltin, Precursor 14-66, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(2,3-dichloro-pyrazin-5-yl) –6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+Na)^+$ Calc'd for $C_{25}H_{20}Cl_2NaN_6O_3$: 545.09; found 545.29. HPLC retention time: 1.87 minutes (column B).

EXAMPLE 45



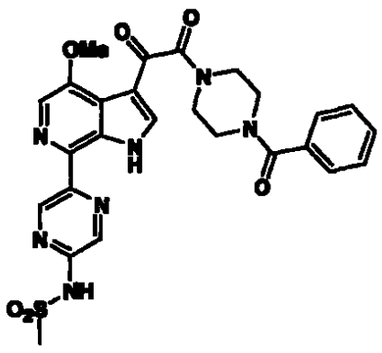
Example 45, was prepared according to the general method described above starting from Precursor 5b and 2-ethoxythiazol-5-yl tributyltin, Precursor 14-71, to provide 1-benzoyl-4-[(4-methoxy-7-(2-ethoxy-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_5O_5S$: 520.17; found 520.24. HPLC retention time: 1.32 minutes (column A).

EXAMPLE 46



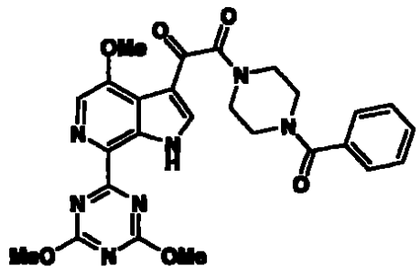
Example 46, was prepared according to the general method described above starting from Precursor 5b and the 2-amino-pyrazin-6-yl stannane, Precursor 14-68, to provide 1-benzoyl-4-[(4-methoxy-7-(2-amino-pyrazin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 486.31. HPLC retention time: 1.22 minutes (column B).

EXAMPLE 47



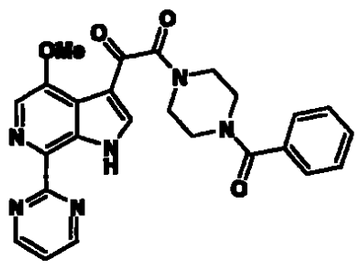
Example 47, was prepared according to the general method described above starting from Precursor 5b and 2-methylsulfonylamino-5-(tri-n-butylstannyl)pyrazine, Precursor 14-69, to provide 1-benzoyl-4-[(7-(2-methylsulfonylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_7O_6S$: 564.17; found 564.21. HPLC retention time: 1.24 minutes (column A).

EXAMPLE 48



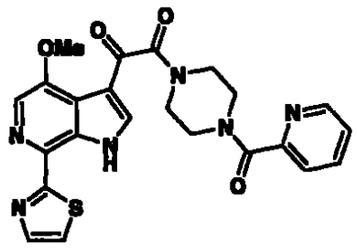
Example 48, was prepared according to the general method described above starting from Precursor 5b and 2,4-dimethoxy-1,3,5-triazin-6-yl tributyltin, Precursor 14-70, to provide 1-benzoyl-4-[(7-(2,4-dimethoxy-1,3,5-triazin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_7O_6$: 532.19; found 532.12. HPLC retention time: 1.28 minutes (column A).

EXAMPLE 49



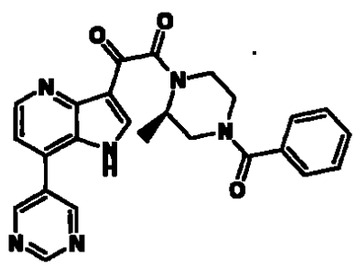
Example 49, was prepared according to the general method described above starting from Precursor 5b and pyrimidin-2-yl tributyltin, Precursor 14-67, to provide 1-benzoyl-4-[(4-methoxy-7-(pyrimidin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.29. HPLC retention time: 1.21 minutes (column A).

EXAMPLE 50



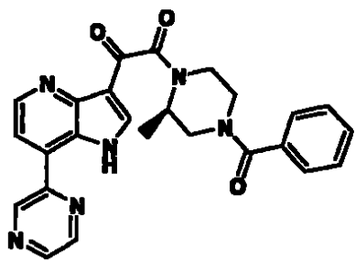
Example 50, was prepared from1-(pyridin-2-yl)-4-[(4-methoxy-7-chloro-6-azaindol-3-yl)-oxoacetyl]piperazine and thiazol-2-yl tributyltin, Precursor 14a-21, according to the general method above to provide 1-(pyridin-2-yl)-4-[(4-methoxy-7-(thiazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{25}N_6O_4S$: 477.13; found 477.22. HPLC retention time: 0.98 minutes (column A).

EXAMPLE 51



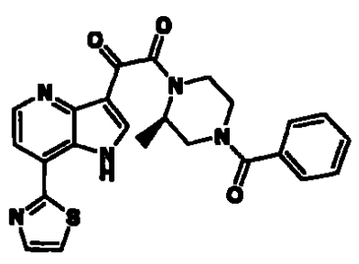
Example 51, was prepared according to the general method described above starting from Precursor 5d and pyrimidin-5-yl tributyltin, Precursor 14-9, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(pyrimidin-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_3$: 455.18; found 455.16. HPLC retention time: 0.98 minutes (column A).

EXAMPLE 52



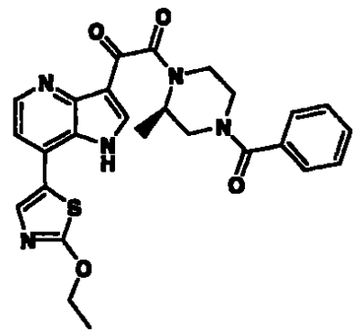
Example 52, was prepared according to the general method described above starting from Precursor 5d and pyrimidin-2-yl tributyltin, Precursor 14a-1, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(pyrazin-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_3$: 455.18; found 455.16. HPLC retention time: 1.09 minutes (column A).

EXAMPLE 53



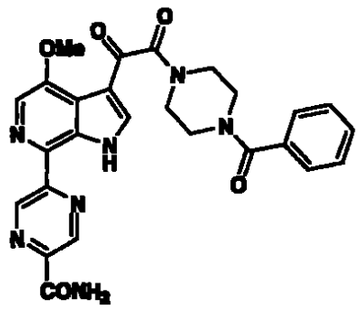
Example 53, was prepared according to the general method described above starting from Precursor 5d and thiazol-2-yl tributyltin, Precursor 14a-21, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(thiazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_5O_3S$: 460.14; found 460.26. HPLC retention time: 1.02 minutes (column A).

EXAMPLE 54



Example 54, was prepared according to the general method described above starting from Precursor 5d and 2-ethoxythiazol-5-yl tributyltin, Precursor 14-71, to provide 1-benzoyl-3-(R)-methyl-4-[(7-(2-ethoxy-thiazol-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_5O_4S$: 504.17; found 4504.18. HPLC retention time: 1.26 minutes (column A).

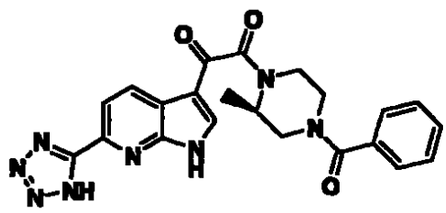
EXAMPLE 55



The compound of Example 15, 1-benzoyl-4-[(4-methoxy-7-(2-(1,1-dimethylethylaminocarbonyl)-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine (20 mg) was dissolved in 1 drop of concentrated sulfuric acid. After 30 minutes, the mixture was diluted with 2 mL of methanol. The resulting solution was injected into a Shimadzu automated preparative HPLC System and the HPLC purification afforded the compound of Example 55, 1-benzoyl-4-[(4-methoxy-7-(2-aminocarbonyl-pyrazin-

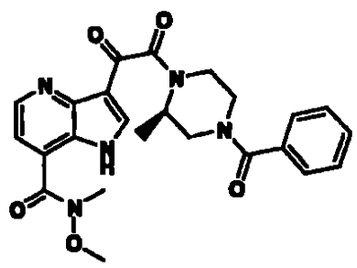
5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine (1 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_7O_5$: 514.78; found 514.22. HPLC retention time: 1.44 minutes (column B).

EXAMPLE 56



An excess of NH_4Cl (27mg) was added into a solution of 1-(benzoyl)-3-(R)-methyl-4-[(6-cyano-7-azaindol-3-yl)-oxoacetyl]piperazine (20 mg) and NaN_3 (16 mg) in DMF. The reaction was heated to reflux for 12 h. After cooling down, the mixture was concentrated under reduced pressure and the residue was purified using Shimadzu automated preparative HPLC System to give 1-benzoyl-3-(R)-methyl-4-[(6-(tetrazol-1-yl)-7-azaindol-3-yl)-oxoacetyl]piperazine (6.3mg). MS *m/z*: $(M+H)^+$ Calc'd for $C_{22}H_{21}N_8O_3$: 445.17; Found 3445.16. HPLC retention time: 1.42 minutes (column B); Column B: PHX-LUNA C18 4.6 x 30 mm.

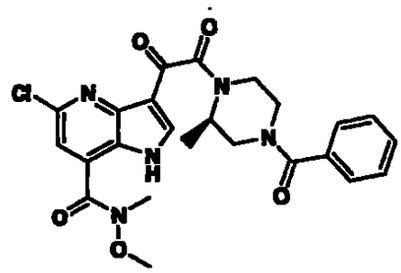
EXAMPLE 57



Preparation of 1-benzoyl-3-(R)-methyl-4-[(7-(methoxymethylamino)carbonyl)-4-azaindol-3-yl)-oxoacetyl]piperazine: A mixture of Precursor 13 (267 mg), N,O-dimethylhydroxylamine hydrogen chloride (248 mg), carbon tetrabromide (844 mg), pyridine (202 mg) and triphenylphosphine (668 mg) in

dichloromethane (10 mL) was stirred at room temperature for 10 hours. After solvent was removed under vaccum, the residue was purified by using silica gel chromatography to afford 1-(benzoyl)-3-(R)-methyl-4-[(7-(methoxymethylamino)carbonyl)-4-azaindol-3-yl)-oxoacetyl]piperazine (56 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{26}N_5O_5$: 464.19; found 464.25. HPLC retention time: 1.02 minutes (column A).

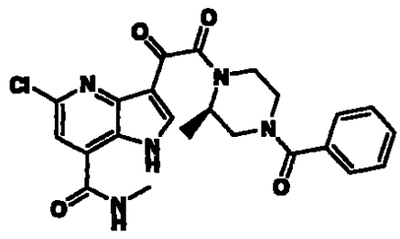
EXAMPLE 58



Example 58 was prepared according to the same procedure used in preparing Example 57 with the exception of using Precursor 11 as a starting material instead of Precursor 13. The procedure provided 1-benzoyl-3-(R)-methyl-4-[(5-chloro-(7-(methoxymethylamino)carbonyl)-4-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{25}ClN_5O_5$: 498.15; found 498.12. HPLC retention time: 1.39 minutes (column A).

General procedure A to prepare CO-NR1R2 fromCOOH

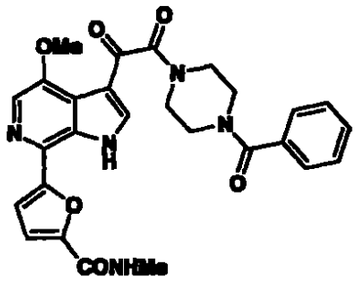
EXAMPLE 59



Preparation of 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(methylamino)carbonyl)-4-azaindol-3-yl)-oxoacetyl]piperazine: A mixture of Precursor 11 (25 mg), methylamine (2M in THF, 0.08 mL), EDC (26 mg), HOBT (11.2 mg) and diisopropylethylamine (43 mg) in tetrahydrofuran (5 mL) was stirred at room temperature for 10 hours. After the solvent was removed under vaccum, the residue was purified by using silica gel chromatography to afford 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(methylamino)carbonyl)-4-azaindol-3-yl)-oxoacetyl]piperazine (13.6 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{29}ClN_5O_4$: 468.14; found 468.03. HPLC retention time: 1.33 minutes (column A).

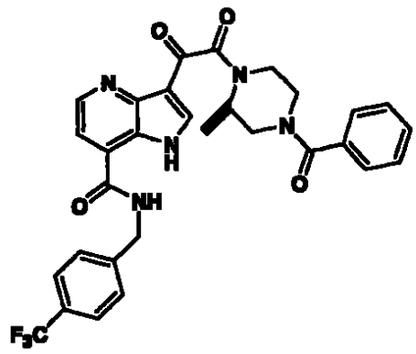
This general produre A is applied to prepare examples 94 and 135:

EXAMPLE 94



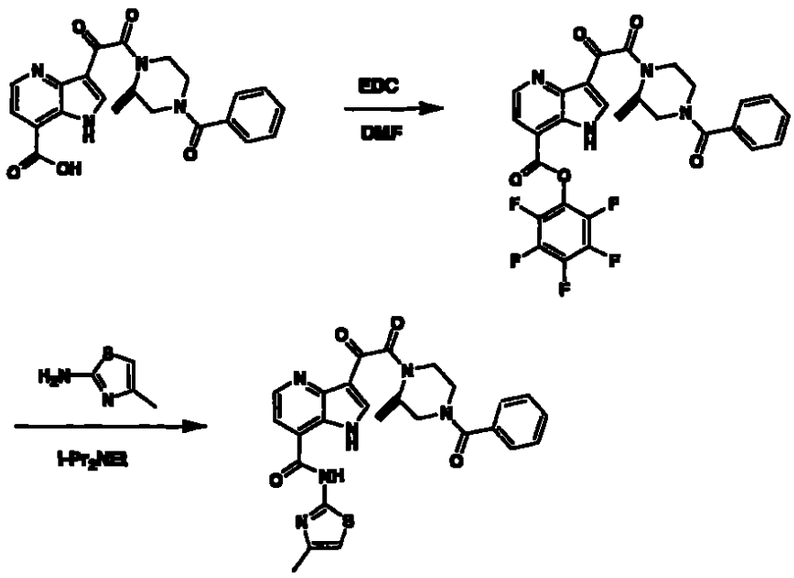
Example 94,1-benzoyl-4-[(4-methoxy-7-(2-methylaminocarbonyl-furan-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^1H NMR (500 MHz, CD_3OD) δ8.37 (s, 1H), 8.06 (s, 1H), 7.48 – 7.26 (m, 7H), 4.08 (s, 3H), 3.83 – 3.44 (m, 8H), 2.96 (s, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{26}N_5O_6$: 516.19; found 516.14. HPLC retention time: 1.35 minutes (column A).

EXAMPLE 135



Example 135, (R)-1-benzoyl-3-methyl-4-[(7-(4-trifluoromethylbenzylamino) carbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{27}F_3N_5O_4$: 578.20; found 578.39. HPLC retention time: 1.47 minutes (column G).

General procedure B to prepare CO-NR1R2 fromCOOH



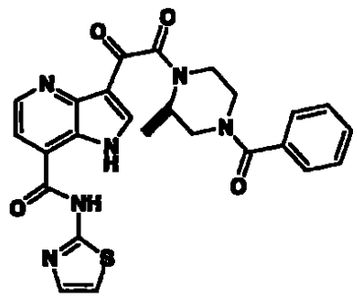
Preparation of Example 136, (R)-1-benzoyl-3-methyl-4-[(7-(4-methylthiazol-2-yl)aminocarbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine:

To a solution of (R)-1-benzoyl-3-methyl-4-[(7-hydroxylcarbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine (146mg) in DMF (5ml) at room temperature was added pentafluorophenyl (70.3mg) followed by EDC (73.23mg). The reaction mixture was stirred at room temperature for 8 hours. The crude product was diluted with methylene chloride and was washed with water, 0.1N HCl and brine. The organic phase was dried over MgSO4, filtered and concentrated. The pentafluorophenyl ester was used in the following reaction without further purification.

To a stirred solution of 4-methyl-2-amino-thiazole (39.6mg) and Hunig's base (49.4mg) in DMF (5ml) at room temperature was added a solution of pentafluorophenyl ester (1/3 of the product obtained in the previous step described above) in DMF (2 ml). The reaction mixture was stirred at room temperature for 16 hours. The crude product was diluted with methylene chloride and was washed with Na2CO3 (sat.) and brine. The organic phase was dried over MgSO4, filtered and concentrated. The residue was purified using Shimadzu automated preparative HPLC System to give (R)-1-benzoyl-3-methyl-4-[(7-(4-methylthiazol-2-yl)aminocarbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine (3.6mg). MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_4S$: 517.17; found 517.41. HPLC retention time: 1.25 minutes (column A).

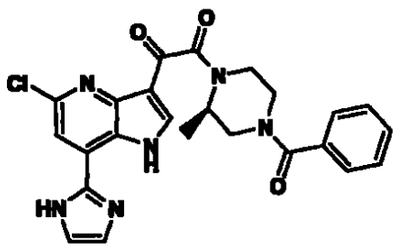
This general produre B is applied to prepare example 137:

EXAMPLE 137



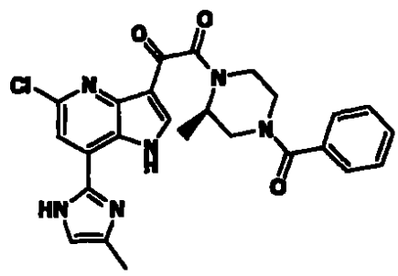
Example 137, (R)-1-benzoyl-3-methyl-4-[(7-(thiazol-2-yl)aminocarbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4S$: 503.15; found 503.29. HPLC retention time: 1.33 minutes (column A).

EXAMPLE 60



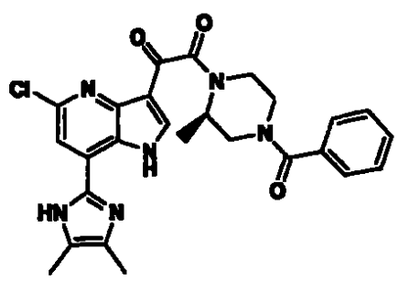
Preparation of 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(imidazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine: A mixture of Precursor-10 (34 mg), glyoxal (40% in water, 0.2 mL) and ammonia acetate (139 mg) in methanol was heated up to reflux for 10 hours. After cooling down, the mixture was concentrated under reduced pressure and the residue was purified using Shimadzu automated preparative HPLC System to provide 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(imidazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine (1.8 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}ClN_6O_3$: 477.14; found 477.13. HPLC retention time: 1.17 minutes (column A).

EXAMPLE 61



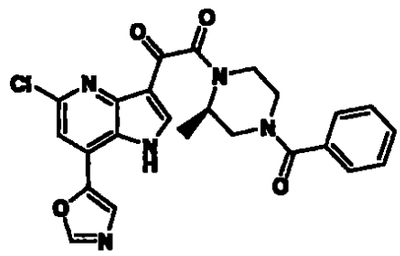
Example 61 was prepared according to the same procedure used for preparing Example 60 with the exception of using methylglyoxal as a starting material instead of glyoxal to provide1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(4-methyl-imidazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}ClN_6O_3$: 491.16; found 491.13. HPLC retention time: 1.26 minutes (column A).

EXAMPLE 62



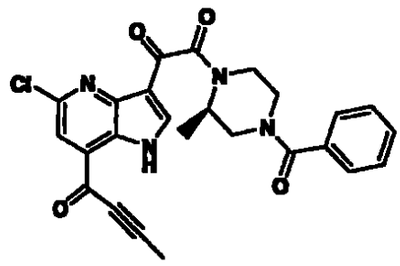
Example 62 was prepared according to the same procedure used for preparing Example 60 with the exception of using dimethylglyoxal as a starting material instead of glyoxal to provide 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(4,5-dimethyl-imidazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}ClN_6O_3$: 505.18; found 505.10. HPLC retention time: 1.24 minutes (column A).

EXAMPLE 63



Preparation of 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(oxazol-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine: A mixture of Precursor 10 (27.6 mg), tosylmethyl isocyanide (12.3 mg) and K_2CO_3 (8.7 mg) in MeOH was heated up to reflux for 10 hours. After cooling down, the mixture was concentrated under reduced pressure and the residue was purified using Shimadzu automated preparative HPLC System to provide 1-(benzoyl)-3-(R)-methyl-4-[(5-chloro-7-(oxazol-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine (17.7 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{21}ClN_5O_4$: 478.13; found 478.03. HPLC retention time: 1.48 minutes (column A).

EXAMPLE 64

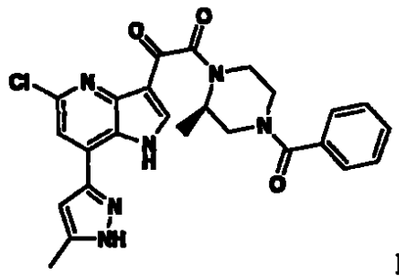


I-64

Step 1: Preparation of I-64, 1-benzoyl-3-(R)-methyl-4-[(7-(2-propynyl)carbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine: Propynyllithium (21 mg) was added to a solution of Example 52 (41 mg) in tetrahydrofuran (5 ml) at –78°C. The reaction was quenched with methanol at –25°C in 2 hours. After solvents were removed under vaccum, the residue was carried to the further reactions without any purification.

I-64, 1-benzoyl-3-(R)-methyl-4-[(7-(2-propynyl)carbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{22}ClN_4O_4$: 477.13; found 477.17. HPLC retention time: 1.46 minutes (column A).

Step 2: Preparation of Example 64:



Example 64

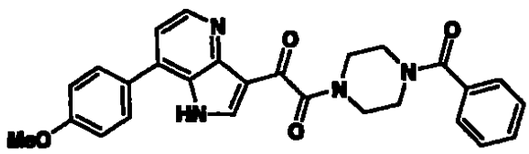
Preparation of Example 64, 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(3-methyl-pyrazol-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine: A mixture of I-64 . (crude product from Step 1) and hydrazine (0.22 mL) in EtOAc (2 mL) and water (2 mL) was stirred at room temperature for 24 hours. Then solvents were removed under vaccum, and the residue was purified using Shimadzu automated preparative HPLC System to give 1-benzoyl-3-(R)-methyl-4-[(5-chloro-7-(3-methyl-pyrazol-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine (9 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}ClN_6O_3$: 491.16; found 491.19. HPLC retention time: 1.42 minutes (column A).

EXAMPLES 65-67

The procedure for the preparation of Examples 65-67 is the same as that described previously for the preparation of Precursor 5a and is as follows: Potassium 7-(4-methoxyphenyl)-4-azaindole-3-glyoxylate, Precursor 4c (147 mg, 0.44 mmol), an appropriate 1-benzoylpiperazine derivative (0.44 mmol), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) (101 mg, 0.44 mol) and Hunig's Base (0.5 mL) were combined in 5 mL of DMF. The mixture was stirred at rt for 8 h. DMF was removed *via* evaporation at reduced pressure and the residue was purified using a Shimadzu automated preparative HPLC System to give

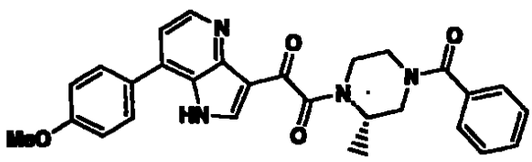
the corresponding 1-benzoyl-4-[(7-(4-methoxyphenyl)-4-azaindol-3-yl)-oxoacetyl]-piperazine derivative.

EXAMPLE 65



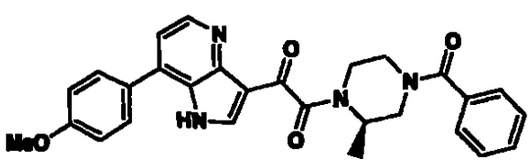
Example 19, 1-(benzoyl)-4-[(7-(4-methoxy)-4-azaindol-3-yl)-oxoacetyl]piperazine was prepared from potassium 7-(4-methoxyphenyl)-4-azaindole-3-glyoxylate and 1-(benzoyl)piperazine according to the above general procedure. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{25}N_4O_4$: 469.19; found 469.16. HPLC retention time: 1.26 minutes (column A).

EXAMPLE 66



Example 66, 1-benzoyl-3-(S)-methyl-4-[(7-(4-methoxy)-4-azaindol-3-yl)-oxoacetyl]piperazine was prepared from potassium 7-(4-methoxyphenyl)-4-azaindole-3-glyoxylate and the corresponding 1-(benzoyl)-3-methylpiperazine according to the above general procedure. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{27}N_4O_4$: 483.20; found 483.17. HPLC retention time: 1.30 minutes (column A).

EXAMPLE 67

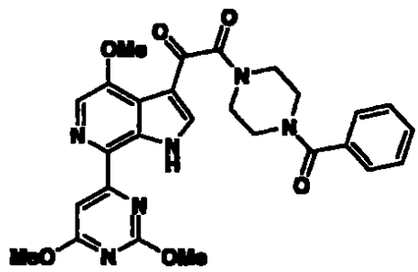


Example 67, 1-benzoyl-3-(R)-methyl-4-[(7-(4-methoxyphenyl)-4-azaindol-3-yl)oxoacetyl]piperazine was prepared from potassium 7-(4-methoxyphenyl)-4-azaindole-3-glyoxylate and the corresponding 1-benzoyl-3-methylpiperazine according to the above general procedure. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{27}N_4O_4$: 483.20; found 483.16. HPLC retention time: 1.28 minutes (column A).

EXAMPLES 68-79 and 81

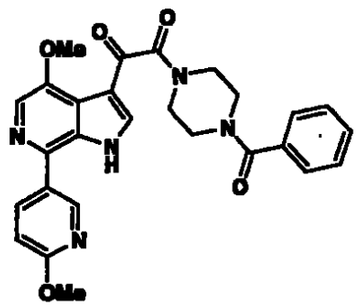
Examples 68-79 and 81 were prepared according to the same general method as previously described for Examples 16-54.

EXAMPLE 68



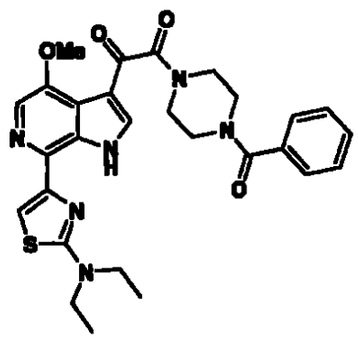
Example 68, was prepared from Precursor 5b and the 2,4-dimethoxypyrimidin-6-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2,6-dimethoxy-pyrimidin-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.13 (s, 1H), 7.52 (s, 1H), 7.42 (m, 5H), 4.11 (s, 3H), 4.06 (s, 3H), 4.00 – 3.40 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{27}N_6O_6$: 531.20; found 531.24. HPLC retention time: 1.54 minutes (column A).

EXAMPLE 69



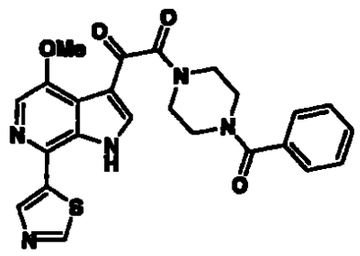
Example 69, was prepared from Precursor 5b and the 6-methoxypyridin-3-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(6-methoxy-pyridin-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ 8.69 (s, 1H), 8.63 (s, 1H), 8.11 (m, 2H), 7.49 (m, 5H), 7.10 (d, 1H, J = 8.65 Hz), 4.16 (s, 3H), 4.06 (s, 3H), 4.00 – 3.40 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{26}N_5O_5$: 500.09; found 500.20. HPLC retention time: 1.11 minutes (column A).

EXAMPLE 70



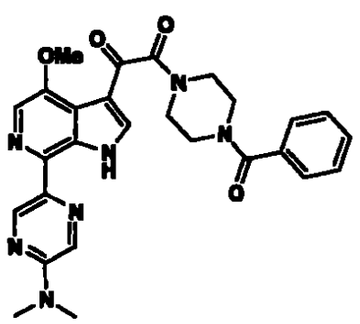
Example 70, was prepared from Precursor 5b and the 2-diethylamino-thiazol-4-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-diethylamino-thiazol-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ 8.47 (s, 1H), 7.97 (m, 2H), 7.49 (m, 5H), 4.08 (s, 3H), 3.64 (m, 12H), 1.35 (m, 6H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{31}N_6O_4S$: 547.21; found 547.22. HPLC retention time: 1.35 minutes (column A).

EXAMPLE 71



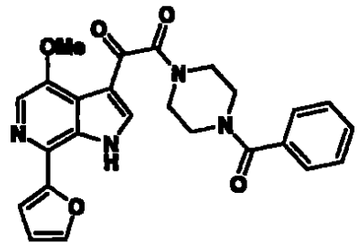
Example 71, was prepared from Precursor 5b and the thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.64 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.46 (m, 5H), 4.00 (s, 3H), 3.55 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_5O_4S$: 476.14; found 476.17. HPLC retention time: 1.13 minutes (column A).

EXAMPLE 72



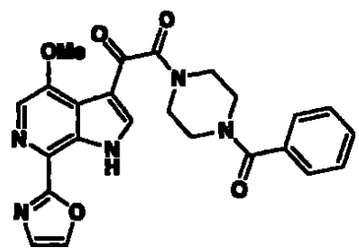
Example 72, was prepared from Precursor 5b and the 2-dimethylamino-pyrazin-5-yl stannane to provide 1-(benzoyl)-4-[(4-methoxy-7-(2-dimethylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{28}N_7O_4$: 514.22; found 514.29. HPLC retention time: 1.27 minutes (column A).

EXAMPLE 73



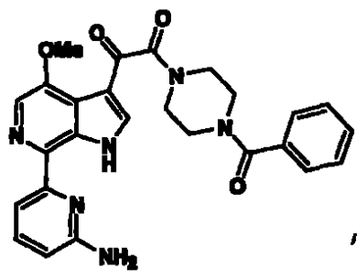
Example 73, was prepared from Precursor 5b and the furan-2-yl stannane to provide 1-(benzoyl)-4-[(4-methoxy-7-(furan-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_5$: 459.17; found 459.25. HPLC retention time: 1.15 minutes (column A).

EXAMPLE 74



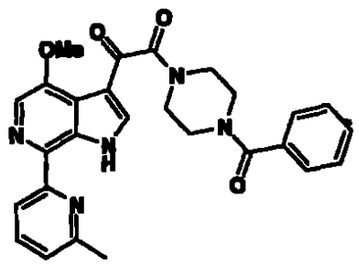
Example 74, was prepared from Precursor 5b and the oxazol-2-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(oxazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^1H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.64 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.46 (m, 5H), 4.00 (s, 3H), 3.55 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_5O_5$: 460.16; found 460.23. HPLC retention time: 1.22 minutes (column A).

EXAMPLE 75



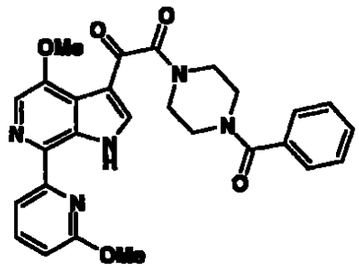
Example 75, was prepared from Precursor 5b and the 6-aminopyridin-2-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-aminopyridin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_4$: 485.19; found 485.24. HPLC retention time: 1.15 minutes (column A).

EXAMPLE 76



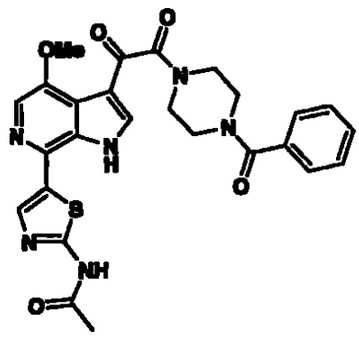
Example 76, was prepared from Precursor 5b and the 6-methylpyridin-2-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-methyl-pyridin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{26}N_5O_4$: 484.20; found 484.22. HPLC retention time: 1.24 minutes (column A).

EXAMPLE 77



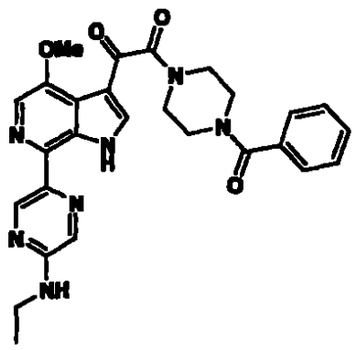
Example 77, was prepared from Precursor 5b and the 6-methoxypyridin-2-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-methoxy-pyridin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{26}N_5O_5$: 500.19; found 500.23. HPLC retention time: 1.26 minutes (column A).

EXAMPLE 78



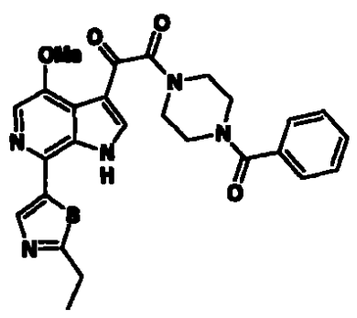
Example 78, was prepared from Precursor 5b and the 2-acetylamino-thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-acetylamino-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_5S$: 533.16; found 533.18. HPLC retention time: 1.21 minutes (column A).

EXAMPLE 79



Example 79, was prepared from Precursor 5b and the 2-ethylamino-pyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-ethylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{28}N_7O_4$: 514.22; found 514.18. HPLC retention time: 1.31 minutes (column A).

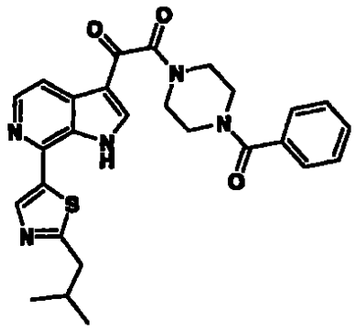
EXAMPLE 88



Example 88, was prepared from Precursor 5b and the 2-ethyl-thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-ethyl-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_5O_4S$: 504.17; found 514.32. HPLC retention time: 1.50 minutes (column A).

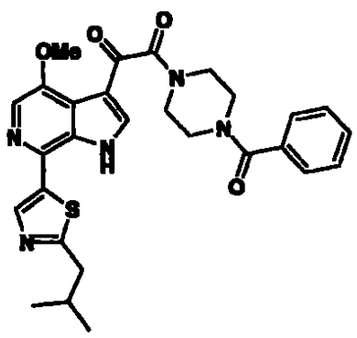
159

EXAMPLE 89



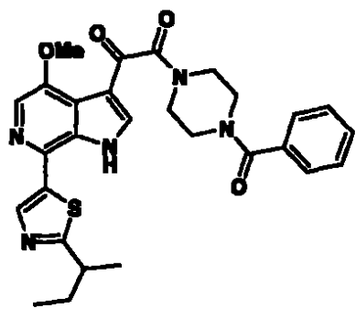
Example 89, was prepared from Precursor 5k and the 2-isobutyl-thiazol-5-yl stannane to provide 1-benzoyl-4-[(7-(2-isobutyl-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{28}N_5O_3S$: 502.19; found 502.26. HPLC retention time: 1.56 minutes (column E).

EXAMPLE 90



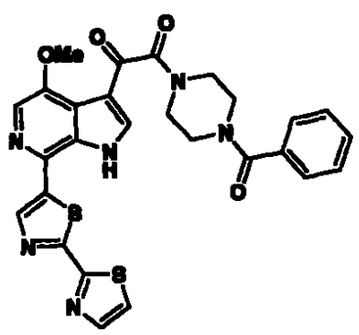
Example 90, was prepared from Precursor 5b and the 2-isobutyl-thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-isobutyl-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{30}N_5O_4S$: 532.20; found 532.27. HPLC retention time: 1.57 minutes (column E).

EXAMPLE 91



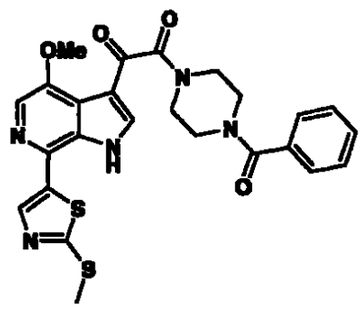
Example 91, was prepared from Precursor 5b and the 2-(2-butyl)-thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-(2-butyl)-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{30}N_5O_4S$: 532.20; found 532.27. HPLC retention time: 1.57 minutes (column E).

EXAMPLE 92



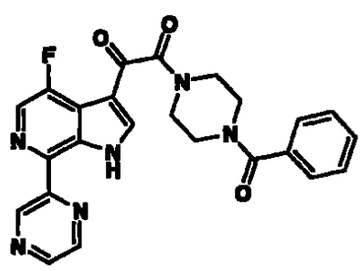
Example 92, was prepared from Precursor 5b and the 2-(thiazol-2-yl)-thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-(thiazol-2-yl)-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{23}N_6O_4S_2$: 559.12; found 559.18. HPLC retention time: 1.55 minutes (column E).

EXAMPLE 93



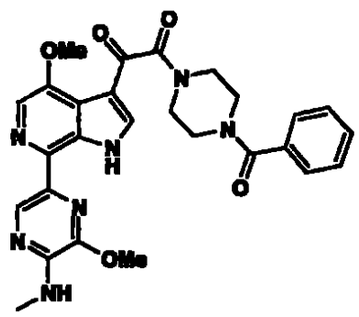
Example 93, was prepared from Precursor 5b and the 2-methylthio-thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-methylthio-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_5O_4S_2$: 522.13; found 522.17. HPLC retention time: 1.45 minutes (column E).

EXAMPLE 95



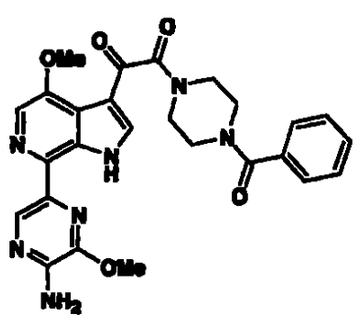
Example 95, was prepared from Precursor 5i and the pyrazin-2-yl stannane to provide 1-benzoyl-4-[(4-fluoro-7-(pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^1H NMR (500 MHz, $CDCl_3$) δ9.89 (s, 1H), 8.70 – 8.34 (m, 4H), 7.46 (m, 5H), 3.80 – 3.50 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{20}FN_6O_3$: 459.16; found 459.33. HPLC retention time: 1.46 minutes (column G).

EXAMPLE 100



Example 100, was prepared from Precursor 5b and the 2-methylamino-3-methoxy-pyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-methylamino-3-methoxy-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.65 (s, 1H), 8.43 (s, 1H), 7.95 (s, 1H), 7.45 (m, 5H), 4.21 (s, 3H), 4.12 (s, 3H), 3.89 – 3.32 (m, 8H), 3.06 (s, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{28}N_7O_5$: 530.22; found 530.19. HPLC retention time: 1.31 minutes (column A).

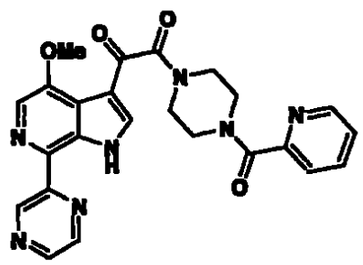
EXAMPLE 101



Example 101, was prepared from Precursor 5b and the 2-amino-3-methoxy-pyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-amino-3-methoxy-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.67 (s, 1H), 8.34 (s, 1H), 7.96 (s, 1H), 7.48 (m, 5H), 4.22 (s, 3H), 4.12 (s, 3H), 3.92

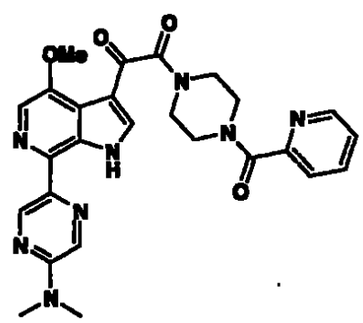
– 3.32 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_7O_5$: 516.20; found 516.23. HPLC retention time: 1.27 minutes (column A).

EXAMPLE 102



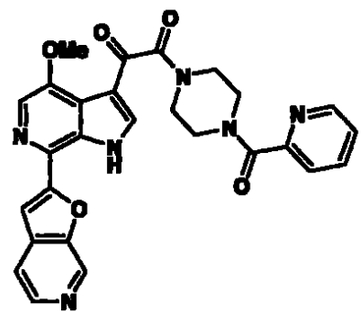
Example 102, was prepared from Precursor 51 and the pyrazin-2-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^1H NMR (500 MHz, CD_3OD) δ9.59 (s, 1H), 8.79 – 7.51 (m, 8H), 4.13 (s, 3H), 3.95 –3.34 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_7O_4$: 472.17; found 472.25. HPLC retention time: 1.15 minutes (column A).

EXAMPLE 103



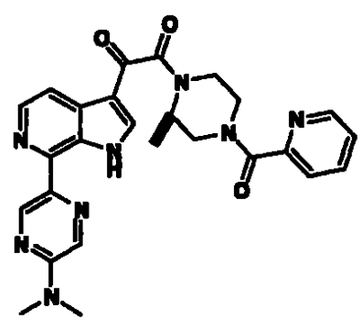
Example 103, was prepared from Precursor 51 and the 2-dimethylamino-pyrazin-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(2-dimethylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_8O_4$: 515.22; found 515.16. HPLC retention time: 1.29 minutes (column A).

EXAMPLE 104



Example 104, was prepared from Precursor 5b and the 6-aza-benzofuran-2-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(6-aza-benzofuran-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, $CDCl_3$) δ8.48 (d, 1H, J = 8.5 Hz), 8.36 (s, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.64 (d, 1H, J = 8.55 Hz), 7.41 (m, 4H), 6.92 (s, 1H), 4.12 (s, 3H), 3.87 – 3.38 (m, 8H). *MS m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{24}N_5O_5$: 510.18; found 510.33. HPLC retention time: 1.33 minutes (column A).

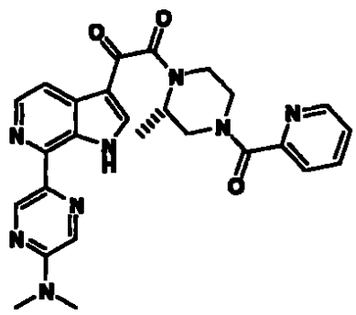
EXAMPLE 105



Example 105, was prepared from Precursor 5m and the 2-dimethylamino-pyrazin-5-yl stannane to provide (R)-1-picolinoyl-3-methyl-4-[(7-(2-dimethylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. *MS m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_8O_3$: 499.22; found 499.27. HPLC retention time: 1.17 minutes (column A).

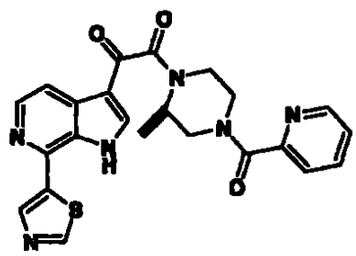
162

EXAMPLE 106



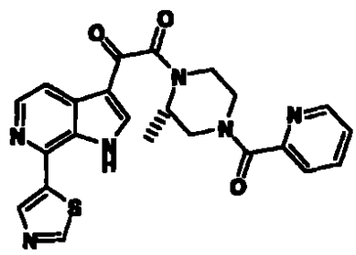
Example 106, was prepared from Precursor 5n and the 2-dimethylamino-pyrazin-5-yl stannane to provide (S)-1-picolinoyl-3-methyl-4-[(7-(2-dimethylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ9.08 – 7.49 (m, 9H), 5.00 – 3.15 (m, 13H), 1.44 – 1.27 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_8O_3$: 499.22; found 499.27. HPLC retention time: 1.19 minutes (column A).

EXAMPLE 109



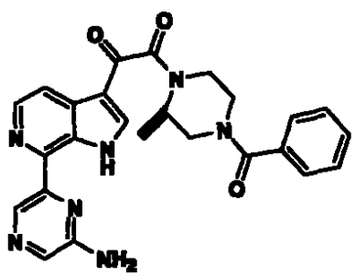
Example 109, was prepared from Precursor 5m and the thiazol-5-yl stannane to provide (R)-1-picolinoyl-3-methyl-4-[(7-(thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. . ^{1}H NMR (500 MHz, CD_3OD) δ9.42 – 7.49 (m, 9H), 4.98 – 3.14 (m, 7H), 1.43 – 1.26 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{21}N_6O_3S$: 461.14; found 461.28. HPLC retention time: 1.11 minutes (column A).

EXAMPLE 110



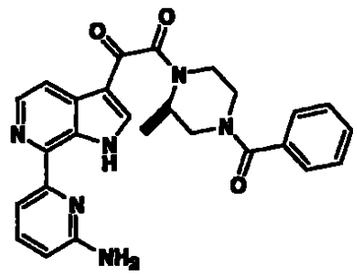
Example 110, was prepared from Precursor 5n and the thiazol-5-yl stannane to provide (S)-1-picolinoyl-3-methyl-4-[(7-(thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. . ^{1}H NMR (500 MHz, CD_3OD) δ9.44 – 7.48 (m, 9H), 4.98 – 3.15 (m, 7H), 1.43 – 1.26 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{21}N_6O_3S$: 461.14; found 461.27. HPLC retention time: 1.13 minutes (column A).

EXAMPLE 111



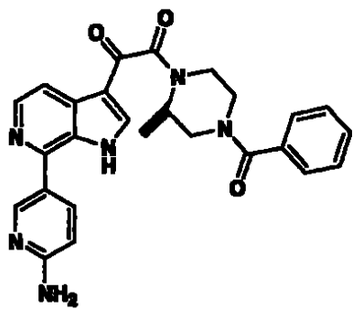
Example 111, was prepared from Precursor 5f and the 2-amino-pyrazin-6-yl stannane to provide (R)-1-benzoyl-3-methyl-4-[(7-(2-amino-pyrazin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.68 – 7.45 (m, 10H), 4.89 – 3.13 (m, 7H), 1.39 – 0.99 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_3$: 470.19; found 470.31. HPLC retention time: 1.30 minutes (column A).

EXAMPLE 112



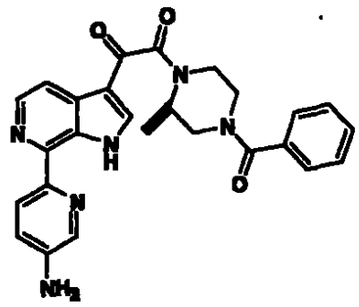
Example 112, was prepared from Precursor 5f and the 2-amino-pyridin-6-yl stannane to provide (R)-1-benzoyl-3-methyl-4-[(7-(2-amino-pyridin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.65 – 6.89 (m, 11H), 4.90 – 3.12 (m, 7H), 1.39 – 0.99 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_3$: 469.20; found 469.32. HPLC retention time: 1.26 minutes (column A).

EXAMPLE 113



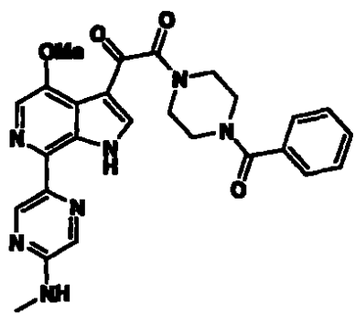
Example 113, was prepared from Precursor 5f and the 2-amino-pyridin-5-yl stannane to provide (R)-1-benzoyl-3-methyl-4-[(7-(2-amino-pyridin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.75 – 7.19 (m, 11H), 4.91 – 3.12 (m, 7H), 1.38 – 1.25 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_3$: 469.20; found 469.34. HPLC retention time: 1.05 minutes (column A).

EXAMPLE 114



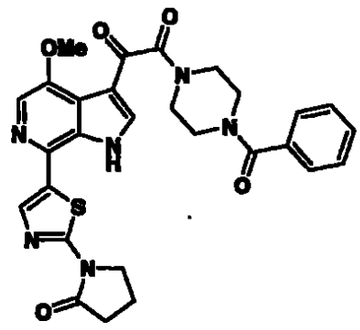
Example 114, was prepared from Precursor 5f and the 5-amino-pyridin-2-yl stannane to provide (R)-1-benzoyl-3-methyl-4-[(7-(5-amino-pyridin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.67 – 7.20 (m, 11H), 4.88 – 3.13 (m, 7H), 1.39 – 1.25 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_3$: 469.20; found 469.33. HPLC retention time: 1.22 minutes (column A).

EXAMPLE 115



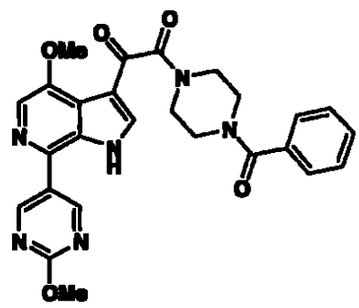
Example 115, was prepared from Precursor 5b and the 2-methylamino-pyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-methylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.90 (s, 1H), 8.61 (s, 1H), 8.18 (s, 1H), 7.92 (s, 1H), 7.46 (m, 5H), 4.12 (s, 3H), 3.85 – 3.40 (m, 8H), 3.02 (s, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_7O_4$: 500.20; found 500.23. HPLC retention time: 1.24 minutes (column A).

EXAMPLE 116



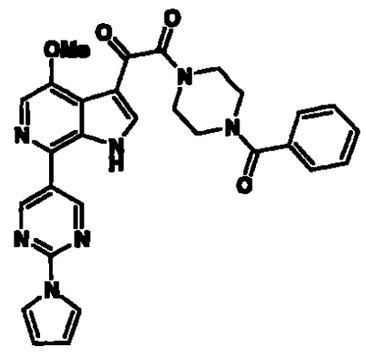
Example 116, was prepared from Precursor 5b and the 2-(2-pyrrolidinon-1-yl)-thiazol-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-((2-pyrrolidinon-1-yl)-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{27}N_6O_5S_2$: 559.18; found 559.11. HPLC retention time: 1.39 minutes (column E).

EXAMPLE 117



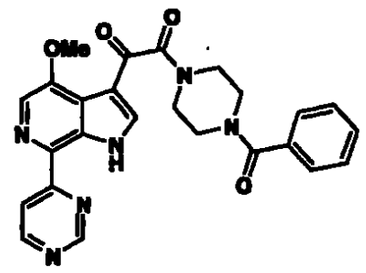
Example 117, was prepared from Precursor 5b and the 2-methoxy-pyrimidin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-methoxy-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_5$: 501.19; found 501.12. HPLC retention time: 1.21 minutes (column E).

EXAMPLE 118



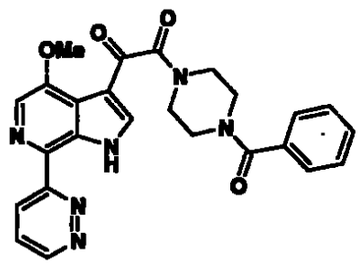
Example 118, was prepared from Precursor 5b and the 2-(pyrrol-1-yl)-pyrimidin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-(pyrrol-1-yl)-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{26}N_7O_4$: 536.20; found 536.33. HPLC retention time: 1.44 minutes (column C).

EXAMPLE 119



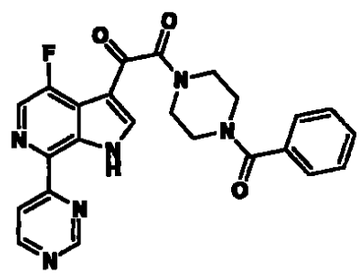
Example 119, was prepared from Precursor 5b and the pyrimidin-4-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^1H NMR (500 MHz, CD_3OD) δ9.29 (s, 1H), 8.88 (d, 1H, J = 5.4 Hz), 8.48 (d, 1H, J = 5.25 Hz), 8.26 (s, 1H), 8.18 (s, 1H), 7.43 (m, 5H), 4.13 (s, 3H), 3.85 – 3.47 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.32. HPLC retention time: 1.35 minutes (column G).

EXAMPLE 120



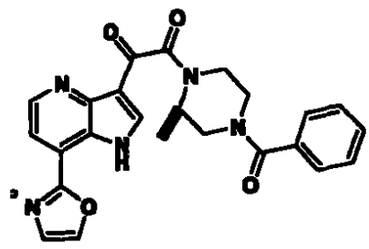
Example 119, was prepared from Precursor 5b and the pyridazin-3-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(pyridazin-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ9.16 (s, 1H), 8.77 (d, 1H, J = 8.5 Hz), 8.26 (d, 1H, J = 3.05 Hz), 8.18 (s, 1H), 7.68 (m, 1H), 7.43 (m, 5H), 4.13 (s, 3H), 3.85 – 3.47 (m, 8H). MS m/z: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.16. HPLC retention time: 1.35 minutes (column G).

EXAMPLE 125



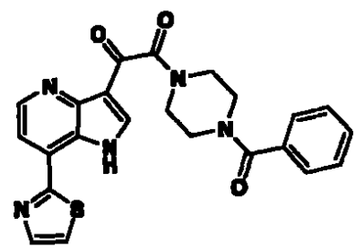
Example 125, was prepared from Precursor 5i and the pyrimidin-4-yl stannane to provide 1-benzoyl-4-[(4-fluoro-7-(pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ9.36 (s, 1H), 8.96 (d, 1H, J = 5.35 Hz), 8.58 (d, 1H, J = 5.10 Hz), 8.43 (s, 1H), 8.38 (s, 1H), 7.43 (m, 5H), 3.85 – 3.47 (m, 8H). MS m/z: $(M+H)^+$ Calc'd for $C_{24}H_{20}FN_6O_2$: 459.16; found 459.15. HPLC retention time: 1.48 minutes (column A).

EXAMPLE 126



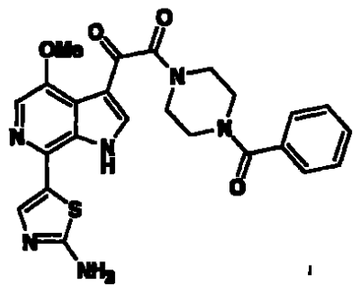
Example 126, was prepared from Precursor 5i and the oxazol-2-yl stannane to provide (R)-1-benzoyl-3-Methyl-4-[7-(oxazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_5O_4$: 444.17; found 444.25. HPLC retention time: 1.13 minutes (column A).

EXAMPLE 131



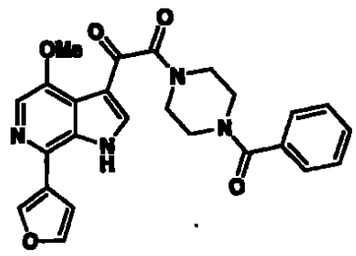
Example 131, was prepared from Precursor 5p and the thiazol-2-yl stannane to provide 1-benzoyl-4-[7-(thiazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{20}N_5O_3S$: 446.13; found 446.04. HPLC retention time: 1.12 minutes (column A).

EXAMPLE 80



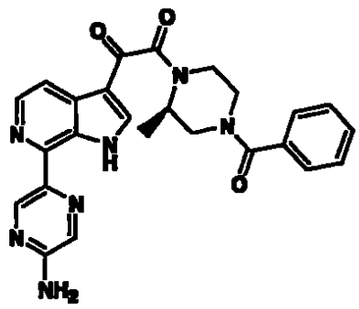
Preparation of Example 80, 1-benzoyl-4-[(4-methoxy-7-(2-amino-thioazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine: A mixture of Example 78 (9 mg), TFA (3 mL) and water (1 mL) was stirred at 80 °C for 10 hours. After solvent was removed under vaccum, the residue was purified by using silica gel chromatography to afford 1-benzoyl-4-[(4-methoxy-7-(2-amino-thioazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine (3 mg); MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{23}N_6O_3S$: 491.15; found 491:21. HPLC retention time: 1.20 minutes (column A).

EXAMPLE 81



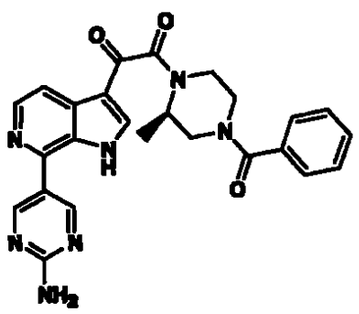
Example 81, was prepared from Precursor 5b and the furan-3-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(furan-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_5$: 459.17; found 459.24. HPLC retention time: 1.13 minutes (column A).

EXAMPLE 150



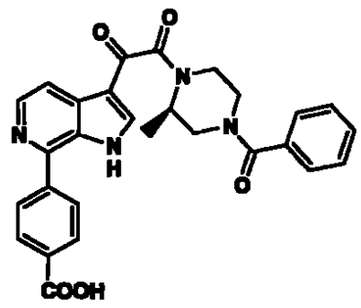
Example 150, was prepared from Precursor 5f and the 5-amino-pyrazin-2-yl stannane to provide (R)-1-benzoyl-3-methyl-4-[(7-(5-amino-pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_3$: 470.19; found 470.19. HPLC retention time: 1.14 minutes (column G).

EXAMPLE 153



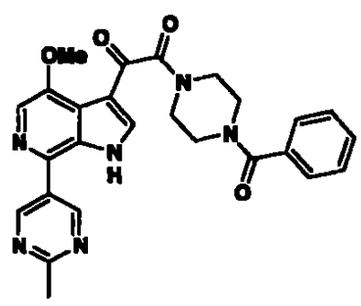
Example 153, was prepared from Precursor 5f and the 2-amino-pyrimidin-5-yl stannane to provide (R)-1-benzoyl-3-methyl-4-[(7-(2-amino-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_3$: 470.19; found 470.22. HPLC retention time: 1.07 minutes (column G).

EXAMPLE 170



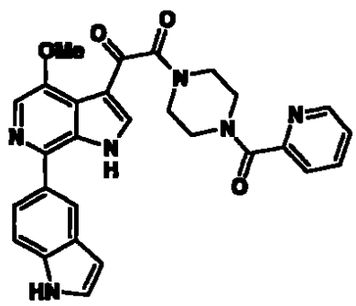
Example 170, was prepared from Precursor 5f and the 4-borono-bezoic acid to provide (R)-1-benzoyl-3-methyl-4-[(7-(hydoxylcarbonyl-benzen-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{25}N_4O_5$: 497.18; found 497.10. HPLC retention time: 1.25 minutes (column H).

EXAMPLE 171



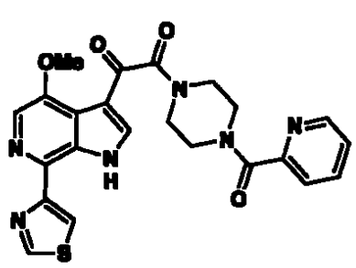
Example 171, was prepared from Precursor 5b and the 2-methyl-pyrimidin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-methyl-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_4$: 485.19; found 485.20. HPLC retention time: 1.14 minutes (column C).

EXAMPLE 172



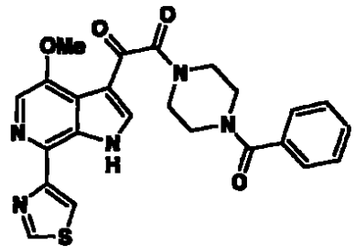
Example 172, was prepared from Precursor 5l and the 5-indole boronic acid to provide 1-picolinoyl-4-[(4-methoxy-7-(indol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{25}N_6O_4$: 509.19; found 509.33. HPLC retention time: 1.14 minutes (column J).

EXAMPLE 173



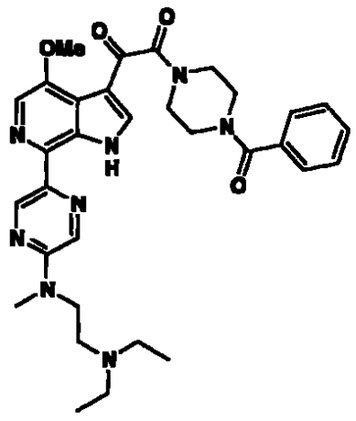
Example 173, was prepared from Precursor 5l and the thiazol-4-yl stannane to provide 1-picolinoyl -4-[(4-methoxy-7-(thiazol-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{21}N_6O_4S$: 477.13; found 477.06. HPLC retention time: 0.92 minutes (column G).

EXAMPLE 174



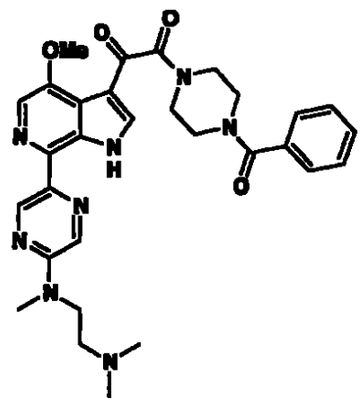
Example 174, was prepared from Precursor 5b and the thiazol-4-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(thiazol-4-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{22}N_5O_4S$: 476.14; found 476.13. HPLC retention time: 1.12 minutes (column G).

EXAMPLE 175



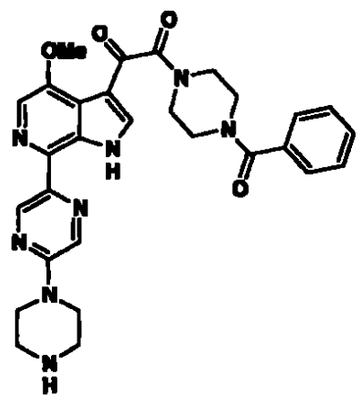
Example 175, was prepared from Precursor 5b and the 2-(N-diethylaminoethyl-N-methyl)aminopyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-(N-diethylaminoethyl-N-methyl)aminopyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{32}H_{39}N_8O_4$: 599.31; found 599.29. HPLC retention time: 1.11 minutes (column G).

EXAMPLE 176



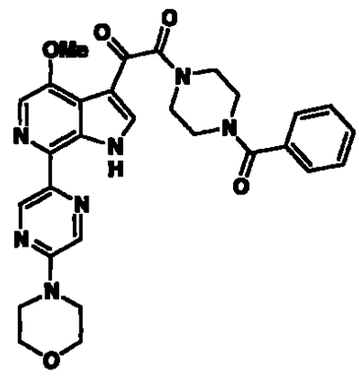
Example 176, was prepared from Precursor 5b and the 2-(N-dimethylaminoethyl-N-methyl)aminopyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-(N-dimethylaminoethyl-N-methyl)aminopyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{35}N_8O_4$: 571.28; found 571.23. HPLC retention time: 1.06 minutes (column G).

EXAMPLE 177



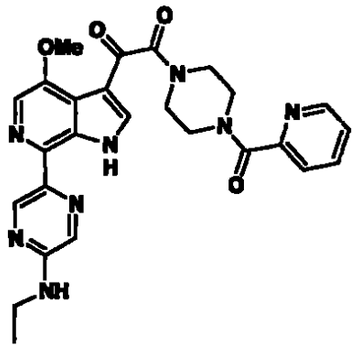
Example 177, was prepared from Precursor 5b and the 2-(N-piperazinyl)-pyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-(N-piperazinyl)-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{31}N_8O_4$: 555.25; found 555.19. HPLC retention time: 1.05 minutes (column G).

EXAMPLE 178



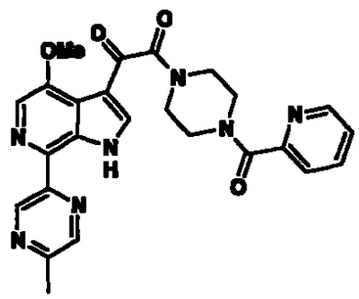
Example 178, was prepared from Precursor 5b and the 2-(4-morpholinyl)-pyrazin-5-yl stannane to provide 1-benzoyl-4-[(4-methoxy-7-(2-(4-morpholinyl)-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{30}N_7O_5$: 556.23; found 556.18. HPLC retention time: 1.27 minutes (column G).

EXAMPLE 179



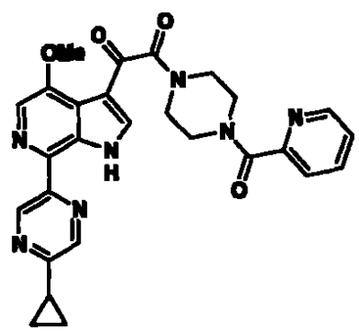
Example 179, was prepared from Precursor 5l and the 2-ethylaminopyrazin-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(2-ethylaminopyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_8O_4$: 515.22; found 515.14. HPLC retention time: 1.13 minutes (column G).

EXAMPLE 180



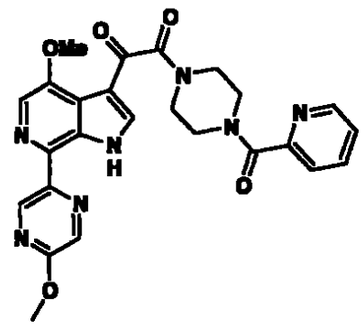
Example 180, was prepared from Precursor 51 and the 2-methylpyrazin-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(2-methylpyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 486.16. HPLC retention time: 1.08 minutes (column G).

EXAMPLE 181



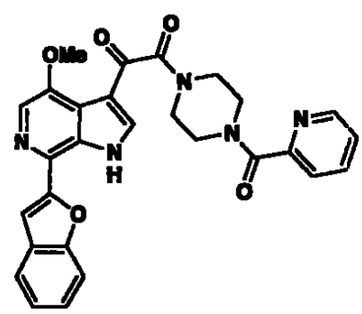
Example 181, was prepared from Precursor 51 and the 2-cyclopropanyl-pyrazin-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(2-cyclopropanyl-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{26}N_7O_4$: 512.20; found 512.12. HPLC retention time: 1.35 minutes (column G).

EXAMPLE 182



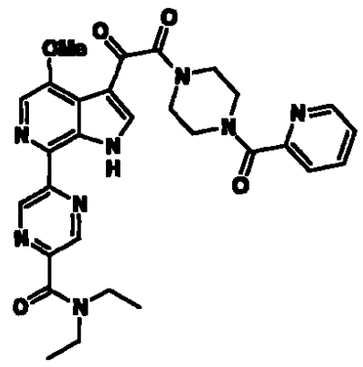
Example 182, was prepared from Precursor 5l and the 2-methoxy-pyrazin-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(2-methoxy-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_5$: 502.18; found 502.08. HPLC retention time: 1.15 minutes (column G).

EXAMPLE 183



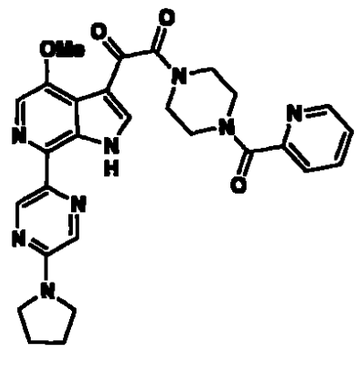
Example 183, was prepared from Precursor 5l and the 2-benzofuran boronic acid to provide 1-picolinoyl-4-[(4-methoxy-7-(benzofuran-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{24}N_5O_5$: 510.18; found 510.08. HPLC retention time: 1.33 minutes (column G).

EXAMPLE 184



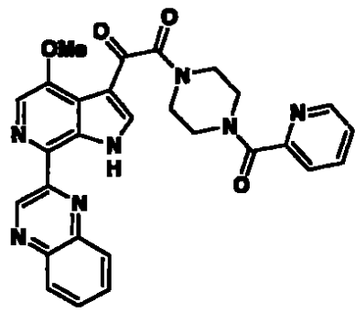
Example 184, was prepared from Precursor 5l and the 2-diethylaminocarbonyl-pyrazin-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(2-diethylaminocarbonyl-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{31}N_8O_5$: 571.24; found 571.19. HPLC retention time: 1.55 minutes (column J).

EXAMPLE 185



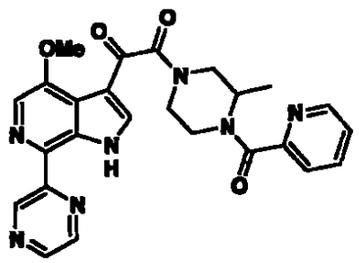
Example 185, was prepared from Precursor 5l and the 2-(N-pyrrolinyl)-pyrazin-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(2-(N-pyrrolinyl)-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{29}N_8O_4$: 541.23; found 541.18. HPLC retention time: 1.30 minutes (column J).

EXAMPLE 186



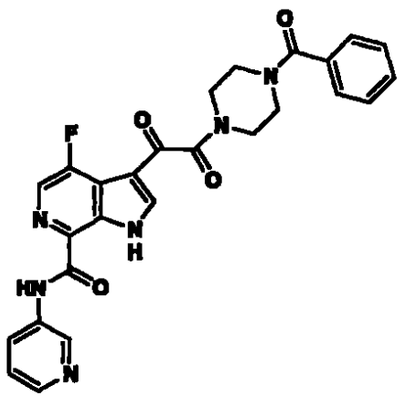
Example 186, was prepared from Precursor 5l and the quinoxalin-2-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(quinoxalin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{24}N_7O_4$: 522.19; found 522.14. HPLC retention time: 1.68 minutes (column J).

EXAMPLE 194



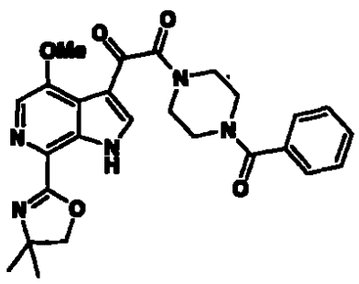
Example 194, was prepared from Precursor 5v and the pyrazin-2-yl stannane to provide 2-methyl-1-picolinoyl-4-[(4-methoxy-7-(pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 486.14. HPLC retention time: 1.50 minutes (column G).

EXAMPLE 147



Precursor 5i (16.5 mg, 0.05 mmol) in DMF (1 mL) was treated with *N*-benzoylpiperazine hydrochloride, DEBPT (15 mg, 0.05 mmol) and Hunig's base (34 μL, 0.2 mmol) at rt for 18h. The solvent was removed in vacuum and the residue was purified by reverse phase preparative HPLC. The fractions showing the right LC/MS(ES^+) m/z $(M+H)^+$ = 501 were collected, concentrated and purified again using a preparative TLC (5% MeOH/CH_2Cl_2) to afford the title compound as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 11.2 (s, 1H), 10.0 (s, 1H), 9.21 (s, 1 H), 8.51 (s, 1H), 8.41 (s, 1H), 8.40 (m, 1 H), 8.32 (s, 1H), 7.62 (m, 1H), 7.45 (m, 5H), 3.90-3.50 (bm, 8H).

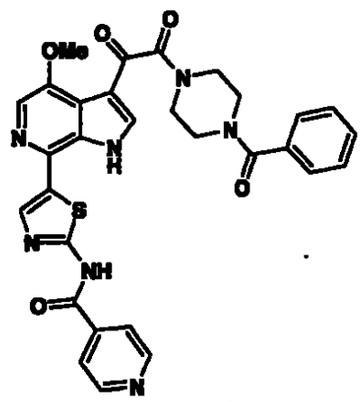
EXAMPLE 156



Example 156, was prepared from Precursor 5b and the 4,4-dimethyloxazolin-2-yl stannane to provide 1-benzoyl-4-[(7-(4,4-dimethyloxazolin-2-yl)-6-azaindol-3-

yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{28}N_5O_5$: 490.21; found 490.22. HPLC retention time: 1.20 minutes (column C).

EXAMPLE 169

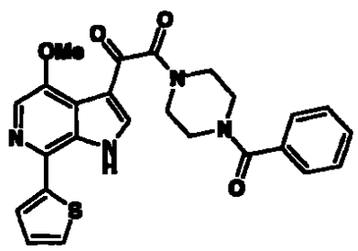


Example 169, was prepared from Precursor 5b and the 2-(4-pyridinecarboxamido)-thiazol-5-yl stannane to provide 1-benzoyl-4-[(7-(2-(4-pyridinecarboxamido)-thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{26}N_7O_5S$: 596.17; found 596.14. HPLC retention time: 1.32 minutes (column C).

EXAMPLES 82-86, 98, 107, 108, 129, 130, 132, 133, 134

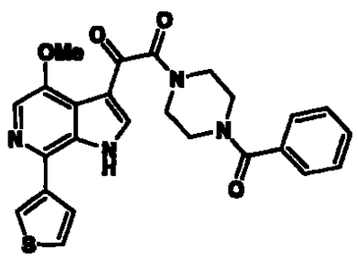
Examples 82-86, 98, 107,108, 127, 128, 129, 130, 132, 133 and 134 were prepared according to the general procedure as previously described for Examples 2-14.

EXAMPLE 82



Example 82, was prepared from Precursor 5b and thien-2-yl boronic acid to provide 1-benzoyl-4-[(4-methoxy-7-(thiophen-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_4S$: 475.14; found 475.31. HPLC retention time: 1.14 minutes (column A).

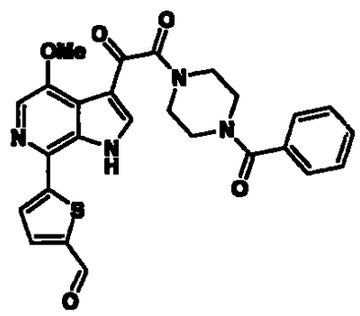
EXAMPLE 83



Example 83, was prepared from Precursor 5b and thien-2-yl boronic acid to provide 1-benzoyl-4-[(4-methoxy-7-(thiophen-3-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_4S$: 475.14; found 475.33. HPLC retention time: 1.16 minutes (column A).

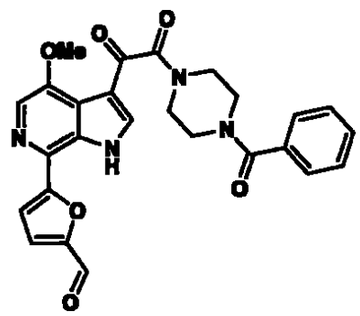
173

EXAMPLE 84



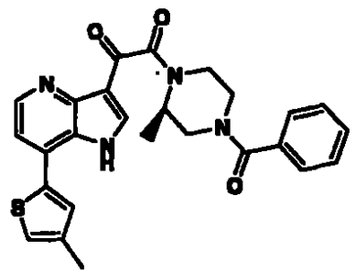
Example 84, was prepared from Precursor 5b and 5-carbonylthien-2-yl boronic acid to provide 1-benzoyl-4-[(4-methoxy-7-(5-carbonyl-thiophen-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{23}N_4O_5S$: 503.14; found 503.23. HPLC retention time: 1.31 minutes (column A).

EXAMPLE 85



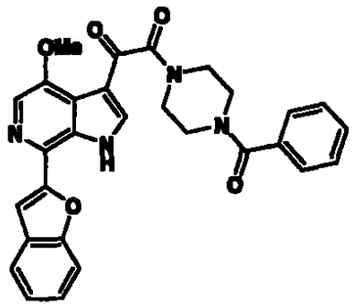
Example 76, was prepared from Precursor 5b and 5-carbonylfuran-2-yl boronic acid to provide 1-(benzoyl)-4-[(4-methoxy-7-(5-carbonyl-furan-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{23}N_4O_6$: 487.16; found 487.28. HPLC retention time: 1.44 minutes (column A).

EXAMPLE 86



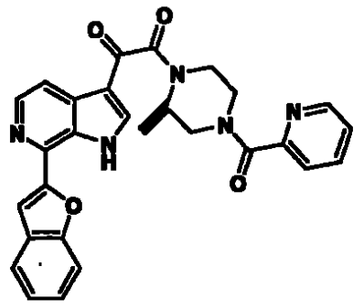
Example 86, was prepared from Precursor 5d and 4-methylthien-2-yl boronic acid to provide 1-benzoyl-3-(R)-methyl-4-[(7-(4-methyl-thiophen-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_4O_3S$: 473.16; found 473.26. HPLC retention time: 1.28 minutes (column A).

EXAMPLE 98



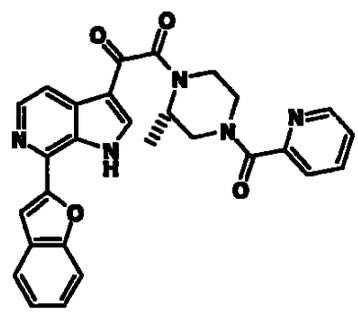
Example 98, was prepared from Precursor 5d and 2-benzofuranyl boronic acid to provide 1-benzoyl-3-(R)-methyl-4-[(7-(benzofuran-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.09 (s, 1H), 7.70-7.26 (m, 10H), 4.03 (s, 3H), 3.97 – 3.49 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{25}N_4O_5$: 509.18; found 509.18. HPLC retention time: 1.50 minutes (column A).

EXAMPLE 107



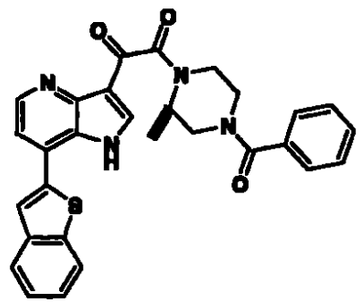
Example 107, was prepared from Precursor 5m and 2-benzofuranyl boronic acid to provide (R)-1-picolinoyl-3-methyl-4-[(7-(benzofuran-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.77 – 7.38 (m, 12H), 4.99 – 3.16 (m, 7H), 1.44 – 1.27 (m, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{24}N_5O_4$: 494.18; found 494.24. HPLC retention time: 1.35 minutes (column A).

EXAMPLE 108



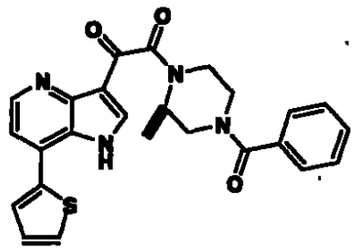
Example 108, was prepared from Precursor 5n and 2-benzofuranyl boronic acid to provide (S)-1-picolinoyl-3-methyl-4-[(7-(benzofuran-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{24}N_5O_4$: 494.18; found 494.23. HPLC retention time: 1.37 minutes (column A).

EXAMPLE 127



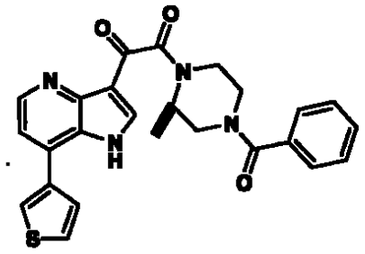
Example 127, was prepared from Precursor 5i and the benzothiophen-2-yl boronic acid to provide (R)-1-benzoyl-3-Methyl-4-[7-(benzothiophen-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{25}N_4O_3S$: 509.16; found 509.21. HPLC retention time: 1.42 minutes (column A).

EXAMPLE 128



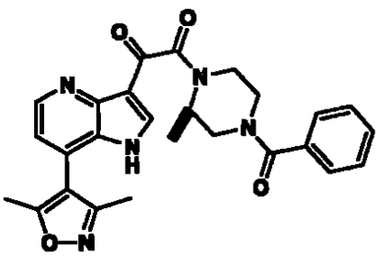
Example 128, was prepared from Precursor 5i and the thiophen-2-yl boronic acid to provide (R)-1-benzoyl-3-Methyl-4-[7-(thiophen-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_3S$: 459.15; found 459.27. HPLC retention time: 1.22 minutes (column A).

EXAMPLE 129



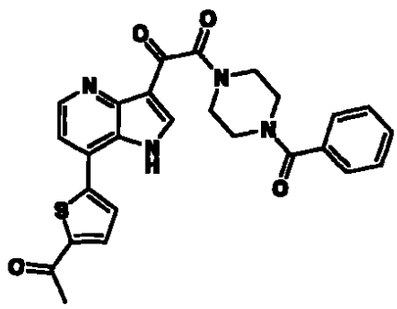
Example 129, was prepared from Precursor 5i and the thiophen-3-yl boronic acid to provide (R)-1-benzoyl-3-Methyl-4-[7-(thiophen-3-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_3S$: 459.15; found 459.34. HPLC retention time: 1.31 minutes (column A).

EXAMPLE 130



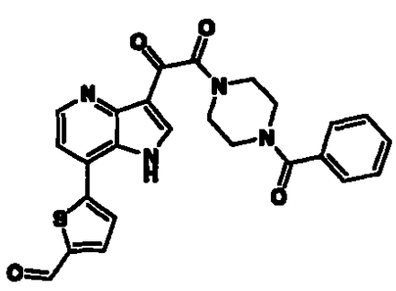
Example 130, was prepared from Precursor 5i and the 2,5-dimethyl-isoxazol-4-yl boronic acid to provide (R)-1-benzoyl-3-Methyl-4-[7-(2,5-dimethyl-isoxazol-4-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_5O_4$: 472.20; found 472.28. HPLC retention time: 1.14 minutes (column A).

EXAMPLE 132



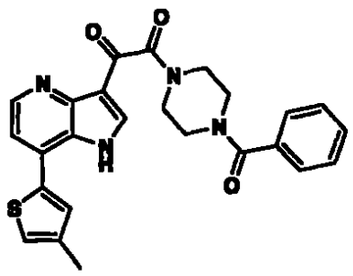
Example 132, was prepared from Precursor 5p and the 2-methylcarbonyl-thiophen-5-yl boronic acid to provide 1-benzoyl-4-[7-(2-methylcarbonyl-thiophen-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{23}N_4O_4S$: 487.14; found 487.20. HPLC retention time: 1.14 minutes (column A).

EXAMPLE 133



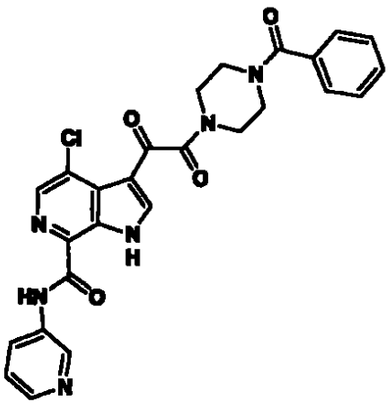
Example 133, was prepared from Precursor 5p and the 2-carbonyl-thiophen-5-yl boronic acid to provide 1-benzoyl-4-[7-(2-carbonyl-thiophen-5-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{21}N_4O_4S$: 473.13; found 473.11. HPLC retention time: 1.14 minutes (column A).

EXAMPLE 134



Example 134, was prepared from Precursor 5p and the 4-methyl-thiophen-2-yl boronic acid to provide 1-benzoyl-4-[7-(4-methyl-thiophen-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_3S$: 459.15; found 459.08. HPLC retention time: 1.26 minutes (column G).

EXAMPLE 152

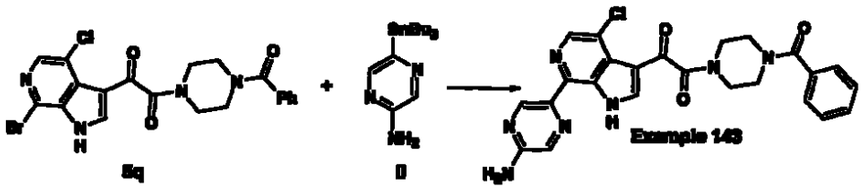


Preparation of Example 152:

To a mixture of acid precursor 16 (30 mg, 68 μmol), 3-aminopyridine (26 mg, 0.27 mmol) and DMAP (50 mg, 0.41 mmol) was added THF (2 ml), and then EDC (60 mg, 0.31 mmol). The reaction mixture was stirred at ambient temperature for 16 hours. The LC/MS analysis indicated that the major product was the activated ester. The reaction mixture was then added into a DMF (2 ml) solution of 3-aminopyridine (400 mg, 4.25 mmol) and stirred at ambient temperature for 16 hours. After addition

of MeOH (4 ml), the reaction mixture was purified by preparative reverse phase HPLC to give the TFA salt of the title compound using the method: Start %B = 30, Final %B = 75, Gradient time = 25 min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 10.41 – 11.08 min. ^{1}H NMR: (DMSO-d_6) δ 13.04 (s, 1H), 11.17 (s, 1H), 9.17 (s, 1H), 8.53 (s, 1H), 8.35 (m, 3H), 7.44 (b s, 6H), 3.75 – 3.37 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 517, 519; HPLC R_t = 1.653.

EXAMPLE 143

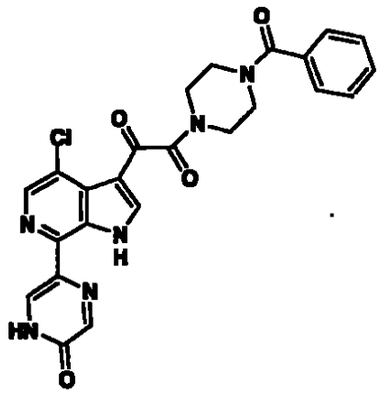


5q ii

Prep of Example 143:

To a mixture of precursor 5q (31 mg, 65 μmol) and $Pd(PPh_3)_4$ (20 mg, 17 μmol) was added 1,4-dioxane (1 ml) and ii (30 mg, 78 μmol). The reaction mixture was heated in a sealed tube at 145°C for 4 hours. After cooling to ambient temperature, the reaction mixture was added MeOH (4 ml) and then filtered. The filtrate was purified by preparative reverse phase HPLC to give the TFA salt of the title compound using the method: Start %B = 25, Final %B = 90, Gradient time = 20 min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 11.14 – 11.92 min. ^{1}H NMR: (DMSO-d_6) δ 12.71 (s, 1H), 9.01 (s, 1H), 8.36 (s, 1H), 8.27 (s, 1H), 8.08 (s, 1H), 7.44 (b s, 5H), 7.44 (b s, 2H), 3.75 – 3.37 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 490, 492; HPLC R_t = 2.250.

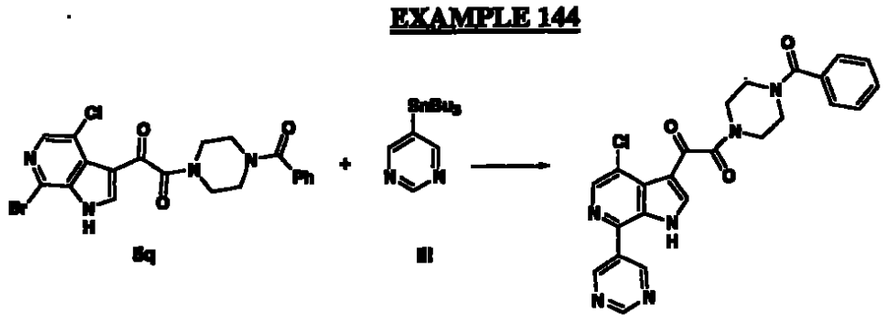
EXAMPLE 149



Preparation of Example 49:

To a suspension of compound of Example 143 (12 mg, 24 μmol) in sulfuric acid (5%, 2 ml), was charged sodium nitrite (22 mg, 0.32 mol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and then at ambient temperature for 1 hour. After addition of MeOH (4 ml), the reaction mixture was purified by preparative reverse phase HPLC to give a TFA solvate of title compound using the method: Start %B = 20, Final %B = 85, Gradient time = 15 min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 10.67- 11.36 min. ^{1}H NMR: (DMSO-d_6) δ 12.62 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 8.18 (s, 1H), 7.44 (b s, 5H), 3.80 – 3.30 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 491, 493; HPLC R_t = 2.193.

EXAMPLE 144



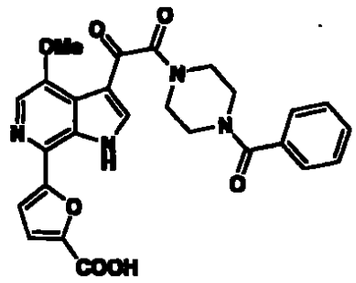
5q iii

Preparation of Example 144:

To a mixture of precursor 5q (50 mg, 105 μmol) and $Pd(PPh_3)_4$ (50 mg, 43 μmol) was added 1,4-dioxane (1 ml) and iii (77 mg, 210 μmol). The reaction mixture was

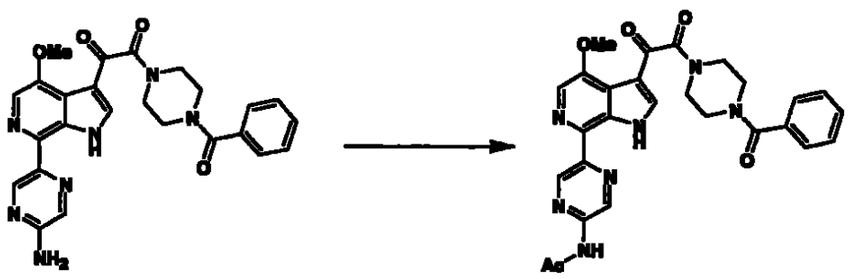
heated in a sealed tube at 145°C for 16 hours. After cooling to ambient temperature, the reaction mixture was added MeOH (4 ml) and then filtered. The filtrate was purified by reverse phase HPLC to give the TFA salt of the title compound of using the method: Start %B = 15, Final %B = 100, Gradient time = 20 min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 11.80 – 12.31 min. ^{1}H NMR: (CD_3OD) δ 9.32 (s, 1H), 9.25 (s, 2H), 8.50 (s, 1H), 8.44 (s, 1H), 7.47 (b s, 5H), 4.00 – 3.44 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 475, 477; HPLC R_t = 1.833.

EXAMPLE 87



Preparation of Example 87, 1-benzoyl-4-[(4-methoxy-7-(2-hydroxycarbonyl-furan-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine: A mixture of the compound of Example 85 (19 mg), $NaClO_2$ (9.2 mg) in a mixed solution of CH_3CN (3 mL) and water (0.5 mL) was stirred at room temperature for 24 hours. After the reaction was quenched by 1N NaOH solution (1 ml), the mixture was extracted with diethyl ether (3 x 10 mL). The aqueous phase was acidified with 1N HCl to give a yellow solid precipitate (5mg) which was the product shown. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{23}N_6O_7$: 503.16; found 503.19. HPLC retention time: 1.37 minutes (column A).

General Procedure of Converting $-NH_2$ Group to –NHCOR Group

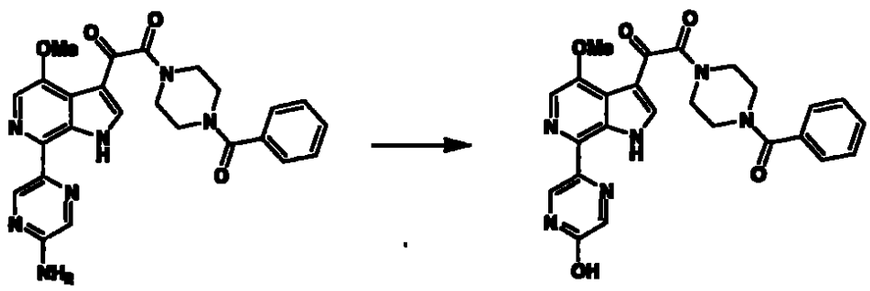


Preparation of Example 99, 1-(benzoyl)-4-[(4-methoxy-7-(2-acetylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine: 1-(benzoyl)-4-[(4-methoxy-7-(2-amino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine (4mg) and acetic anhydride (20mg) were dissolved in pyridine (0.5ml). The reaction was stirred for three hours at room temperature. After reaction was quenched with MeOH (1ml), solvents were concentrated to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide 3.0 mg of the desired compound, 1-(benzoyl)-4-[(4-methoxy-7-(2-acetylamino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ9.58 (s, 1H), 9.25 (s, 1H), 8.45 (s, 1H), 8.10 (s, 1H), 7.49 (m, 5H), 4.12 (s, 3H), 3.84 – 3.35 (m, 8H), 2.27 (s, 3H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{26}N_7O_5$: 528.20; found 528.22. HPLC retention time: 1.33 minutes (column A).

General Procedure of Converting $-NH_2$ Group to –OH Group

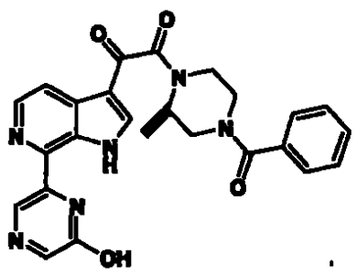
Preparation of Example 97, 1-(benzoyl)-4-[(4-methoxy-7-(2-hydroxyl-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine: 1-(benzoyl)-4-[(4-methoxy-7-(2-amino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine (15 mg) and $NaNO_2$ (10 mg) was added into a H_2SO_4 solution (0.1ml of concentrated H_2SO_4 diluted with 0.3 ml of water). The reaction was stirred at room temperature for one hour. Then, the reaction mixture was neutralized with a saturated Na_2CO_3 solution (10 ml). The solvents were concentrated to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide 4.2mg of the desired compound, 1-(benzoyl)-4-[(4-methoxy-7-(2-hydroxyl-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. ^{1}H NMR (500 MHz, CD_3OD) δ8.55 (s, 1H), 8.44 (s, 1H), 8.31

(s, 1H), 8.01 (s, 1H), 7.49 (m, 5H), 4.12 (s, 3H), 3.84 – 3.64 (m, 8H). MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_5$: 487.17; found 487.22. HPLC retention time: 1.13 minutes (column A).



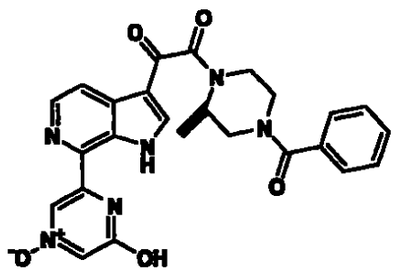
This general procedure is applied to prepare examples 121, 122,123,124,155, 157, and 162.

EXAMPLE 121



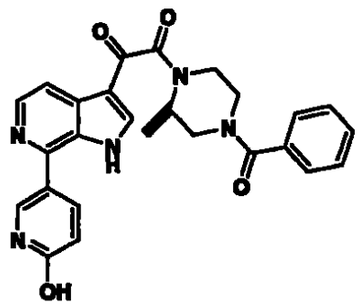
Example 121, (R)-1-(benzoyl)-3-methyl-4-[(4-methoxy-7-(2-hydroxyl-pyrazin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.17. HPLC retention time: 1.39 minutes (column G).

EXAMPLE 121-2



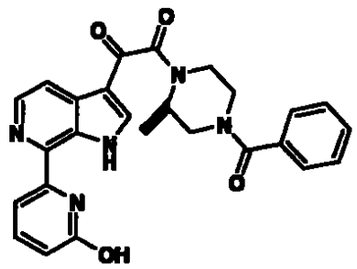
Example 121-2, (R)-1-(benzoyl)-3-methyl-4-[(4-methoxy-7-(2-hydroxyl-4-oxo-pyrazin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine was isolated during the preparation of Example 121. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_5$: 487.17; found 487.17. HPLC retention time: 1.08 minutes (column G).

EXAMPLE 122



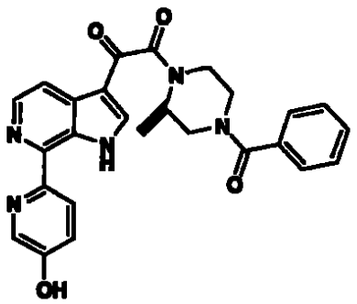
Example 122, (R)-1-(benzoyl)-3-methyl-4-[(4-methoxy-7-(2-hydroxyl-pyridin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_5O_4$: 470.18; found 470.17. HPLC retention time: 1.03 minutes (column G).

EXAMPLE 123



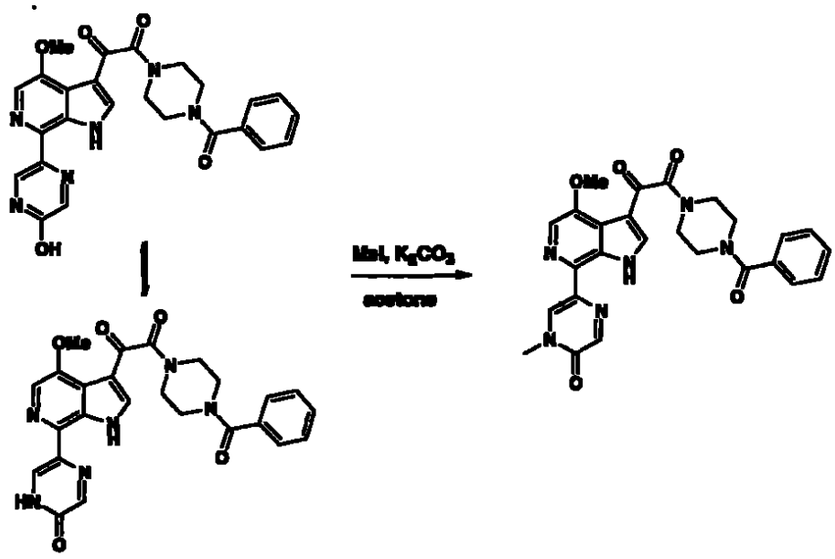
Example 123, (R)-1-(benzoyl)-3-methyl-4-[(4-methoxy-7-(2-hydroxyl-pyridin-6-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_5O_4$: 470.18; found 470.14. HPLC retention time: 1.28 minutes (column G).

EXAMPLE 124



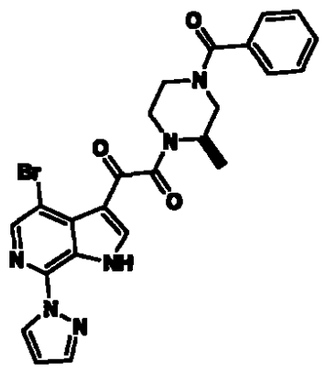
Example 124, (R)-1-(benzoyl)-3-methyl-4-[(4-methoxy-7-(5-hydroxyl-pyridin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{24}N_5O_4$: 470.18; found 470.13. HPLC retention time: 1.21 minutes (column G).

Preparation of Example 138



Preparation of Example 138, 1-(benzoyl)-4-[(4-methoxy-7-(1-methylpyrazin-2-on-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine: 1-(benzoyl)-4-[(4-methoxy-7-(2-hydroxyl-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine (6mg), MeI (5mg) and K_2CO_3 (4 mg)were dissolved in acetone (5 ml). The reaction was stirred for four hours at room temperature. After solid was filtered away, the mother liquid was concentrated to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide 3.0 mg of the desired compound, 1-(benzoyl)-4-[(4-methoxy-7-(1-methylpyrazin-2-on-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_5$: 501.19; found 501.14. HPLC retention time: 1.08 minutes (column G).

EXAMPLE 139

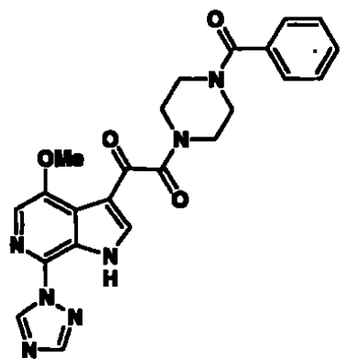


Precursor 4i was dissolved in DMF (2 ml), and to which *N*-benzoyl-(*R*)-methylpiperazine hydrochloride (0.092 g, 0.45 mmol) and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT, 0.180 g, 0.60 mmol) were added, followed by *N,N*-diisopropylethylamine (0.15 ml, 0.87 mmol). The reaction mixture was stirred for 2 h at r.t., and then the volatile evaporated under high vacuum. Water was added to the mixture to induce precipitation, and the solids were filtered and dried *in vacuo*. Purification of the crude solid by preparative thin layer chromatography (5% *Me*OH/ CH_2Cl_2), and subsequent washing with ether gave the title compound; ^{1}H NMR: ($CDCl_3$) δ 8.78 (s, 1H), 8.32 (s, 1H), 8.28 (s, 1H) 7.84 (s, 1H), 7.44 (b s, 5H), 6.56 (s, 1H), 5.00–3.00 (b m, 7H), 1.45–1.20 (b s, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 521, 523; HPLC R_t = 1.677.

Preparation of N-linked Azaindole Heterocylic Derivatives from the Corresponding Bromide or Chloride. An example of a typical procedure:

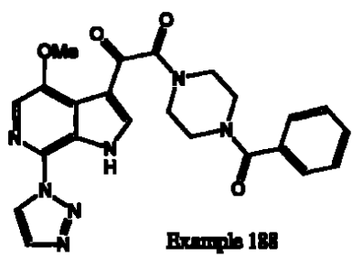
A general reaction condition is shown with the preparation of example 187. Other analogs, examples 188 – 193, were prepared via the same reaction condition.

EXAMPLE 187



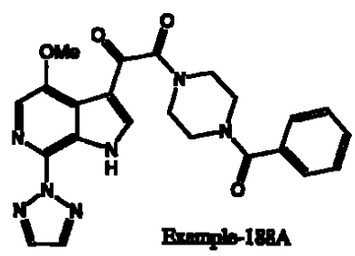
Preparation of compound of Example 187: Precursor 5b (30 mg), 1,2,4-triazole (145 mg), Cu (4.4 mg) and K2CO3 (9.6 mg) were combined in a sealed tube which was degassed before being sealed. The mixture was heated to 160°C for 8 hours. After being allowed to cool down to ambient temperature, the mixture was diluted with MeOH (14 ml) and dichloromethane (7 ml). After filtration, the filtrate was concentrated to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide 12.9 mg of the desired compound 187, 1-benzoyl-4-[(4-methoxy-7-(1,2,4-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{22}N_7O_4$: 460.17; found 460.33. HPLC retention time: 1.45 minutes (column J).

EXAMPLE 188 and EXAMPLE 188A



Example 188

and



Example 188A

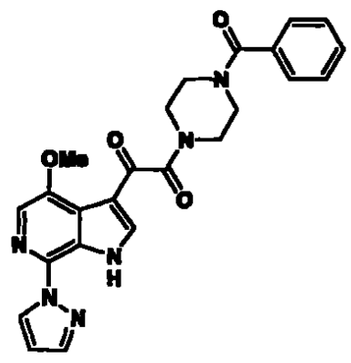
Example 188 and 188A, were prepared according to the general method described above starting from Precursor 5z and 1,2,3-triazole to provide Example 188 and Example 188A.

Precursor 5z (0.050 g), 0.050g Cu powder, 0.025g K2CO3 and 6 equivalents of 1,2,3 triazole were heated at 150C for 16 hrs. The reaction was allow to cool to ambient temperature and was dissolved in MeOH and purified by Prep HPLC as described above in the general methods to provide Example 188 (0.0237g brown solid,yield 44%) and the the other isomer Example 188a.

Example 188, 1-benzoyl-4-[(4-methoxy-7-(1,2,3-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{22}N_7O_4$: 460.17; found 460.34. HPLC retention time: 1.50 minutes (column J); 1.29 minutes (column L). ^1H NMR (500 MHz, CD_3OD) δ8.86 (s, 1H), 8.34 (s, 1H), 7.97 (m, 2H), 7.48 (b, 5H), 4.08 (s, 3H), 3.89-3.56 (m, 8H).

Example 188A, 1-benzoyl-4-[(4-methoxy-7-(1,2,3-triazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{22}N_7O_4$: 460.17; found 460.34. HPLC retention time: 1.39 minutes (column J). ^1H NMR (500 MHz, CD_3OD) δ8.32 (s, 1H), 7.76 (s, 1H), 7.45 (b, 7H), 4.07 (s, 3H), 3.80-3.30 (m, 8H).

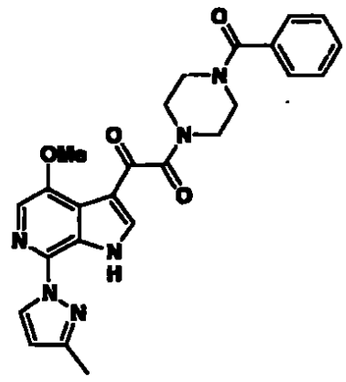
EXAMPLE 189



182

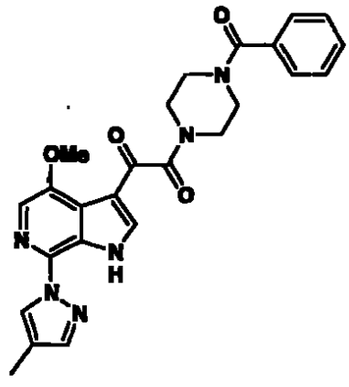
Example 189, was prepared from Precursor 5b and pyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(1-pyrazolyl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{23}N_6O_4$: 459.18; found 459.01. HPLC retention time: 0.92 minutes (column G).

EXAMPLE 190



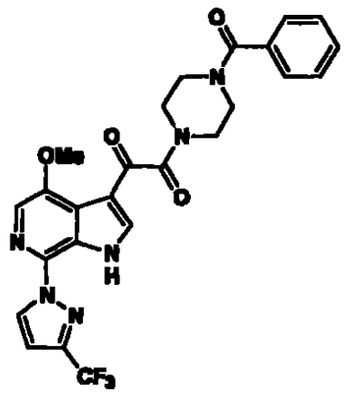
Example 190, was prepared from Precursor 5b and 3-methylpyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-methylpyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_6O_4$: 473.19; found 473.09. HPLC retention time: 1.49 minutes (column G).

EXAMPLE 191



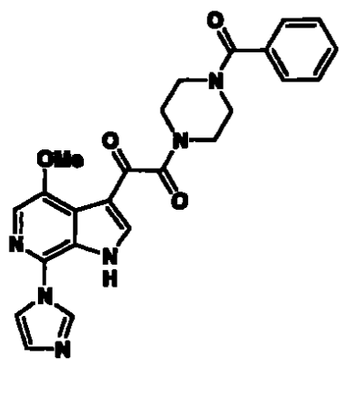
Example 191, was prepared from Precursor 5b and 4-methylpyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(4-methylpyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_6O_4$: 473.19; found 473.09. HPLC retention time: 1.52 minutes (column G).

EXAMPLE 192



Example 192, was prepared from Precursor 5b and 3-trifluoromethylpyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-trifluoromethylpyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{22}F_3N_6O_4$: 527.17; found 527.09. HPLC retention time: 1.64 minutes (column G).

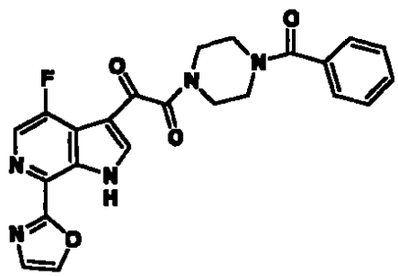
EXAMPLE 193



183

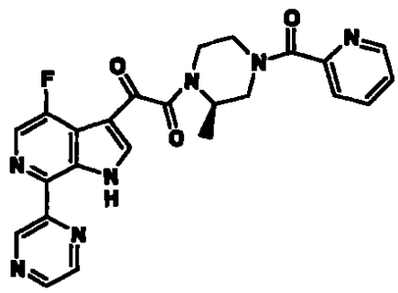
Example 193, was prepared from Precursor 5b and imidazole to provide 1-benzoyl-4-[(4-methoxy-7-(1-imidazolyl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{23}N_6O_4$: 459.18; found 459.26. HPLC retention time: 1.22 minutes (column G).

EXAMPLE 140



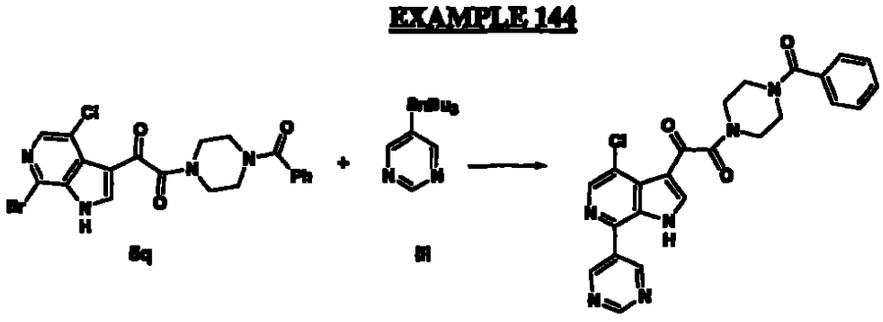
The title compound was prepared according to general procedures described before (Sn-coupling). H NMR: 8.41(m, 1H); 8.33(m, 1H); 8.16(m, 1H); 7.53(m, 1H); 7.47(bs, 5H); 3.97-3.54(m, 8H). LC/MS: (ES^+) m/z$(m+H)^+$ = 448, Rt = 1.28min.

EXAMPLE 141



The title compound was prepared according to general procedures described before (Sn-coupling). ^{1}H-NMR: 9.71-9.70(m, 1H); 8.80-8.79(m, 1H); 8.66-8.42(m, 2H); 8.41-8.35(m, 2H); 7.99-7.92(m,1H), 7.69-7.53(m, 1H); 7.48-7.44(m, 1H); 5.05-3.15(m, 8H). LC/MS: (ES^+) m/z $(m+H)^+$ = 474. Rt = 1.26min.

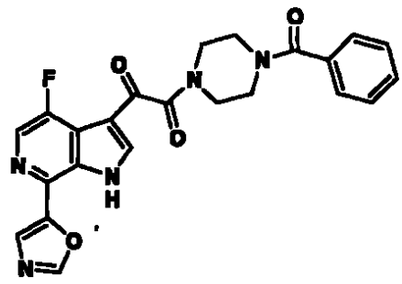
EXAMPLE 144



Preparation of Example 144:

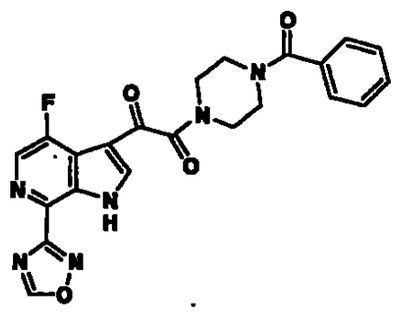
To a mixture of precursor 5q (50 mg, 105 μmol) and $Pd(PPh_3)_4$ (50 mg, 43 μmol) was added 1,4-dioxane (1 ml) and iii (77 mg, 210 μmol). The reaction mixture was heated in a sealed tube at 145°C for 16 hours. After cooling to ambient temperature, the reaction mixture was added MeOH (4 ml) and then filtered. The filtrate was purified by reverse phase HPLC to give the TFA salt of the title compound of using the method: Start %B = 15, Final %B = 100, Gradient time = 20 min, Flow Rate = 25 ml/min, Column : YMC C18 5um 20 x 100mm, Fraction Collection: 11.80 – 12.31 min. ^{1}H NMR: (CD_3OD) δ 9.32 (s, 1H), 9.25 (s, 2H), 8.50 (s, 1H), 8.44 (s, 1H), 7.47 (b s, 5H), 4.00 – 3.44 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 475, 477; HPLC R_t = 1.833.

EXAMPLE 145



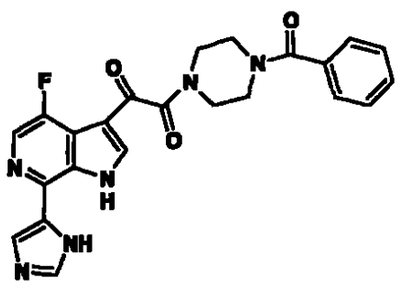
The title compound was prepared following the procedure described before for example 146 and precursor 4k. ^{1}H NMR: 8.35-8.33(m, 2H); 8.11(s, 1H); 7.89(s, 1H); 7.43(bs, 5H); 3.89-3.49(m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 448. Rt = 1.18min.

EXAMPLE 146



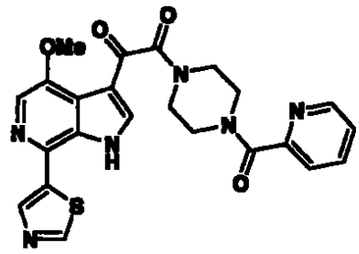
Precursor 4m (0.26 mmol) was dissolved in DMF (1 mL) and treated with *N*-benzoylpiperazine hydrochloride (59 mg, 0.26 mmol), DEBPT (79 mg, 0.26 mmol) and Hunig's base (90 µL, 0.52 mmol) and the reaction mixture was stirred at rt for 18h. The solvent was removed in vacuum and the residue was purified by reverse phase preparative HPLC. The fractions showing the right LC/MS:(ES^+) m/z $(M+H)^+$ = 449 were collected, concentrated and purified again using a preparative TLC (5% $MeOH/CH_2Cl_2$) to afford the title compound as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.7 (s, 1H), 9.00 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 7.45 (m, 5H), 3.9-3.5 (bm, 8H).

EXAMPLE 148



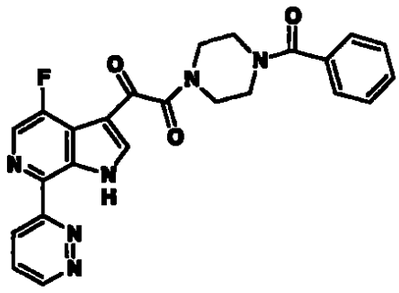
The title compound was prepared from precursor 4n using the same coupling conditions described for the last step of the preparation of precursor 5i. ^{1}H NMR: 8.82(m, 1H); 8.48-8.45(m, 1H); 8.37-8.33(m, 1H); 8.26-8.23(m, 1H); 7.47(bs, 5H); 3.97-3.54(m, 8H). LC/MS: (ES^+) m/z$(m+H)^+$ = 447 Rt = 0.94min.

EXAMPLE 151



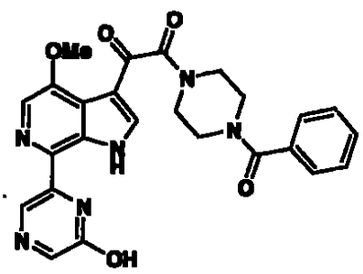
Example 151, was prepared from Precursor 51 and the thiazol-5-yl stannane to provide 1-picolinoyl-4-[(4-methoxy-7-(thiazol-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{21}N_6O_4S$: 477.13; found 477.13. HPLC retention time: 0.94 minutes (column G).

EXAMPLE 154



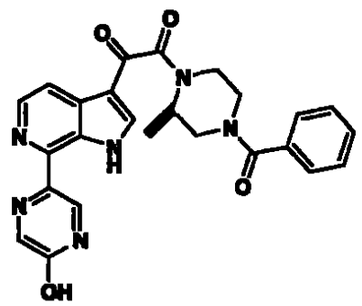
The title compound was prepared according to general procedures described before (Sn-coupling). ^{1}H-NMR: 9.23-9.22 (m, 1H); 8.83-8.81(m, 1H); 8.43 (m, 1H); 8.36 (m, 1H); 7.75-7.73 (m,1H), 7.44 (bs, 5H); 3.85-3.49 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+ = 459$. Rt = 1.39min.

EXAMPLE 155



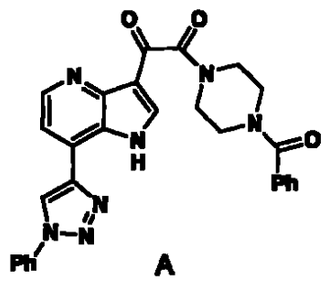
Example 155, 1-(benzoyl)-4-[(4-methoxy-7-(2-hydroxyl-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_5$: 487.17; found 487.14. HPLC retention time: 1.30 minutes (column G).

EXAMPLE 157



Example 157, (R)-1-(benzoyl)-3-methyl-4-[(4-methoxy-7-(5-hydroxyl-pyrazin-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.16. HPLC retention time: 1.09 minutes (column G).

EXAMPLE 161

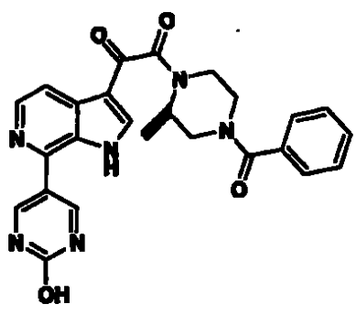


A

$C_{28}H_{23}N_7O_3$
Exact Mass: 505.19
Mol. Wt.: 505.53

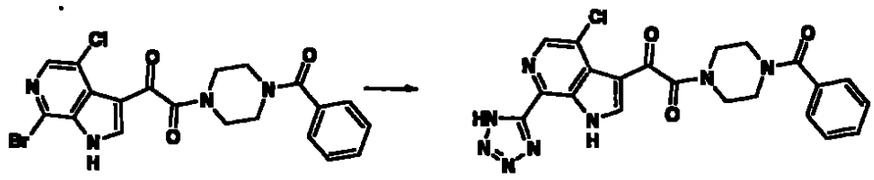
Example 161 was prepared from precursor 5p and 3-phenyl-5-tributylstannyl-1,2,3-triazole using the general tin coupling procedure provided earlier: ^1H NMR (500 MHz, DMSO) δ 9.67 (s, 1H), 8.81 (s, 1H), 8.72 (d, J = 5.4 Hz, 1H), 8.25 (d, J = 6.1 Hz, 1H), 8.00 (dd, J = 8.2, 1.8 Hz, 1H), 7.68 (dd, J = 8.2, 7.4 Hz, 2H), 7.60 (tt, J = 7.4, 1.8 Hz, 2H), 7.48 (br s, 5H), 4.04-3.46 (m, 8H). MS *m/z*: $(M+H)^+$ calcd for $C_{28}H_{24}N_7O_3$: 506.19; found 506.15. HPLC retention time: 1.21 minutes (XTERRA C18 S7 3.0 x 50 mm)).

EXAMPLE 162



Example 162, (R)-1-(benzoyl)-3-methyl-4-[(4-methoxy-7-(2-hydroxyl-pyrimidin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_6O_4$: 471.18; found 471.13. HPLC retention time: 0.95 minutes (column G).

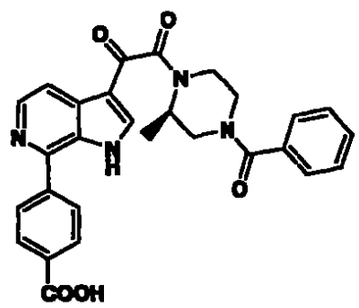
EXAMPLE 163



5q

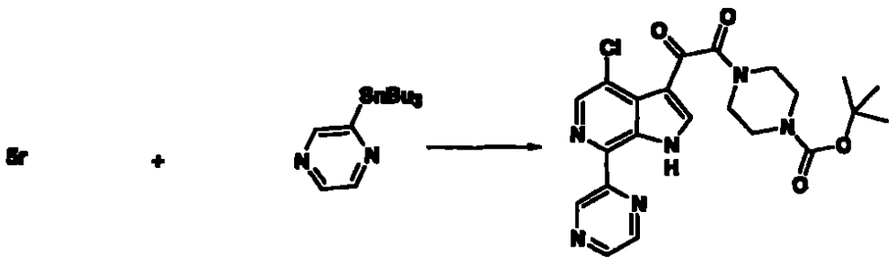
To a solution of precursor 5q (50 mg, 0.11 mmol) in DMF (1 ml) was added CuCN (30 mg, 0.335 mmol). The reaction mixture was heated at 170°C for 30 min. After cooling to ambient temperature, the reaction mixture was diluted with MeOH (15 ml), filtered under gravity, and the filtrate evaporated *in vacuo* to afforded a brownish residue which is a cyanoprecursor. To the residue in DMF (1 ml) was added sodium azide (61 mg, 0.95 mmol) and ammonium chloride (50 mg, 0.95 mmol). The mixture was heated at 90°C for one hour. The reaction mixture was then diluted with MeOH (4 ml), filtered, and the filtrate purified by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 80, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : XTERRA C18 5 um 30 x 100 mm, Fraction Collection: 11.26 – 11.71 min. The material was homogenous by ^{1}H NMR and HPLC, although the mass spectrum indicated an extra peak at $(M+H)^+ = 431$; ^{1}H NMR: (CD_3OD) 8.41 (s, 1H), 8.12 (s, 1H), 7.47 (b s, 5H), 3.97 – 3.47 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+ = 465, 467$; HPLC $R_t = 1.937$

EXAMPLE 164



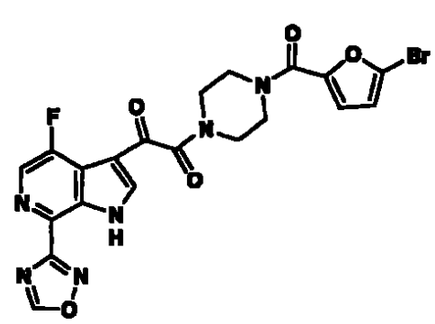
Example 164, was prepared from Precursor 5a and the 4-hydroxycarbonylphenyl boronic acid to provide 1-benzoyl-4-[7-(4-hydroxycarbonylphenyl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{25}N_4O_5$: 497.18; found 497.22. HPLC retention time: 1.20 minutes (column C).

EXAMPLE 165



Compound of Example 165 was prepared in a similar manner to compound of Example 143 starting with precursor 5r, but at 125°C for 22 hours and purification by preparative thin layer chromatography (4% MeOH/CH_2Cl_2). ^1H NMR: ($CDCl_3$) δ 11.85 (s, 1H), 9.91 (d, J = 1.6 Hz, 1H), 8.70 (d, J = 2.6 Hz, 1H), 8.65 (dd, J = 1.6, 2.6 Hz, 1H), 8.52 (s, 1H), 8.35 (d, J = 3.1 Hz, 1H), 3.73 (b m, 2H), 3.56 (b m, 4H), 3.53 (b m, 2H), 1.48 (s, 9H); LC/MS: (ES+) m/z $(M+H)^+$ = 471, 473; HPLC R_t = 1.690.

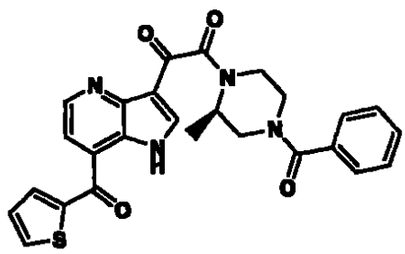
EXAMPLE 167



Precursor 4m (0.098 mmol) was dissolved in DMF (1 mL) and treated with *N*-[5-(2-Bromofuroyl)]piperazine hydrochloride (30 mg, 0.098 mmol), DEBPT (60 mg, 0.19 mmol) and Hunig's base (70 μL, 0.19 mmol) and the reaction mixture was stirred at

rt for 18h. The solvent was removed in vacuum and the residue was purified by reverse phase preparative HPLC. The fractions showing the right LC/MS:(ES^+) m/z $(M+H)^+$ = 518,520 were collected, concentrated and purified again using a preparative TLC (5% $MeOH/CH_2Cl_2$) to afford the title compound as a white solid. ^1H-NMR (500 MHz, $CDCl_3$) δ 10.7 (s, 1H), 9.00 (s, 1H), 8.54 (s, 1 H), 8.40 (s, 1H), 7.06 (d, *J*=3.4 Hz, 1H), 6.46 06 (d, *J*=3.4 Hz, 1H), 3.90-3.66 (bm, 8H).

EXAMPLE 168

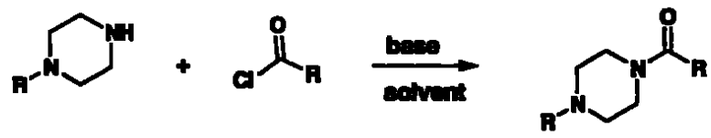


Example 168, 1-benzoyl-3-(R)-methyl-4-[(7-(2-thienylcarbonyl)-4-azaindol-3-yl)-oxoacetyl]piperazine, was prepared from a reaction 1-benzoyl-3-(R)-methyl-4-[(7-(methoxymethylamino)carbonyl)-4-azaindol-3-yl)-oxoacetyl]piperazine and 2-thienyl lithium by using the same procedure for the preapartion of I-64, 1-benzoyl-3-(R)-methyl-4-[(7-(2-propynyl)carbonyl-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{23}N_4O_4S$: 487.14; found 487.11. HPLC retention time: 1.31 minutes (column A).

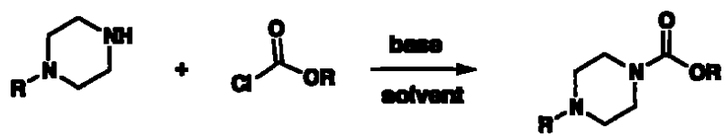
General procedure for the preparation of piperazine amides or carbamides:

The free nitrogen atom of piperazine could be masked as amides or carbamides via reactions of piperazine with acyl halides, acyl acids or acyl halo formates, which are shown in the following schemes 80 and 81.

Scheme 80

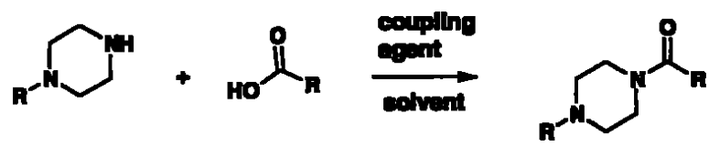


base = Et_3N, IPr_2NEt, pyridine, DBU, DMAP
solvent = THF, ether, CH_2Cl_2, DMF, dioxane, benzene



base = Et_3N, IPr_2NEt, pyridine, DBU, DMAP
solvent = THF, ether, CH_2Cl_2, DMF, dioxane, benzene

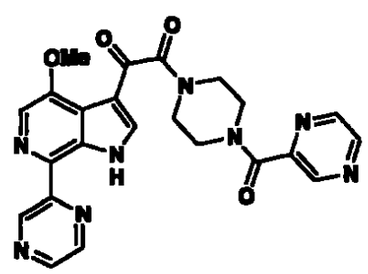
Scheme 81



coupling agent = DDC, EDAC, DEBPT
solvent = THF, ether, CH_2Cl_2, dioxane, DMF, benzene

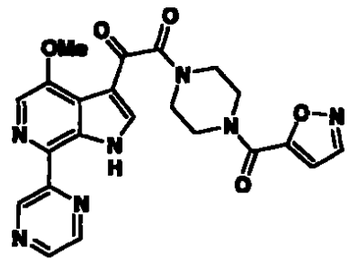
Example 195 – 199 were prepared via a procedure demonstrated in Scheme 80. The typical procedure is presented in the synthesis of Example 195.

EXAMPLE 195



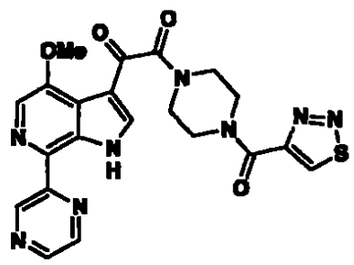
Example 195: Precursor 5u (40 mg), pyrazine carbonyl chloride (50 mg) and *I*-Pr_2NEt (0.2 g) were combined in 1 ml of THF. After the reaction was stirred at room temperature for 16 h, the mixture was concentrated *in vacuo* to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide the desired compound 195 (4.7 mg). MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{21}N_8O_4$: 473.17; found 473.42. HPLC retention time: 1.14 minutes (column C).

EXAMPLE 196



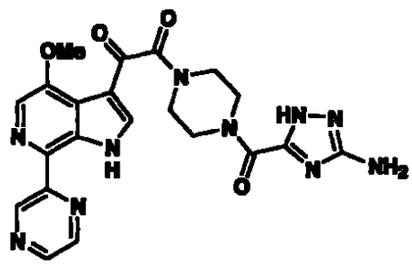
Example 196, was prepared from Precursor 5u and 4-isoxazole carbonyl chloride. MS *m/z*: $(M+H)^+$ Calc'd for $C_{22}H_{20}N_7O_5$: 462.15; found 462.41. HPLC retention time: 1.09 minutes (column C).

EXAMPLE 197



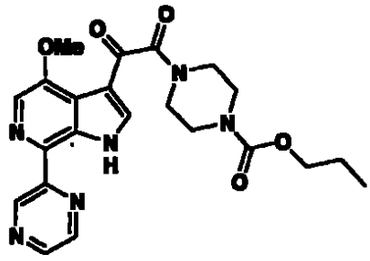
Example 197, was prepared from Precursor 5u and 4-(1,2,3-thiodiazole)-carbonyl chloride. MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{19}N_8O_4S$: 479.12; found 479.31. HPLC retention time: 1.17 minutes (column C).

EXAMPLE 198



Example 198, was prepared from Precursor 5u and 5-(3-amino-1,2,4-triazole)-carbonyl chloride. MS *m/z*: $(M+H)^+$ Calc'd for $C_{21}H_{21}N_{10}O_4$: 477.17; found 477.36. HPLC retention time: 0.97 minutes (column C).

EXAMPLE 199

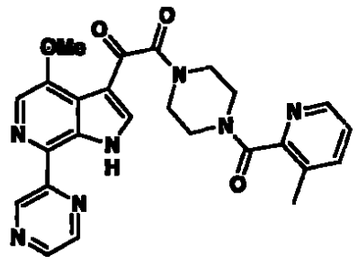


Example 199, was prepared from Precursor 5u and propanyl chloro formate. MS *m/z*: $(M+H)^+$ Calc'd for $C_{22}H_{25}N_6O_5$: 453.19; found 453.17. HPLC retention time: 1.53 minutes (column M).

Example 200 – 201 were prepared via a procedure demonstrated in Scheme 81. The typical procedure is presented in the synthesis of Example 200.

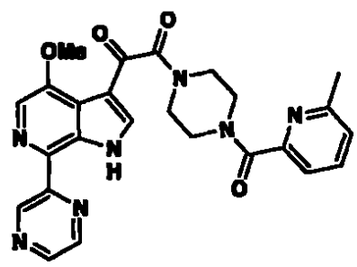
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EXAMPLE 200



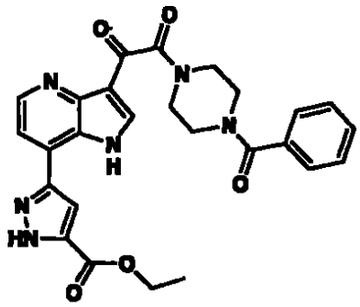
Example 200: 3-methyl-2-picolinic acid (140 mg), EDAC (190 mg) pentafluorophenol (180 mg) were combined in DMF, and, the reaction was stirred for 12 hours. Precursor 3u was then added and resulted mixture was stirred at room temperature for another 16 hours. Solvents were removed *in vacuo* to give a residue which was purified using a Shimadzu automated preparative HPLC System to provide the desired compound 200 (28 mg). MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 486.14. HPLC retention time: 1.08 minutes (column G).

EXAMPLE 201



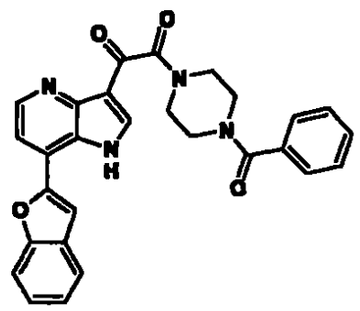
Example 201, was prepared from Precursor 5u and 6-methyl-2-picolinic acid. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 486.28. HPLC retention time: 1.44 minutes (column G).

EXAMPLE 202



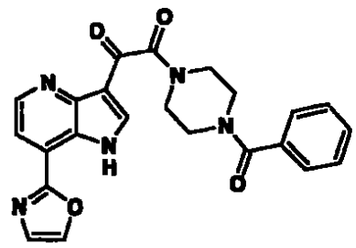
Example 202, was prepared from Precursor 5p and the ethyl pyrazol-5-yl stannane carboxylate to provide 5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-1H-pyrrolo[3,2-b]pyridin-7-yl}-2H-pyrazole-3-carboxylic acid ethyl ester. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_5$: 501.18; found 501.13. HPLC retention time: 1.14 minutes (column G).

EXAMPLE 203



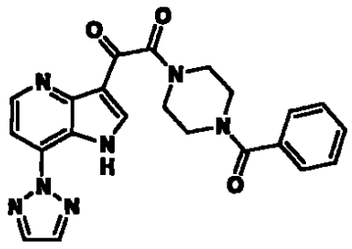
Example 202, was prepared from Precursor 5p and the benzofuran-2-yl stannane to provide 1-(7-benzofuran-2-yl-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{21}N_4O_4$: 479.16; found 479.07. HPLC retention time: 1.31 minutes (column G).

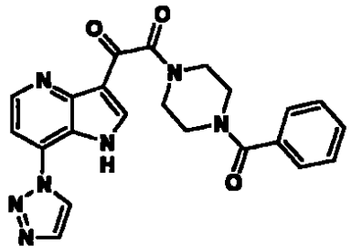
EXAMPLE 204



Example 204, was prepared from Precursor 5p and the oxazol-2-yl stannane to provide 1-benzoyl-4-[7-(oxazol-2-yl)-4-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{23}H_{20}N_5O_4$: 430.14; found 430.07. HPLC retention time: 2.08 minutes (column E, 10 minute gradient).

EXAMPLE 205 and EXAMPLE 206

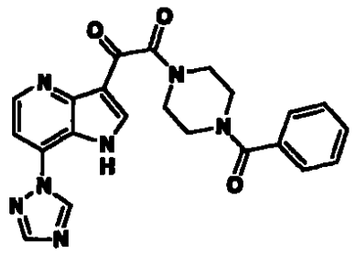




Example 205 and 206. In a sealed tube -(4-benzoyl-piperazin-1-yl)-2-(7-chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)-ethane-1,2-dione (30 mg, 0.076 mmol) , 1*H*-1,2,3-triazole (160 mg, 2.3 mmol) , Cu (0) (10 mg, 0.16 mmol) and K_2CO_3 (11 mg, 0.080 mmol) were heated at 160° C for 16h. The reaction mixture was diluted with MeOH, filtered through celite and concentrated. The reaction mixture was diluted with MeOH, filtered through celite and concentrated. The residue was purified by preparative HPLC to provide 1-(4-benzoyl-piperazin-1-yl)-2-(7-[1,2,3]triazol-2-yl-1H-pyrrolo[3,2-b]pyridin-3-yl)-ethane-1,2-dione: ^{1}H NMR (300 MHz, CD_3OD) δ 8.79 (d, *J* = 6.6 Hz, 1H), 8.79 (s, 1H), 8.48 (d, *J* = 6.6 Hz, 1H), 8.40 (s, 2H), 7.48 (br s, 5H), 4.00- 3.55 (m, 8H). MS *m/z* $(M+H)^+$ calcd for $C_{22}H_{20}N_7O_3$: 430.15; found 430.29. HPLC retention time 0.91 min (Column G); and 1-(4-benzoyl-piperazin-1-

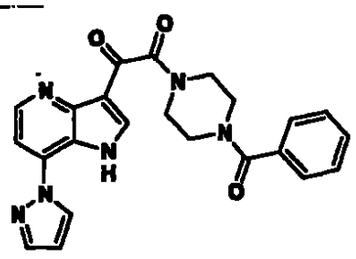
yl)-2-(7-[1,2,3]triazol-1-yl-1H-pyrrolo[3,2-b]pyridin-3-yl)-ethane-1,2-dione: ^{1}H NMR (300 MHz, CD_3OD) δ 8.97 (d, J = δ1.2 Hz, 1H), 8.70 (d, J = 5.6 Hz, 1H), 8.48 (s, 1H), 8.06 (d, J = 1.2 Hz, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.47 (br s, 5H), 4.00- 3.45 (m, 8H). MS m/z $(M+H)^+$ calcd for $C_{22}H_{20}N_7O_3$: 430.15; found 430.29. HPLC retention time 0.90 min (Column G).

EXAMPLE 207



Example 207, was prepared as in Example 205 from Precursor 5p and 1,2,4-triazole to provide 1-(4-benzoyl-piperazin-1-yl)-2-(7-[1,2,4]triazol-1-yl-1H-pyrrolo[3,2-b]pyridin-3-yl)-ethane-1,2-dione. ^{1}H NMR (300 MHz, CD_3OD) δ 9.73 (s, 1H), 8.82 (d, J = 6.6 Hz, 1H), 8.77 (s, 1H), 8.55 (s, 1H), 8.32 (d, J = 6.6 Hz, 1H), 7.48 (br s, 5H), 4.00- 3.45 (m, 8H). MS m/z $(M+H)^+$ calcd for $C_{22}H_{20}N_7O_3$: 430.15; found 430.27. HPLC retention time 0.87 min (Column G).

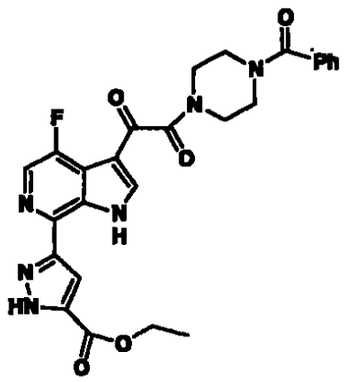
EXAMPLE 208



Example 208, was prepared as in Example 205 from Precursor 5p and pyrazole to provide 1-(4-Benzoyl-piperazin-1-yl)-2-(7-pyrazol-1-yl-1H-pyrrolo[3,2-b]pyridin-3-yl)-ethane-1,2-dione. ^{1}H NMR (300 MHz, CD_3OD) δ 8.87 (d, J = 2.7 Hz, 1H), 8.70

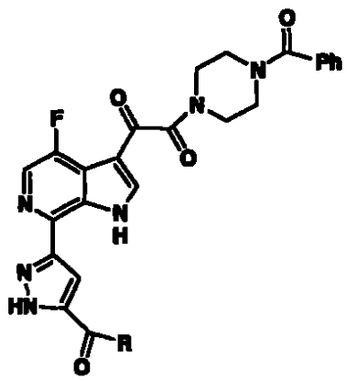
(s, 1H), 8.68 (d, J = 6.6 Hz, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 6.6 Hz, 1H), 7.48 (br s, 5H), 6.85 (dd, J = 2.7, 1.5 Hz, 1H), 4.00- 3.50 (m, 8H). MS m/z $(M+H)^+$ calcd for $C_{23}H_{21}N_6O_3$: 429.16; found 429.23. HPLC retention time 0.87 min (Column G).

EXAMPLE 209



The compound of Example 209 was prepared according to the general method described above starting from Precursor 5i and pyrazol-3-carboxylic ethyl ester-5-tributyltin prepared as described in the following reference: Heterocycles, 1992, 33(2), 813-18. After cooling to ambient temperature, the reaction mixture was concentrated in vacuum. The residue was filtered through filter paper and washed with methanol. The resulting yellow solid was dried in air to provide Compound X; ^{1}H NMR (500MHz, $CDCl_3$): 8.33 (s, 1H); 8.31 (s, 1H); 7.66 (s, 1H); 7.46-7.39 (m, 5H); 4.47-4.42 (q, 2H); 3.98-3.45 (m, 8H); 1.43-1.40 (t, 3H). LC/MS: (ES^+) m/z $(M+H)^+$ = 519. Rt = 1.43min.

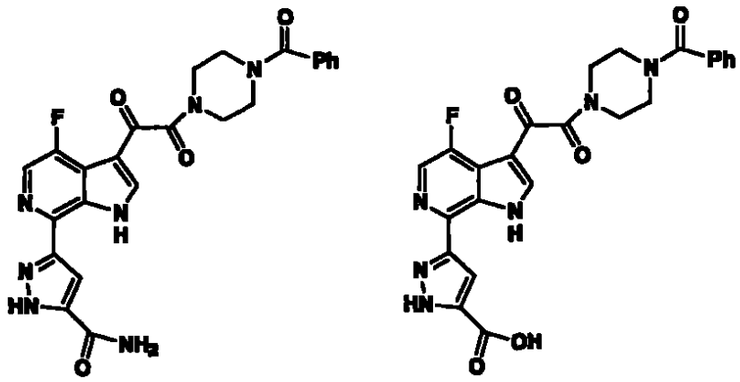
EXAMPLES 210-213



General procedure for the preparation of Examples 210-213

The compound of Example 209 was treated with an excess (>5eq.) of the corresponding amine and stirred in a sealed tube at ambient temperature or 70°C (R = NH_2) for 20hr. The resulting solution was concentrated on a rotary evaporator and purified by reverse phase preparative HPLC.

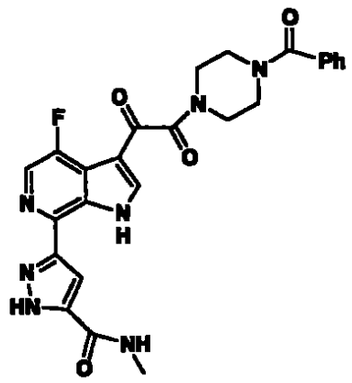
EXAMPLES 210 and 214



Compounds of Example 210 and 214 were prepared from compound of Example 209 and ammonium hydroxide following the procedure described above. X1a: ^{1}H NMR (500MHz, CD_3OD_3): 8.40-8.37 (m, 1H); 8.28-8.27 (m, 1H); 7.58-7.39 (m, 6H); 3.97-3.43 (m, 8H). LC/MS: (ES$^+$) m/z $(M+H)^+$ = 490. Rt = 1.14min. X1b: 8.43 (s, 1H);

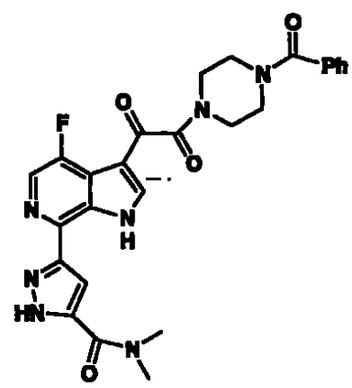
8.29 (s, 1H); 7.56 (s, 1H); 7.45-7.55 (m, 5H); 3.99-3.45 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 491. Rt = 1.12min.

EXAMPLE 211



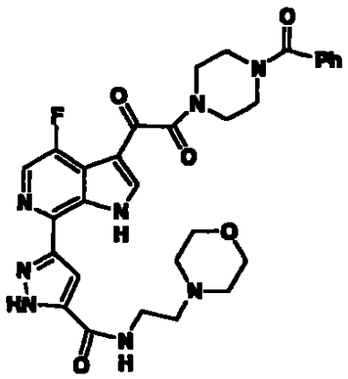
The compound od Example 211 was prepared from the compound of Example 209 and methylamine following the procedure described above. ^1H NMR (500MHz, CD_3OD_3): 8.43 (s, 1H); 8.31 (s, 1H); 7.49 (bs, 5H); 7.45 (s, 1H) 3.97-3.48 (m, 8H); 2.97 (s, 3H). LC/MS: (ES^+) m/z $(M+H)^+$ = 504. Rt = 1.31min.

EXAMPLE 212



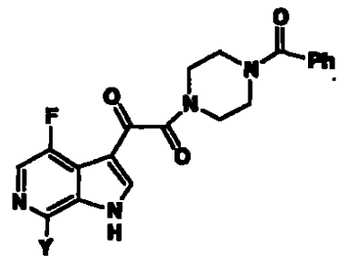
The compound of example 212 was prepared from the compound of example 209 and dimethylamine following the procedure described above. LC/MS: (ES^+) m/z $(M+H)^+$ = 518. Rt = 122min.

COMPOUND 213



The compound of Example 213 was prepared from the compound of Example 209 and *N*-aminoethylmorpholine following the procedure described above. ^{1}H NMR (500MHz, CD_3OD_3): 8.41 (s, 1H); 8.31 (s, 1H); 7.52-7.49 (m, 6H); 4.19-3.20 (m, 20H); LC/MS: (ES$^+$) m/z $(M+H)^+$ = 603. Rt = 1.03min.

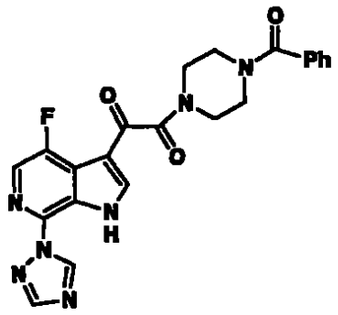
COMPOUNDS OF EXAMPLES 215-222



General procedure for the preparation of compounds of Examples 215-222

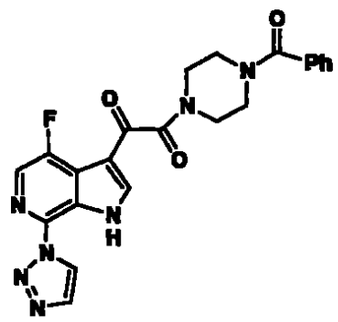
A mixture of precursor 5i, 30 equivalents of the corresponding amine, 1 equivalent of copper powder and 1 equivalent of potassium carbonate was heated at 160°C for 4-7hr in a sealed tube. The reaction was cooled to room temperature and filtered through filter paper. The filtrate was diluted with methanol and purified by preparative HPLC.

EXAMPLE 215



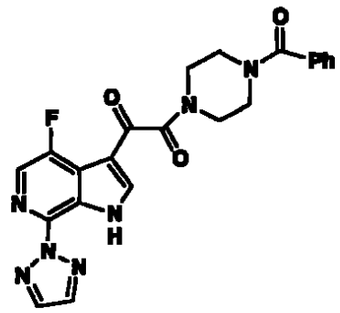
Example 215 was prepared from precursor 5i and 1,2,4-triazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 11.15 (bs, 1H); 9.28 (s, 1H); 8.33-8.34 (m, 1H); 8.22 (s, 1H); 8.10 (s, 1H); 7.46-7.42 (m, 5H); 3.90-3.48 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 448. Rt = 1.21min.

EXAMPLE 216



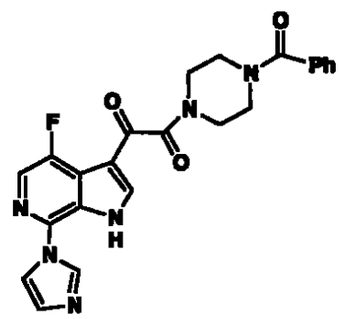
Example 216 was prepared from precursor 5i and 1,2,3-triazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 11.16 (bs, 1H); 8.75 (s, 1H); 8.37-8.37 (s, 1H); 8.15 (s, 1H); 7.92 (s, 1H); 7.43 (bs, 5H); 3.99-3.48 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 448. Rt = 1.28min.

EXAMPLE 217



Example 217 was prepared from precursor 5i and 1,2,3-triazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 11.12 (bs, 1H); 8.78-8.77 (m, 1H); 8.37-8.36 (m, 1H); 8.02-8.0 (m, 2H); 7.45- 7.41 (m, 5H); 4.11-3.45 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 448. Rt = 1.03min.

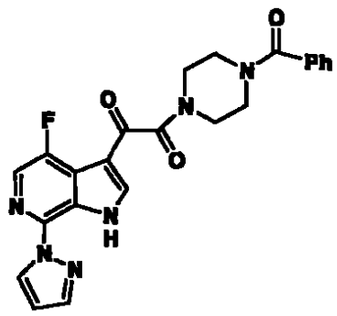
EXAMPLE 218



Example 218 was prepared from precursor 5i and imidazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 13.35 (bs, 1H); 9.49 (s, 1H); 8.35-8.30 (m, 1H); 8.20 (s, 1H); 7.97 (s, 1H); 7.56-7.53 (m, 1H); 7.46-7.41 (m, 5H); 3.98-3.40 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 447. Rt =1.25min.

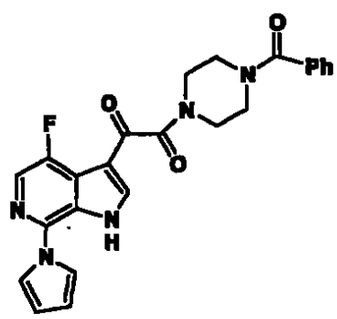
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EXAMPLE 219



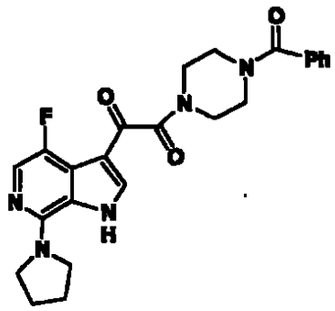
Example 219 was prepared from precursor 5i and pyrazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 11.52 (bs, 1H); 8.65-8.64 (m, 1H); 8.27-8.26 (m, 1H); 8.05-8.04 (m, 1H); 7.81-7.80 (m, 1H); 7.50- 7.35 (m, 5H); 6.54-6.53 (m, 1H); 4.01- 3.47 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+ = 447$. Rt = 1.25min.

EXAMPLE 220



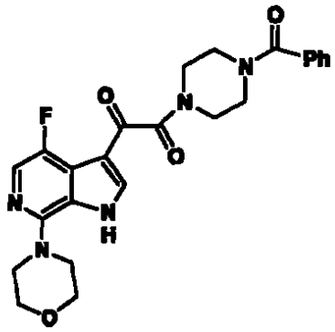
Example 220 was prepared from precursor 5i and pyrrole following the procedure described above. ^{1}H NMR (300MHz, CD_3OD_3): 8.33-8.29 (m, 2H); 7.49-7.40 (m, 5H); 7.38-7.37 (m, 2H); 6.42-6.41 (m, 2H); 3.91-3.40 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+ = 446$. Rt = 1.34min.

EXAMPLE 221

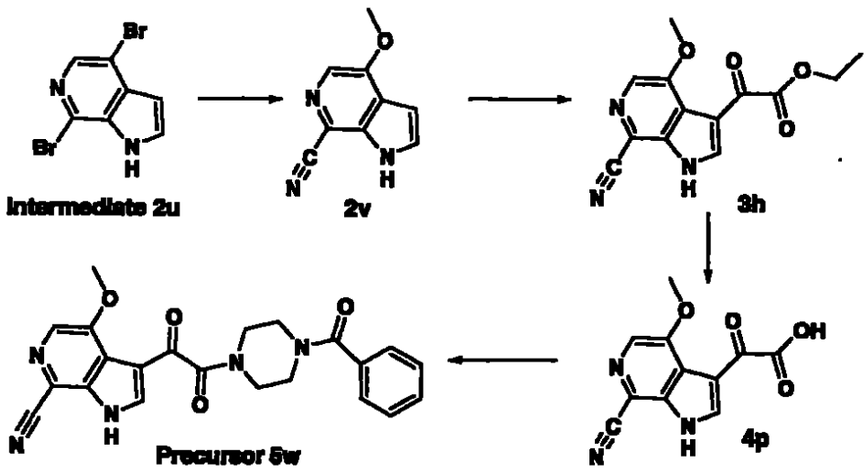


Example 221 was prepared from precursor 5i and pyrrolidine following the procedure described above. ^{1}H NMR (300MHz, CD_3OD_3): 8.37 (s, 1H); 7.61-7.59 (m, 1H); 7.51-7.38 (m, 5H); 4.08-3.23 (m, 12H); 2.25-2.15 (m, 4H). LC/MS: (ES^+) m/z $(M+H)^+$ = 450. Rt = 0.89min.

EXAMPLE 222



Compound of example 222 was prepared from precursor 5i and morpholine following the procedure described above. ^{1}H NMR (300MHz, CD_3OD_3): 8.38 (s, 1H); 7.86-7.84 (m, 1H); 4.14-3.25 (m, 16H). LC/MS: (ES^+) m/z $(M+H)^+$ = 466. Rt = 0.988min.



Preparation of Precursor 5w:

To a mixture of 2u (2.0 g, 7.3 mmol) and CuCN (1.0 g, 11 mmol) was added DMF (20 ml). The reaction mixture was heated at 150°C for 1 hour. After cooling to room temperature, the reaction mixture was added NaOMe (20 ml, 25 wt. % solution in MeOH), and was heated at 110°C for 10 minutes. After cooling to room temperature, the reaction mixture was poured into an aqueous solution of ammonium acetate (sat. 500 ml). The resulting mixture was filtered through a short Celite® pad. The filtrate was extracted with EtOAc (500 ml x 4). The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give a brownish residue, which was triturated with MeOH (5 ml x 3) to provide precursor 2v as a yellow solid (317 mg, 25%). The structure was supported by NOE experiments. ^{1}H NMR: (DMSO-d_6) 12.47 (s, 1H), 8.03 (s, 1H), 7.65 (t, J = 2.8, 1H), 6.70 (dd, J = 2.8, 1.8, 1H), 4.08 (s, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 174; HPLC (alternate conditions B, column G) R_t = 1.320.

Preparation of Precursor 3h:

To 1-ethyl-3-methylimidazolium chloride (85 mg, 0.58 mmol) in a capped vial was quickly added aluminum chloride (231 mg, 1.73 mmol). The mixture was vigorously stirred at room temperature until the formation of the ionic liquid. After cooling to room temperature, the ionic liquid was added compound 2v (50 mg, 0.29 mmol) and ethyl chlorooxoacetate (0.2 ml, 1.79 mmol). The reaction mixture was stirred at room temperature for three hours, cooled to 0°C and quenched by carefully adding ice-water (15 ml). The precipitates were filtered, washed with water (5 ml x 3) and

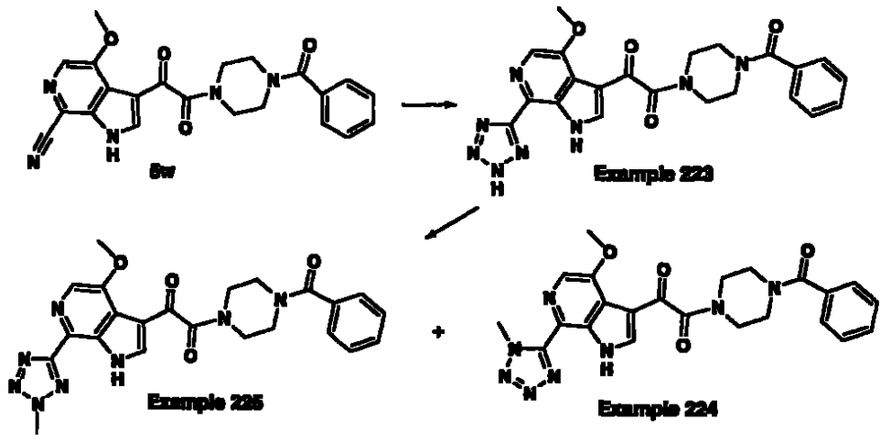
dried *in vacuo* to give 3h as a grayish yellow solid (50 mg, 63%). ^{1}H NMR: (DMSO-d_6) 13.73 (s, 1H), 8.54 (s, 1H), 8.26 (s, 1H), 4.35 (q, J = 7.0, 2H), 4.06 (s, 3H), 1.29 (t, J = 7.0, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 274; HPLC (alternate conditions B, column G) R_t = 1.527.

Preparation of Precursor 4p:

To a mixture of 3h (200 mg, 0.73 mmol) in MeOH (1 ml) was added NaOH (2.5 ml, 1*N* aqueous). The reaction mixture was stirred at room temperature for 30 minutes, and then acidified with hydrochloric acid (1*N*, ~3 ml) to pH about 2. The solid was filtered, washed with water (5 ml x 4), and dried *in vacuo* to give 4p as a brownish solid (160 mg, 89%). Compound 4p was used directly in the following reaction without further purification. LC/MS: (ES+) m/z $(M+H)^+$ = 246; HPLC (alternate conditions B, column G) R_t = 0.777.

Preparation of Precursor 5w:

To a mixture of 4p (160 mg, 0.65 mmol), DEPBT (390 mg, 1.31 mmol) and benzoylpiperazine hydrochloride (222 mg, 0.98 mmol) was added DMF (2 ml) and *N,N*-diisopropylethylamine (1.2 ml, 6.9 mmol). The reaction mixture was stirred at room temperature for 16 hours, and concentrated to remove most of the solvent. The residue was diluted with MeOH (10 ml) and then filtered. The filtrate was purified by preparative reverse phase HPLC using the method: Start %B = 15, Final %B = 70, Gradient time = 30 min, Flow Rate = 40 ml/min, Wavelength = 220 nm, Column : XTERRA C18 5 µm 30 x 100mm, A = 10% MeOH,- 90% H_2O – 0.1% TFA, B = 90% MeOH – 10% H_2O – 0.1% TFA, Fraction Collection: 14.03 – 15.43 min. The structure was supported by NOE experiments. ^{1}H NMR: (DMSO-d_6) 13.66 (s, 1H), 8.45 (s, 1H), 8.25 (s, 1H), 7.45 (s, 5H), 4.07 (s, 3H), 3.80 – 3.40 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 418 HPLC (alternate conditions B, column G) R_t = 1.447.



Preparation of Example 223:

To a mixture of 5w (15 mg, 0.036 mmol), NaN_3 (24 mg, 0.36 mmol), and NH_4Cl (19 mg, 0.36 mmol) was added DMF (1 ml). The reaction mixture was heated at 100°C for three hours. After cooling to room temperature, the reaction mixture was added MeOH (4 ml) and then filtered. The filtrate was purified by preparative reverse phase HPLC using the method: Start %B = 15, Final %B = 75, Gradient time = 15 min, Flow Rate = 40 ml/min, Wavelength = 220 nm, Column : XTERRA C18 5 μm 30 x 100mm, A = 10% MeOH,- 90% H_2O – 0.1% TFA, B = 90% MeOH – 10% H_2O – 0.1% TFA, Fraction Collection: 8.48 – 9.78 min. ^1H NMR: (DMSO-d_6) 12.68 (b s, 1H), 8.26 (s, 1H), 8.24 (s, 1H), 7.46 (s, 5H), 4.09 (s, 3H), 3.86 – 3.30 (b m, overlapping with broad water peak, 8H), one exchangeable proton was not observed due to the presence of water in the sample. LC/MS: (ES+) m/z $(M+H)^+$ = 461 HPLC (alternate conditions B, column G) R_t = 1.392.

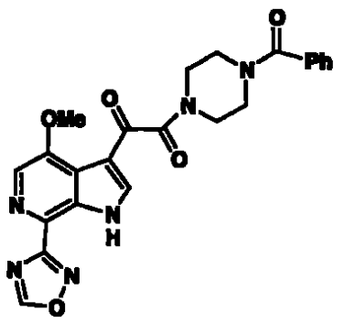
Preparation of Examples 224 and 225:

To the mixture of 5w (10 mg, 0.022 mmol) in MeOH (0.2 ml) and benzene (0.4 ml) was added $TMSCHN_2$ (0.4 ml, 0.1 M*). The reaction mixture was stirred at room temperature for 1.5 hours, followed by purification on preparative TLC (1 x 20 x 20 cm, 500 microns) with 10% MeOH/CH_2Cl_2 to give the two compounds as white solids. Example 224 (2.7 mg, 26%); ^1H NMR: (DMSO-d_6) 12.60 (b s, 1H), 8.31 (s, 1H), 8.23 (s, 1H), 7.46 (s, 5H), 4.50 (s, 3H), 4.15 (s, 3H), 3.80 – 3.30 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 475, HPLC (alternate conditions B, column G) R_t =

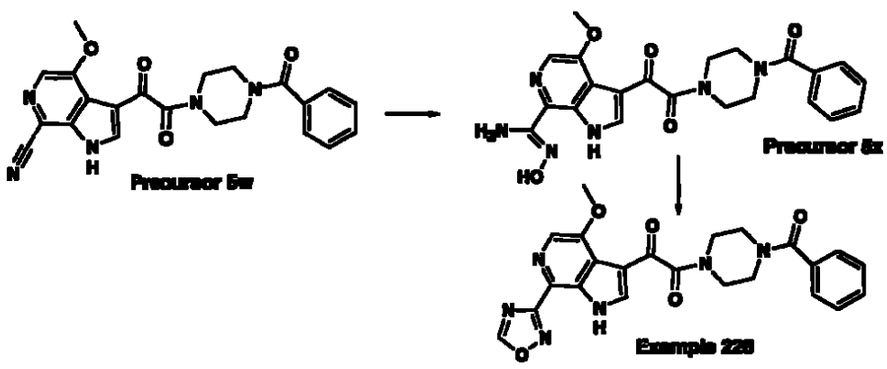
1.672. Example 225 (1.4 mg, 13%), ^{1}H NMR: (DMSO-d_6) 12.40 (b s, 1H), 8.22 (s, 1H), 8.20 (s, 1H), 7.46 (s, 5H), 4.52 (s, 3H), 4.04 (s, 3H), 3.80 – 3.30 (b m, 8H); *LC/MS*: (ES+) m/z $(M+H)^+$ = 475, HPLC (alternate conditions B, column G) R_t = 1.373. These two structures were further supported by nitrogen HMBC analysis.

*$TMSCHN_2$ (0.1 M) was prepared by diluting commercially available $TMSCHN_2$ (0.2 ml, 2.0 M) with hexane (3.8 ml).

EXAMPLE 226



Reaction scheme for prep of example 226



Preparation of Example 226

To a mixture of 5w (85 mg, 0.204 mmol) and hydroxylamine hydrochloride (22 mg, 0.305 mmol) in anhydrous ethanol (3 ml, 200 proof) was added triethylamine (60 µl, 0.4 mmol). The reaction mixture was heated in a capped vial at 100°C for 6 hours. Removal of solvent gave precursor 5x as a white solid, to which was added triethyl orthoformate (3 ml). The mixture was then heated in a capped vial at 100°C for 12

hours. After removal of most of the excess triethyl orthoformate, the residue was diluted with MeOH (6 ml), followed by filtration. The filtrate was purified by preparative reverse phase HPLC using the method: Start %B = 30, Final %B = 50, Gradient time = 20 min, Flow Rate = 40 ml/min, Column : XTERRA C18 5 μm 30 x 100mm, Fraction Collection: 7.57 – 7.98 min. ^{1}H NMR: (DMSO-d_6) 12.41 (s, 1H), 9.87 (s, 1H), 8.27 (s, 1H), 8.24 (s, 1H), 7.45 (s, 5H), 4.06 (s, 3H), 3.68–3.20 (b m, overlapping with broad water peak, 8H); The following HPLC conditions for the analytical LCMS were used: Column: Xterra C18 S7 3 x 50 mm; Gradient Time = 3 min; Flow rate = 4 ml/min. LC/MS: (ES+) m/z $(M+H)^+$ = 461 HPLC R_t = 1.390. Product from a similar run provided the following 1H NMR spectra (methanol-d6) δ 9.32 (s, 1H), 8.28 (s, 2H), 7.83 (s,1H), 7.45 (narrow multiplet, 6H), 4.05 (s,3H), 3.80 (bm, 4H), 3.56 (bm, 4H).

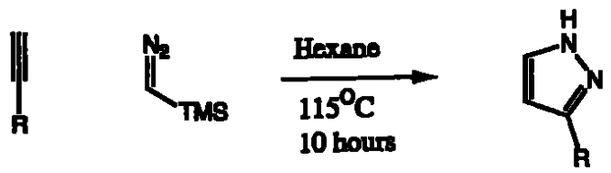
EXAMPLES 227 to 229

Examples 227 to 230 (Table 2-1) were prepared analogously to Example 194 except that the appropriate substituted piperazine was utilized. The preparation of the appropriate substituted piperazines is described for precursors 17a-d or in reference 90b.

General procedures for the preparation of pyrazoles

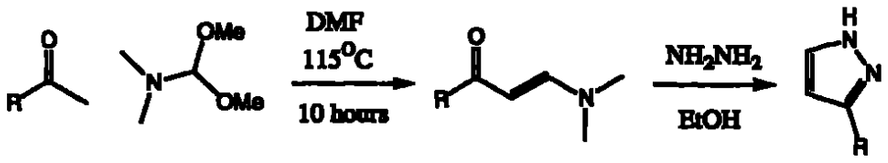
3-Substituted pyrazoles can be prepared *via* the following routes:

Route P-A



Alkyne (1 eq.) was dissolved in a 2M solution of diazomethane (5-10 eq.) in hexane and resulting mixture was heated to 110-115°C for 12 hours. After reaction was quenched with MeOH, removal of solvents provided a residue which was used in the next step without any purification.

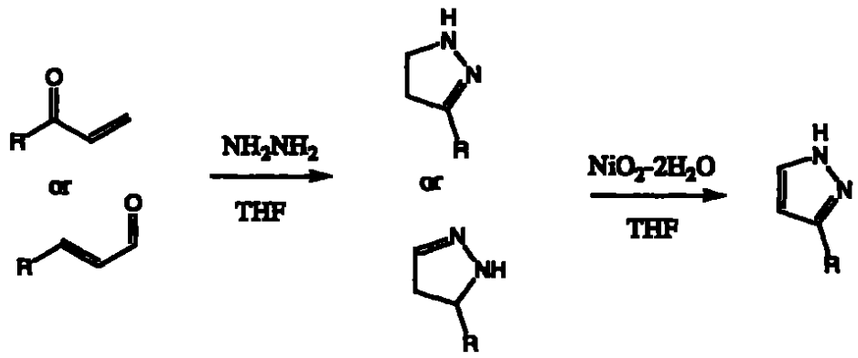
Route P-B



Methyl ketone (1 eq.) was added into a solution of dimethoxy-DMF (5-10 eq.) in DMF and the resulting mixture was heated to 110-115°C for 12 hours. Solvents were then removed under vaccum to provide a residue.

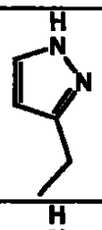
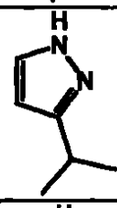
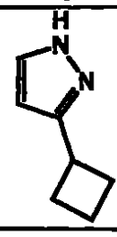
The above residue was mixed with hydrazine (5-10 eq.) in ethanol and the reaction was kept in refluxing for 12 hours. Removal of solvents in vacco gave a residue, which was carried onto further reactions without purification.

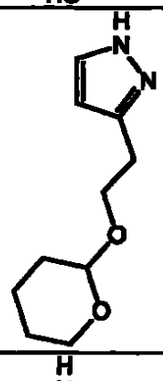
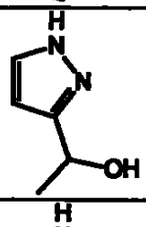
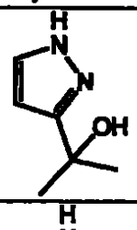
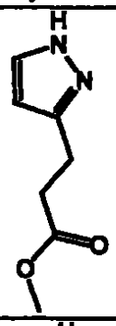
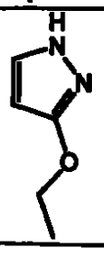
Route P-C

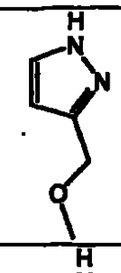
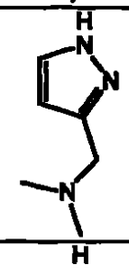
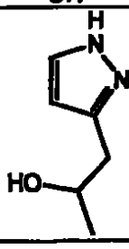


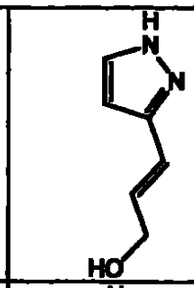
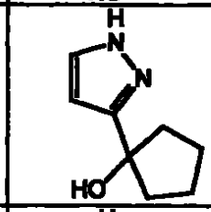
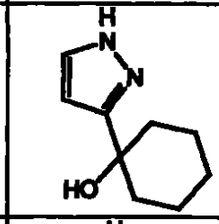
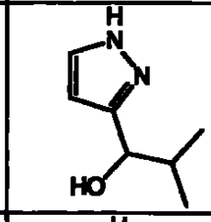
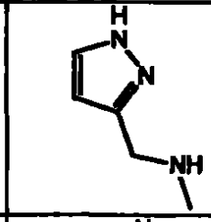
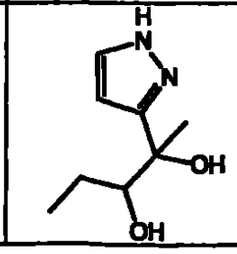
Hydrazine (10-20 eq.) was added into a solution of alkenone or alkenal (1 eq.) in THF and the resulting mixture was heated to 110-115°C for 12 hours. After the mixture cooled down to room temperature, an excess of NiO2-2H2O (5-10 eq.) was then added into the reaction mixture and the reaction was stirred at room temperature for another 12 hours. Insoluble materials were then filtered away and concentration under vaccum provided a residue that was used in the further reactions without purification.

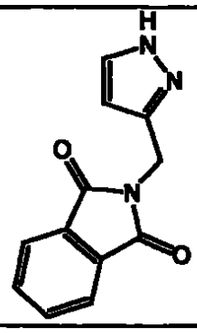
Table I-5 Preparation of Pyrazoles

Compound[a]	Structure	Method Used	HPLC R_t (column)/MS $(M+H)^+$ or $(M+Na)^+$
Pyrazole-001		P-A	0.35 min (column L)
Pyrazole-002		P-A	0.59 min (column L)
Pyrazole-003		P-A	1.07 min (column L) / MS $(M+H)^+$: Calc'd 139.12 Found 139.18
Pyrazole-004		P-A, P-B, P-C	0.53 min (column L)
Pyrazole-005		P-B	0.48 min (column L)
Pyrazole-006		P-A	0.63 min (column L)

Pyrazole-007		P-A	0.21 min (cloumn G)
Pyrazole-008		P-A	0.81 min (column L) / MS (M+H)$^+$: Calc'd 197.13 Found 197.18
Pyrazole-009		P-A	
Pyrazole-010		P-A	0.34 min (column L)
Pyrazole-011		P-A	0.47 min (column L) / MS (M+H)$^+$: Calc'd 155.08 Found 155.06
Pyrazole-012		P-A	0.38 min (column G)

Pyrazole-013		P-A	
Pyrazole-014		P-A	
Pyrazole-015		P-A	0.26 min (column L) / MS $(M+Na)^+$: Calc'd 149.07 Found 149.11
Pyrazole-016		P-A	0.31 min (column L) / MS $(M+H)^+$: Calc'd 141.10 Found 141.17
Pyrazole-017		P-A	0.27 min (column L) / MS $(M+Na)^+$: Calc'd 149.07 Found 149.13

Pyrazole-018		P-A	0.22 min (column L)
Pyrazole-019		P-A	0.61 min (column L) / MS (M+Na)$^+$: Calc'd 175.08 Found 175.14
Pyrazole-020		P-A	0.79 min (column L) / MS (M+Na)$^+$: Calc'd 189.10 Found 189.17
Pyrazole-021		P-A	0.59 min (column L) / MS (M+H)$^+$: Calc'd 141.10 Found 141.18
Pyrazole-022		P-A	0.22 (column L)
Pyrazole-023		P-A	0.34 min (column L) / MS (M+Na)$^+$: Calc'd 193.10 Found 193.14

Pyrazole-024		P-A	1.05 min (column L) / MS (M+H)$^+$: Calc'd 228.08 Found 228.14

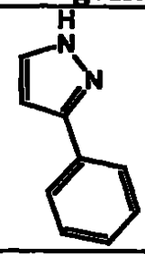
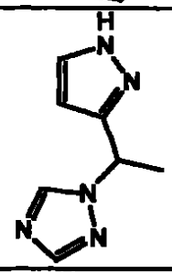
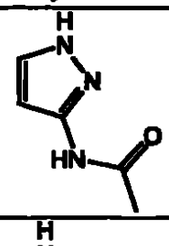
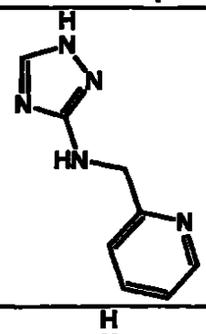
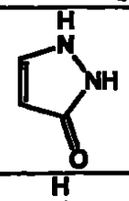
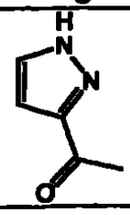
General Procedure Si-Cu

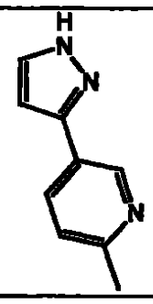
Silicon masked general procedure for attaching pyrazoles, imidazoles and triazoles with melting-points higher than 160°C to C-7 position of azaindoles:

In cases where the meltingpoints of the nitrogen heterocycle to be attached to the azaindole have melting points higher than 160°C, an excess of the heterocycle (usually greater than 3 equivalents) is heated with a larger excess of hexamethydisilazane or chloro trimethylsilane (> 10 equivalents) at temperatures up to 140°C for approximately 12h. The excess silylating reagent is removed in vacuo and the mixture is combined with the azaindole halide and the copper catalyzed reaction is conducted as below.

A mixture of halo-indole or halo-azaindole intermediate, 1-2 equivalents of copper powder, with 1 equivalent preferred for the 4-F,6-azaindole series and 2 equivalents for the 4-methoxy,6-azaindole series; 1-2 equivalents of potassium carbonate, and the the corresponding silylated heterocyclic reagent as prepared above, was heated at 135-160°C for 4 to 9 hours, with 5 hours at 160°C preferred for the 4-F,6-azaindole series and 7 hours at 135°C preferred for the 4-methoxy,6-azaindole series. The reaction mixture was cooled to room temperature and filtered through filter paper. The filtrate was diluted with methanol and purified either by preparative HPLC or silica gel. In many cases no chromatography is necessary, the product can be obtained by crystallization with methanol.

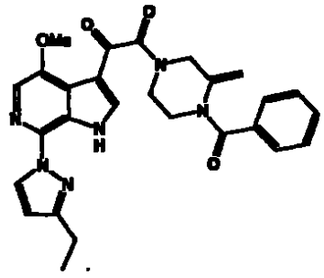
Table I-6 N-containing Heterocycles Applied under General Procedure Si-Cu (Silicon-Masking Conditions)

Entry	N-Containing Heterocycle
HM-01	
HM-02	
HM-03	
HM-04	
HM-05	
HM-06	

HM-07	

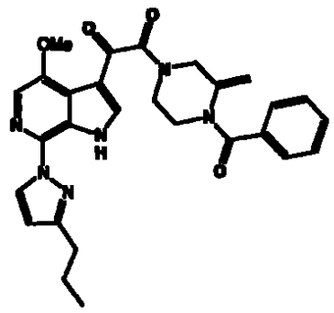
Examples 230 through Example 258, were prepared using the same conditions and method used for synthesizing Example 187:

EXAMPLE 230



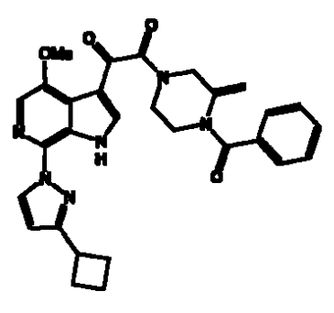
Example 230, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-001 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-ethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{29}N_6O_4$: 501.23; found 501.17. HPLC retention time: 2.30 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLE 231



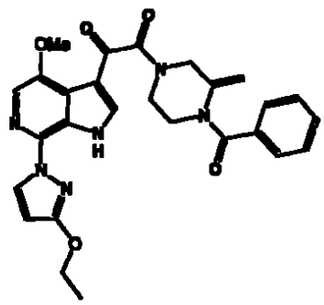
Example 231, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-002 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-propyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{31}N_6O_4$: 515.24; found 515.19. HPLC retention time: 2.47 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLE 232



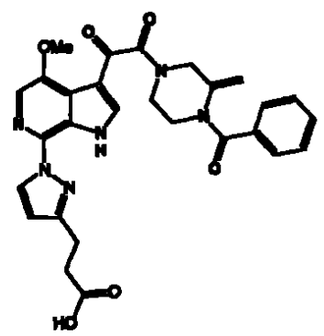
Example 232, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-006 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-cycloputyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{31}N_6O_4$: 527.24; found 527.16. HPLC retention time: 2.53 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLE 233



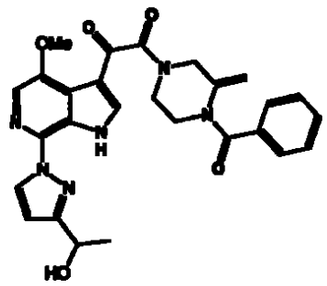
Example 233, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-012 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-ethoxy-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{29}N_6O_5$: 517.22; found 517.17. HPLC retention time: 2.26 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLE 234



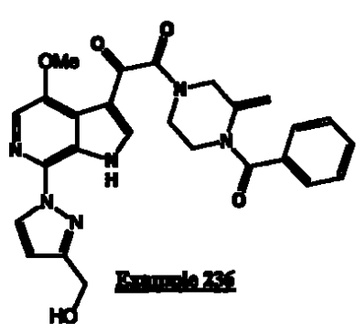
Example 234, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-011 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-(2-hydroxylcarbonylethan-1-yl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{29}N_6O_4$: 545.21; found 545.15. HPLC retention time: 2.08 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLE 235



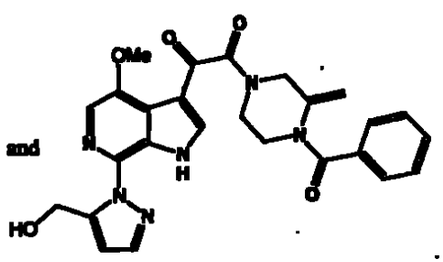
Example 235, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-009 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-(1-hydroxylethyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{29}N_6O_5$: 517.22; found 517.15. HPLC retention time: 1.43 minutes (column G).

EXAMPLES 236 AND 237



Example 236

and



Example 237

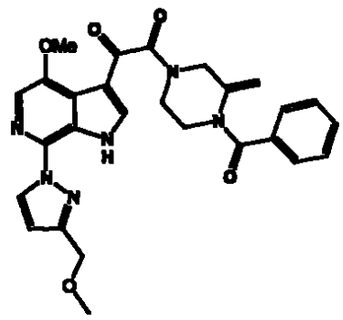
Examples 236 and 237, were prepared according to the general method described above starting from Precursor 5z and Pyrazole-007 to provide Example 236, (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-hydroxylmethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine and Example 237, (R)-1-benzoyl-3-methyl-4-[(4-methoxy-7-(4-hydroxylmethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine.

Example 236, (R)-1-benzoyl-3-methyl-4-[(4-methoxy-7-(3-hydroxylmethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine : MS *m/z*: $(M+H)^+$ Calc'd for

$C_{26}H_{27}N_6O_5$: 503.20; found 503.20. HPLC retention time: 1.87 minutes (column G, flow rate 4ml/min, gradient time 3 min).

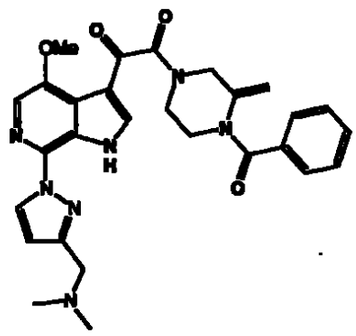
Example 237, (R)-1-benzoyl-3-methyl-4-[(4-methoxy-7-(4-hydroxylmethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine : MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_6O_5$: 503.20; found 503.25. HPLC retention time: 1.31 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLE 238



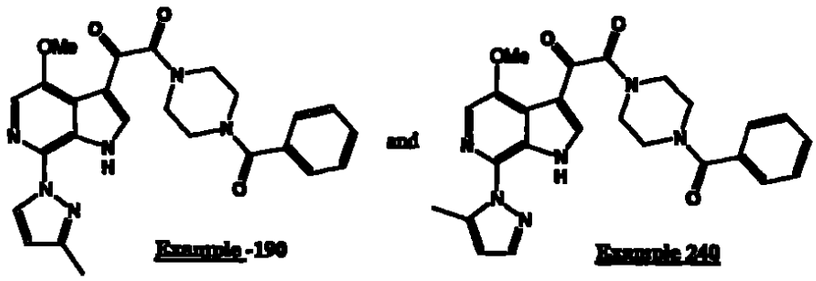
Example 238, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-013 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-methoxymethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{29}N_6O_5$: 517.22; found 517.23. HPLC retention time: 1.95 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLE 239



Example 239, was prepared according to the general method described above starting from Precursor 5z and Pyrazole-014 to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-(N,N-dimethylamino)methyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{32}N_7O_4$: 530.25; found 530.25. HPLC retention time: 1.45 minutes (column G, flow rate 4ml/min, gradient time 3 min).

EXAMPLES 190 AND 240



Example -190 Example 240

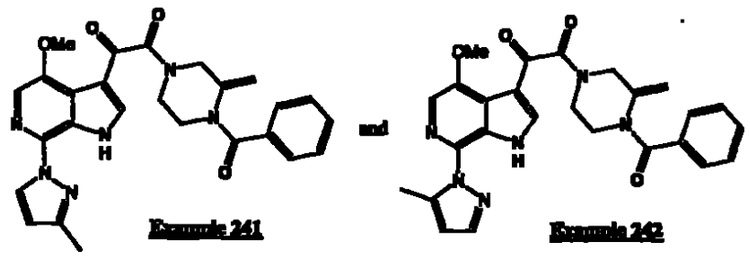
Examples 190 and 240, were prepared according to the general method described above starting from Precursor 5b and 3-methylpyrazole to provide example Example 190 and Example 240.

Example 240, 1-benzoyl-4-[(4-methoxy-7-(5-methyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_6O_4$: 473.19; found 473.19. HPLC retention time: 1.35 minutes (column G).

Example 190, 1-benzoyl-4-[(4-methoxy-7-(3-methyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_6O_4$: 473.19; found 473.17. HPLC retention time: 1.50 minutes (column G).

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EXAMPLES 241 AND 242



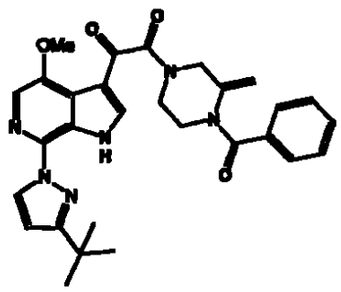
Example 241 and Example 242

Examples 241 and 242, were prepared according to the general method described above starting from Precursor 5z and 3-methylpyrazole.

Example 241, (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-methyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_6O_4$: 487.21; found 486.20. HPLC retention time: 1.54 minutes (column G).

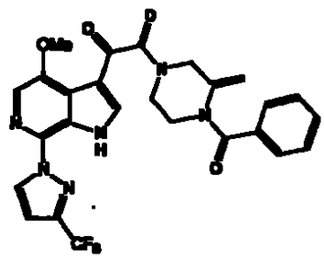
Example 242, (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(5-methyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_6O_4$: 487.21; found 486.20. HPLC retention time: 1.41 minutes (column G).

EXAMPLE 243



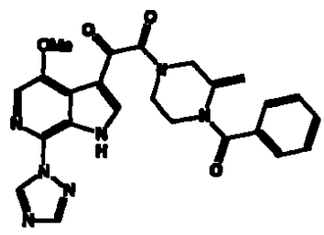
Example 243, was prepared according to the general method described above starting from Precursor 5z and 3-t-butylpyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-t-butyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{30}N_6O_4$: 529.26; found 529.29. HPLC retention time: 1.86 minutes (column G).

EXAMPLE 244



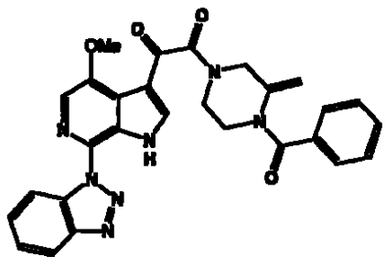
Example 244, was prepared according to the general method described above starting from Precursor 5z and 3-trifluoromethylpyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-trifluoromethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}F_3N_6O_4$: 541.18; found 541.25. HPLC retention time: 1.71 minutes (column G).

EXAMPLE 245



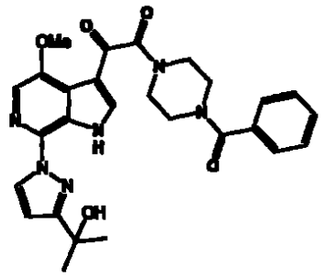
Example 245, was prepared according to the general method described above starting from Precursor 5z and 1,2,4-triazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(1,2,4-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{24}N_7O_4$: 474.19; found 474.23. HPLC retention time: 1.29 minutes (column G).

EXAMPLE 246



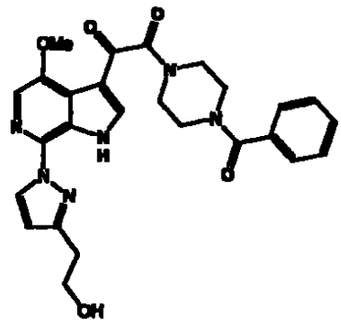
Example 246, was prepared according to the general method described above starting from Precursor 5z and 1,2,3-benzotriazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(1,2,3-benzotriazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{25}N_7O_4$: 524.20; found 524.27. HPLC retention time: 1.68 minutes (column G).

EXAMPLE 247



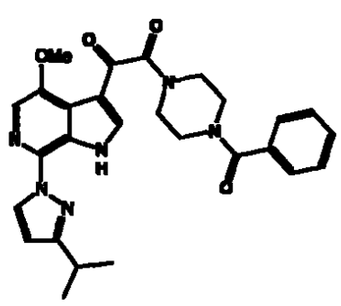
Example 247, was prepared according to the general method described above starting from Precursor 5b and Pyrazole-010 to provide 1-benzoyl-4-[(4-methoxy-7-(3-(1-hydroxyl-1-methylethyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{29}N_6O_5$: 517.22; found 517.37. HPLC retention time: 1.38 minutes (column L).

EXAMPLE 248



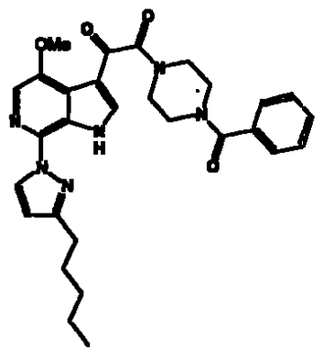
Example 248, was prepared according to the general method described above starting from Precursor 5b and Pyrazole-008 to provide 1-benzoyl-4-[(4-methoxy-7-(3-(3-hydroxylethyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_6O_5$: 503.20; found 503.27. HPLC retention time: 1.16 minutes (column L).

EXAMPLE 249



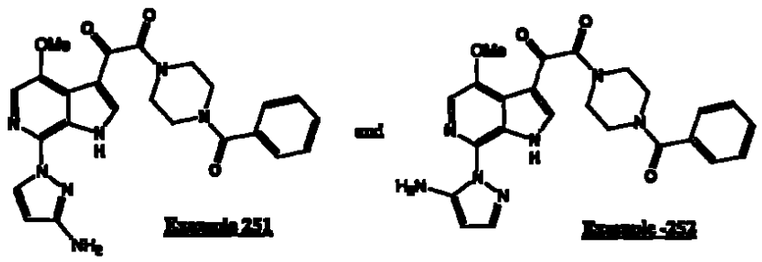
Example 249, was prepared according to the general method described above starting from Precursor 5b and Pyrazole-004 to provide 1-benzoyl-4-[(4-methoxy-7-(3-iso-propyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{29}N_6O_4$: 501.23; found 501.34. HPLC retention time: 1.74 minutes (column L).

EXAMPLE 250



Example 250, was prepared according to the general method described above starting from Precursor 5b and Pyrazole-003 to provide 1-benzoyl-4-[(4-methoxy-7-(3-n-pentyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{33}N_6O_4$: 529.26; found 529.34. HPLC retention time: 1.96 minutes (column L).

EXAMPLES 251 AND APP 252



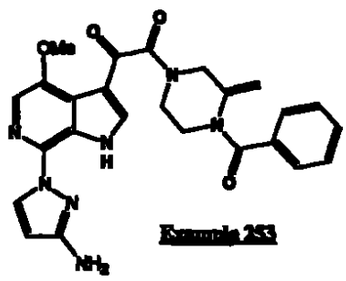
Example 251 Example 252

Examples 251 and 252, were prepared according to the general method described above starting from Precursor 5b and 3-aminopyrazole.

Example 251, 1-benzoyl-4-[(4-methoxy-7-(3-amino-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{24}N_7O_4$: 474.29; found 474.24. HPLC retention time: 1.58 minutes (column G).

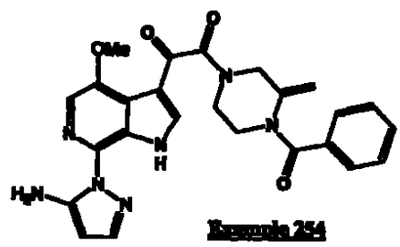
Example 252, 1-benzoyl-4-[(4-methoxy-7-(5-amino-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{24}N_7O_4$: 474.29; found 474.22. HPLC retention time: 1.59 minutes (column G).

EXAMPLES 253 AND 254



Example 253

and



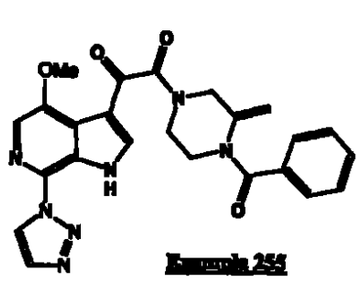
Example 254

Examples 253 and 254, were prepared according to the general method described above starting from Precursor 5z and 3-aminopyrazole.

Example 253, (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-amino-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{26}N_7O_4$: 488.20; found 488.25. HPLC retention time: 1.65 minutes (column G, flow rate = 4 ml/min, gradient time = 3 min).

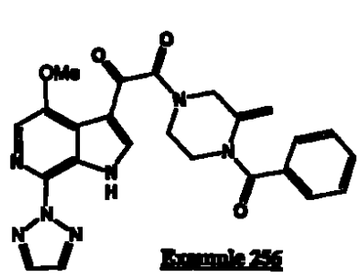
Example 254, (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(5-amino-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{26}N_7O_4$: 488.20; found 488.25. HPLC retention time: 1.74 minutes (column G, flow rate = 4 ml/min, gradient time = 3 min).

EXAMPLES 255 AND 256



Example 255

and



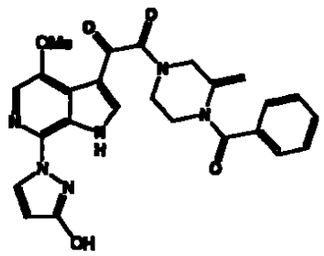
Example 256

Examples 255 and 256, were prepared according to the general method described above starting from Precursor 5z and 1,2,3-triazole. Precursor 5z (0.056 g), 0.056g Cu powder,0.025g K2CO3 and 10 equivalents of 1,2,3 triazole were heated at 155-170 C for 4 hrs. The reaction was allowed to cool to ambient temperature and the residue was dissolved in MeOH and purifed by Prep HPLC. as described above in the general methods to provide Example 255 (0.020g) as a brown solid,yield 34% and the other isomer Example 256.

Example 255, (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(1,2,3-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{24}N_7O_4$: 474.19; found 474.21. HPLC retention time: 1.84 minutes (column G, flow rate = 4 ml/min, gradient time = 3 min). ^1H NMR (500 MHz, CD_3OD) δ8.85 (s, 1H), 8.32 (ss, 1H), 7.94 (m, 2H), 7.48 (m, 5H), 4.07 (ss, 3H), 4.00-3.00 (m, 7H), 1.33 (m, 3H).

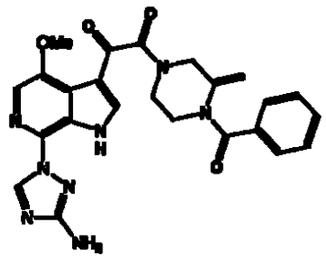
Example 256, (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(1,2,3-triazol-2-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{24}N_7O_4$: 474.19; found 474.21. HPLC retention time: 1.66 minutes (column G, flow rate = 4 ml/min, gradient time = 3 min). ^1H NMR (500 MHz, CD_3OD) δ8.33 (ss, 1H), 8.13 (s, 1H), 7.46 (m, 7H), 4.07 (ss, 3H), 4.00-3.00 (m, 7H), 1.32 (m, 3H).

EXAMPLE 257



Example 257, was prepared according to the general method described above starting from Precursor 5z and 3-hydroxylpyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-hydroxylpyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_6O_5$: 489.19; found 489.15. HPLC retention time: 1.38 minutes (column G).

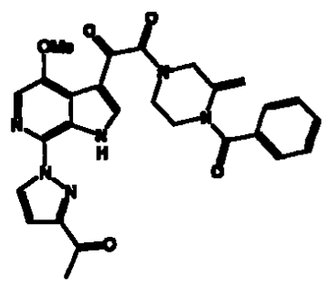
EXAMPLE 258



Example 258, was prepared according to the general method described above starting from Precursor 5z and 3-amino-1,2,4-triazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-amino-1,2,4-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{25}N_8O_4$: 489.20; found 489.24. HPLC retention time: 1.69 minutes (column G).

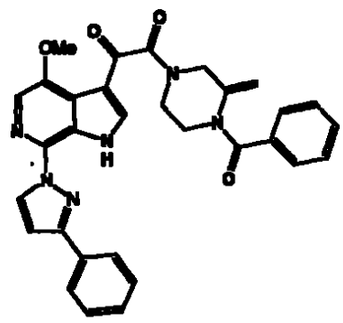
Examples 259 through 265, were prepared according to the Gnereral Procedure Si-Cu (Silicon-Masking conditions) described above:

EXAMPLE 259



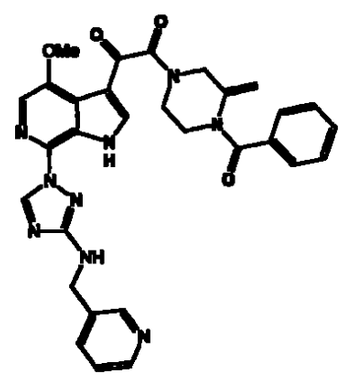
Example 259, was prepared according to the general method Si-Cu(Silicon-Masking) described above starting from Precursor 5z and 3-methylcarbonylpyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-methylcarbonyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{27}N_6O_5$: 515.20; found 515.15. HPLC retention time: 1.51 minutes (column G).

EXAMPLE 260



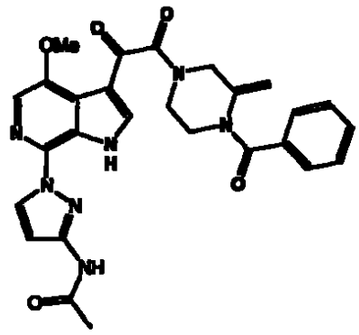
Example 260, was prepared according to the general method Si-Cu (Silicon-Masking) described above starting from Precursor 5z and 3-phenylpyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-phenyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{31}H_{29}N_6O_4$: 549.23; found 549.18. HPLC retention time: 1.82 minutes (column G).

EXAMPLE 261



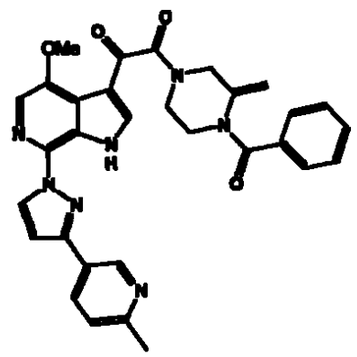
Example 261, was prepared according to the general method Si-Cu (Silicon-Masking) described above starting from Precursor 5z and 3-(3-pyridinemethylamino)-1,2,4-triazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-(3-pyridinemethylamino)-1,2,4-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{30}N_9O_4$: 580.24; found 580.14. HPLC retention time: 1.15 minutes (column G).

EXAMPLE 262



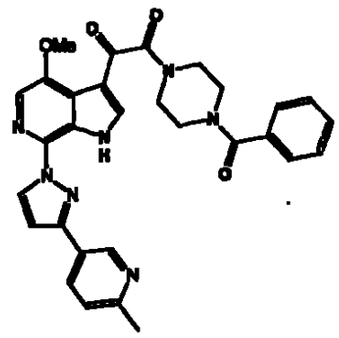
Example 262, was prepared according to the general method Si-Cu (Silicon-Masking) described above starting from Precursor 5z and 3-acetylaminopyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-acetylamino-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{28}N_7O_5$: 530.22; found 530.15. HPLC retention time: 1.41 minutes (column G).

EXAMPLE 263



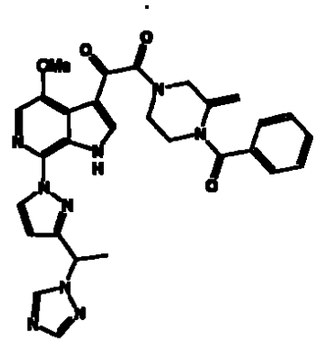
Example 263 was prepared according to the general method Si-Cu (Silicon-Masking) described above starting from Precursor 5z and 3-(2-methylpyridin-5-yl)pyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-(2-methylpyridin-5-yl)pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{31}H_{30}N_7O_4$: 564.24; found 564.26. HPLC retention time: 1.22 minutes (column C).

EXAMPLE 264



Example 264 was prepared according to the general method Si-Cu (Silicon-Masking) described above starting from Precursor 5b and 3-(2-methylpyridin-5-yl)pyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-(2-methylpyridin-5-yl)pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{28}N_7O_4$: 550.22; found 550.26. HPLC retention time: 1.20 minutes (column C).

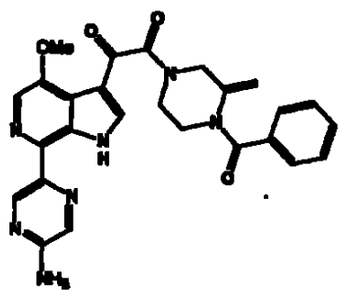
EXAMPLE 265



Example 265 was prepared according to the general method Si-Cu (Silicon-Masking) described above starting from Precursor 5z and 3-(1,2,4-triazol-1-yl)ethyl-pyrazole to provide (R)-1-benzoyl-2-methyl-4-[(4-methoxy-7-(3-(1,2,4-triazol-1-yl)ethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{30}N_9O_4$: 568.24; found 568.13. HPLC retention time: 1.44 minutes (column G).

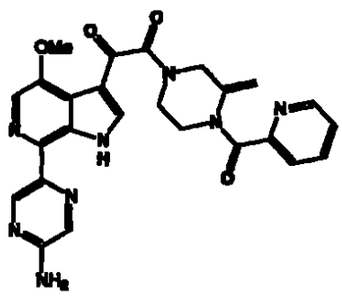
Examples 266 to 270, were prepared according to a procedure analogous to the procedure used synthesize Example 15:

EXAMPLE 266



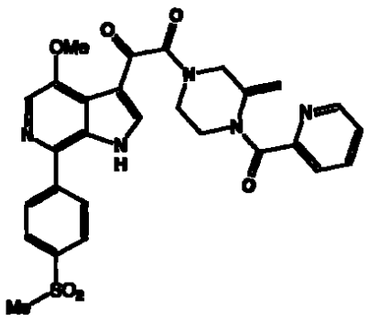
Example 266, was prepared according to the general method described above starting from Precursor 5z and 2-amino-pyrazin-5-yl tributyltin, to provide (R)-1-benzoyl-2-methyl-4-[(7-(2-amino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_7O_4$: 500.20; found 500.26. HPLC retention time: 1.11 minutes (column G).

EXAMPLE 267



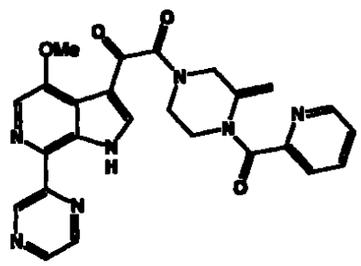
Example 267, was prepared according to the general method described above starting from Precursor 5za and 2-amino-pyrazin-5-yl tributyltin, to provide (R)-1-picolinoyl-2-methyl-4-[(7-(2-amino-pyrazin-5-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_8O_4$: 501.20; found 501.30. HPLC retention time: 1.04 minutes (column J).

EXAMPLE 268



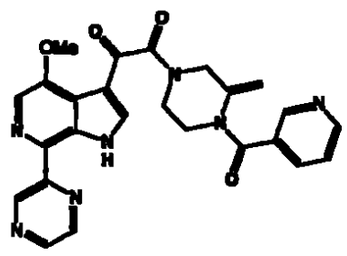
Example 268, was prepared according to the general method described above starting from Precursor 5xa and 4-methylsulfonylphenyl boronic acid, to provide (R)-1-picolinoyl-2-methyl-4-[(7-(4-methylsulfonyl-phenyl-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{28}N_5O_6S$: 562.18; found 562.19. HPLC retention time: 0.86 minutes (column G).

EXAMPLE 269



Example 269, was prepared according to the general method described above starting from Precursor 5xa and tri-butylstannyl pyrazine, to provide (R)-1-picolinoyl-2-methyl-4-[(7-pyrazinyl-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 486.32. HPLC retention time: 1.07 minutes (column G).

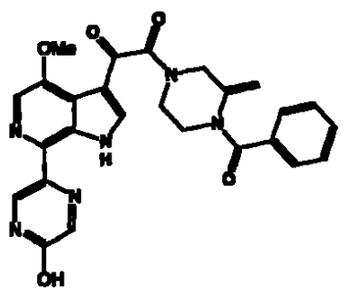
EXAMPLE 270



Example 270, was prepared according to the general method described above starting from Precursor 5y and tri-butylstannyl pyrazine, to provide (R)-1-nicotinoyl-2-methyl-4-[(7-pyrazinyl-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_4$: 486.19; found 486.10. HPLC retention time: 0.96 minutes (column L).

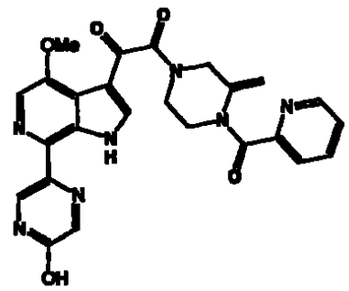
Examples 271 through 272, were prepared using the "General Procedure of Converting –NH_2 Group to –OH Group", exemplified by the preparation of Example 97:

EXAMPLE 271



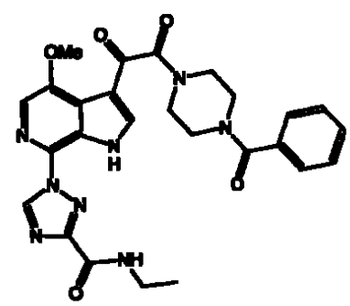
Example 271, was prepared according to the general method described above starting from Example 266 to provide (R)-1-benzoyl-2-methyl-4-[(7-(5-hydroxyl-pyrazin-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{25}N_6O_5$: 501.19; found 501.21. HPLC retention time: 1.08 minutes (column G).

EXAMPLE 272



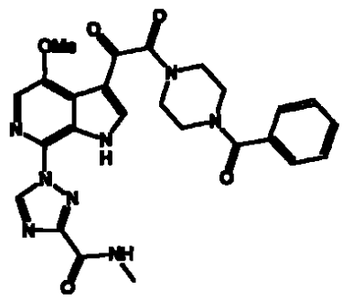
Example 272, was prepared according to the general method described above starting from Example 267 to provide (R)-1-picolinoyl-2-methyl-4-[(7-(5-hydroxyl-pyrazin-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{24}N_7O_5$: 502.18; found 502.19. HPLC retention time: 0.88 minutes (column G).

EXAMPLE 273



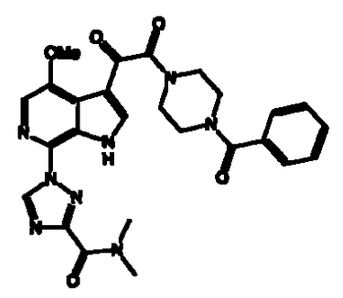
Example 273, was prepared from Precursor 5b and 1H-[1,2,4]-triazole-3-carboxylic acid ethylamide to provide 1-benzoyl-4-[(4-methoxy-7-(3-ethylaminocarbonyl-1,2,4-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_8O_5$: 531.21; found 531.21. HPLC retention time: 1.75 minutes (column G). ^1H NMR (500 MHz, CD_3OD) δ9.35 (s, 1H), 8.34 (s, 1H), 7.86 (s, 1H), 7.48 (b, 5H), 4.06 (s, 3H), 4.00-3.49 (m, 10H), 1.30 (t, 3H, $J = 7.5$ Hz).

EXAMPLE 274



Example 274, was prepared from **Precursor 5b** and 1H-[1,2,4]-triazole-3-carboxylic acid methylamide to provide 1-benzoyl-4-[(4-methoxy-7-(3-methylaminocarbonyl-1,2,4-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{25}H_{25}N_8O_5$: 517.19; found 517.18. HPLC retention time: 1.67 minutes (column G). ^1H NMR (500 MHz, CD_3OD) δ9.36 (s, 1H), 8.35 (s, 1H), 7.88 (s, 1H), 7.48 (b, 5H), 4.06 (s, 3H), 3.80-3.60 (m, 8H), 3.02 (s, 3H).

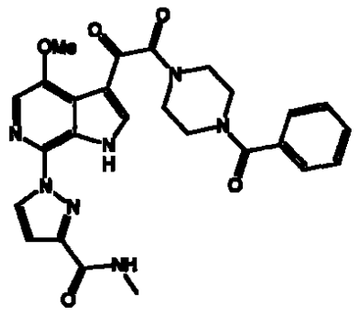
EXAMPLE 275



Example 275, was prepared from **Precursor 5b** and 1H-[1,2,4]-triazole-3-carboxylic acid dimethylamide to provide 1-benzoyl-4-[(4-methoxy-7-(3-dimethylaminocarbonyl-1,2,4-triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{27}N_8O_5$: 531.21; found 531.28. HPLC retention time: 1.71 minutes (column G).

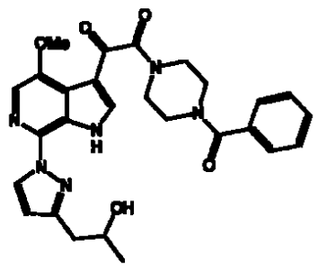
212

EXAMPLE 276



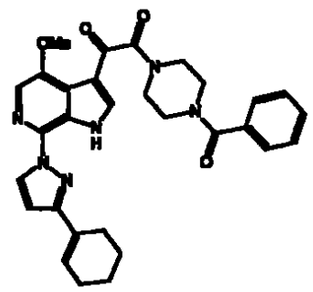
Example 276, was prepared from Precursor 5b and 1H-pyrazole-3-carboxylic acid methylamide to provide 1-benzoyl-4-[(4-methoxy-7-(3-methylaminocarbonyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{26}N_7O_5$: 516.20; found 516.27. HPLC retention time: 1.86 minutes (column G).

EXAMPLE 277



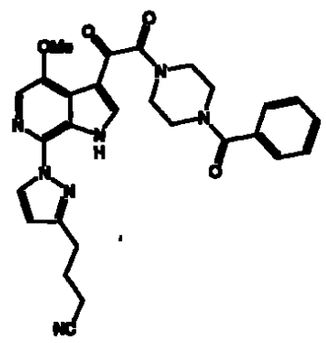
Example 277, was prepared from Precursor 5b and 1-(1H-pyrazol-3-yl)-propan-2-ol to provide 1-benzoyl-4-[(4-methoxy-7-(3-(2-hydroxylpropyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{27}H_{29}N_6O_5$: 517.22; found 517.38. HPLC retention time: 1.42 minutes (column L).

EXAMPLE 278



Example 278, was prepared from **Precursor 5b** and 3-cyclohex-1-enyl-1H-pyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-(cyclohexen-1-yl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{31}N_6O_4$: 539.24; found 539.26. HPLC retention time: 1.96 minutes (column L).

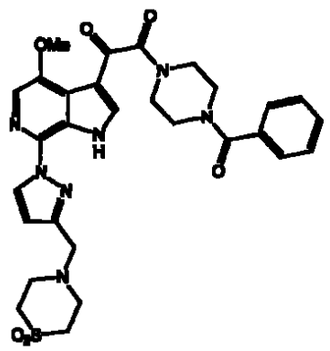
EXAMPLE 279



Example 279, was prepared from **Precursor 5b** and 4-(1H-pyrazol-3-yl)-butyronitrile to provide 1-benzoyl-4-[(4-methoxy-7-(3-(3-cyano-propan-1-yl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{28}N_7O_4$: 526.22; found 526.35. HPLC retention time: 1.51 minutes (column L).

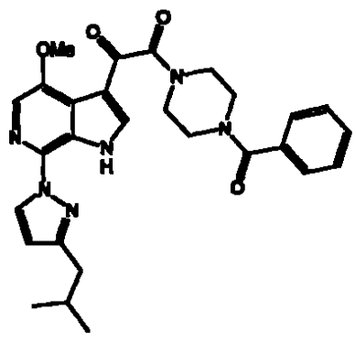
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EXAMPLE 280



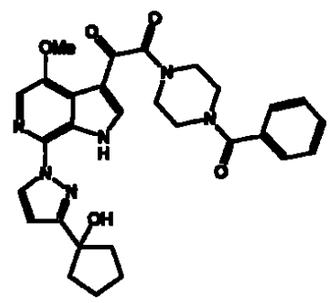
Example 280, was prepared from Precursor 5b and 4-(1H-pyrazol-3-ylmethyl)-thiomorpholine 1,1-dioxide to provide 1-benzoyl-4-[(4-methoxy-7-(3-(1,1-dioxo-thiomorpholin-4-yl)methyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{32}N_7O_6S$: 606.21; found 606.34. HPLC retention time: 1.01 minutes (column L).

EXAMPLE 281



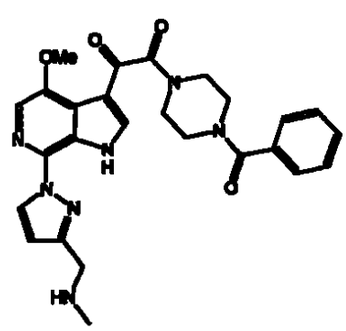
Example 281, was prepared from Precursor 5b and 3-isobutyl-1H-pyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-isobutyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{31}N_6O_4$: 515.24; found 515.35. HPLC retention time: 1.90 minutes (column L).

EXAMPLE 282



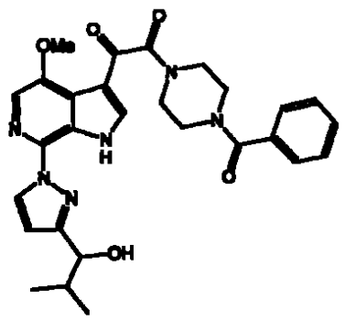
Example-282, was prepared from Precursor 5b and 1-(1H-pyrazol-3-yl)-cyclopentanol to provide 1-benzoyl-4-[(4-methoxy-7-(3-(1-hydroxy-cyclopentyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{31}N_6O_5$: 543.24; found 543.43. HPLC retention time: 1.51 minutes (column L).

EXAMPLE 283



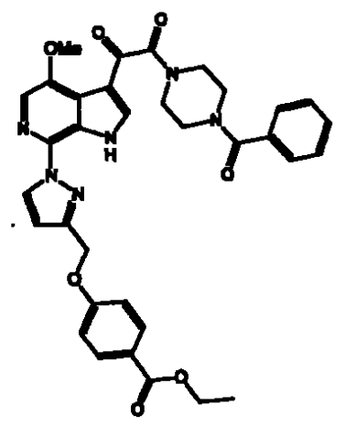
Example 283, was prepared from Precursor 5b and methyl-(1H-pyrazol-3-ylmethyl)-amine to provide 1-benzoyl-4-[(4-methoxy-7-(3-methylaminomethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{28}N_7O_4$: 502.22; found 502.31. HPLC retention time: 1.51 minutes (column L).

EXAMPLE 284



Example 284, was prepared from **Precursor 5b** and 2-methyl-1-(1H-pyrazol-3-yl)-propan-1-ol to provide 1-benzoyl-4-[(4-methoxy-7-(3-(1-hydroxy-2-methyl-propyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine. MS *m/z*: $(M+H)^+$ Calc'd for $C_{28}H_{31}N_6O_5$: 531.24; found 531.43. HPLC retention time: 1.63 minutes (column L).

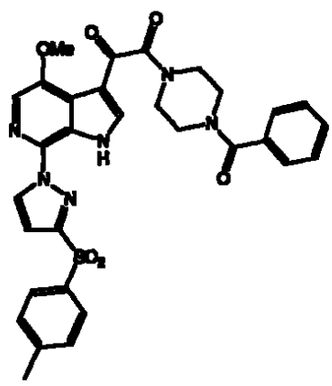
EXAMPLE 285



Example 285, was prepared according to the general method described above starting from **Precursor 5b** and **Pyrazole-025** to provide 1-benzoyl-4-[(4-methoxy-7-(3-(4-ethoxycarbonyl-phenyl)oxymethyl-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{34}H_{33}N_6O_7$: 637.24; found 637.34. HPLC retention time: 1.87 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ8.61 (s, 1H), 8.16 (s, 1H), 8.02 (d, 2H, J = 15 Hz), 7.76 (s, 1H), 7.43 (b,

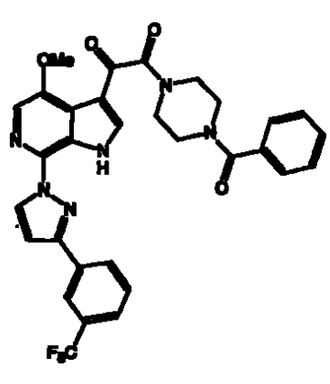
5H), 7.05 (d, 2H, J = 14.5 Hz), 6.60 (s, 1H), 5.29 (s, 2H), 4.33 (q, 2H, J = 12 Hz), 4.03 (s, 3H), 3.80-3.57 (m, 8H), 1.38 (t, 3H, J = 12.0 Hz).

EXAMPLE 286



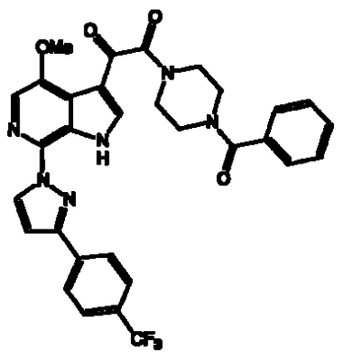
Example 286, was prepared according to the general method described above starting from Precursor 5b and 3-(toluene-4-sulfonyl)-1H-pyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-(toluene-4-sulfonyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS m/z: $(M+H)^+$ Calc'd for $C_{31}H_{29}N_6O_6S$: 613.19; found 613.28. HPLC retention time: 1.69 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ8.64 (s, 1H), 8.21 (s, 1H), 7.94 (d, 2H, J = 8.00 Hz), 7.74 (s, 1H), 7.43 (b, 5H), 7.34 (d, 2H, J = 8.00 Hz), 6.94 (s, 1H), 4.04 (s, 3H), 4.00-3.40 (m, 8H), 2.42 (s, 3H).

EXAMPLE 287



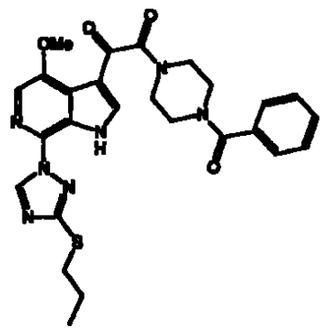
Example 287, was prepared according to the general method described above starting from **Precursor 5b** and 3-(3-trifluoromethyl-phenyl)-1H-pyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-(3-trifluoromethyl-phenyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{31}H_{26}F_3N_6O_4$: 603.20; found 603.32. HPLC retention time: 1.94 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ8.67 (s, 1H), 8.26 (s, 1H), 8.09-7.42 (m, 10H), 6.87 (s, 1H), 4.01 (s, 3H), 4.00-3.62 (m, 8H).

EXAMPLE 288



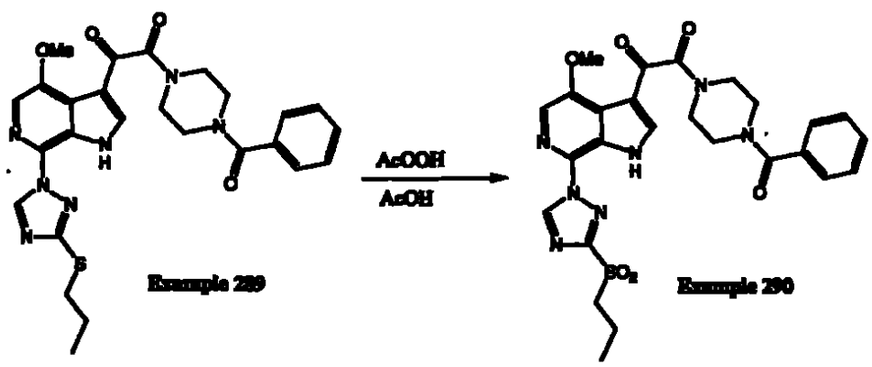
Example 288, was prepared according to the general method described above starting from **Precursor 5b** and 3-(4-trifluoromethyl-phenyl)-1H-pyrazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-(4-trifluoromethyl-phenyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{31}H_{26}F_3N_6O_4$: 603.20; found 603.32. HPLC retention time: 1.96 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ8.69 (s, 1H), 8.26 (s, 1H), 8.09-7.43 (m, 10H), 6.87 (s, 1H), 4.01 (s, 3H), 4.00-3.62 (m, 8H).

EXAMPLE 289



Example 289, was prepared according to the general method described above starting from Precursor 5b and 3-propylsulfanyl-1H-[1,2,4]triazole to provide 1-benzoyl-4-[(4-methoxy-7-(3-propylsulfanyl-[1,2,4]triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{28}N_7O_4S$: 534.19; found 534.32. HPLC retention time: 1.65 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) 89.09 (s, 1H), 8.18 (s, 1H), 7.70 (s, 1H), 7.37 (m, 5H), 4.05 (s, 3H), 3.90-3.30 (m, 8H), 3.18 (t, 2H, J = 11.5 Hz), 1.74 (m, 2H), 1.02 (t, 3H, J = 12.5 Hz).

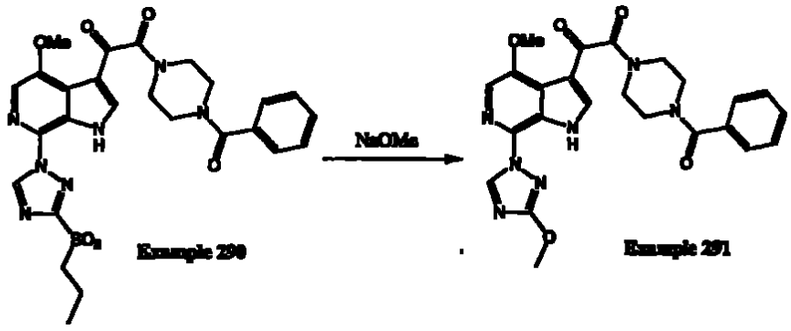
EXAMPLE 290



Example 290 (18mg) was dissolved in 1ml of AcOOH (37% in AcOH) at room temperature and the mixture was kept stirring for 10 hours. Removal of solvents under vaccum provided a redicue, which was purified using Shimadzu automated preparative HPLC System to provide Example 290, 1-benzoyl-4-[(4-methoxy-7-(3-(propane-1-sulfonyl)-[1,2,4]triazol-1-yl)-6-azaindol-3-yl)-

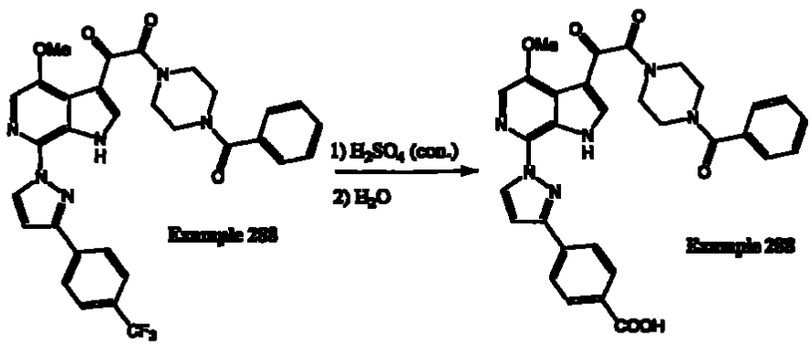
oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{26}H_{28}N_7O_6S$: 566.18; found 566.30. HPLC retention time: 1.44 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ9.33 (s, 1H), 8.24 (s, 1H), 7.80 (s, 1H), 7.43 (m, 5H), 4.08 (s, 3H), 3.90-3.50 (m, 8H), 3.42 (t, 2H, J = 8.00 Hz), 1.90 (m, 2H), 1.09 (t, 3H, J = 7.50 Hz).

EXAMPLE 291



Example 290, obtained from the previous stage, was dissolved in 5ml of MeONa (8 wt% in MeOH) at room temperature and the mixture was heated to 90°C for 10 hours to form 291, 1-benzoyl-4-[(4-methoxy-7-(3-methoxy-[1,2,4]triazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{24}H_{24}N_7O_5$: 490.18; found 490.29. HPLC retention time: 1.36 minutes (column G).

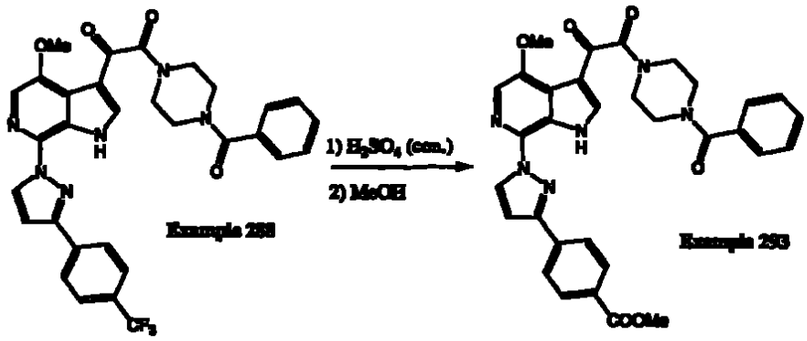
EXAMPLE 292



Example 288 (8mg) was dissolved in 0.2ml of concentrated at room temperature and the mixture was heated to 70°C for 6 hours. Then the mixture was

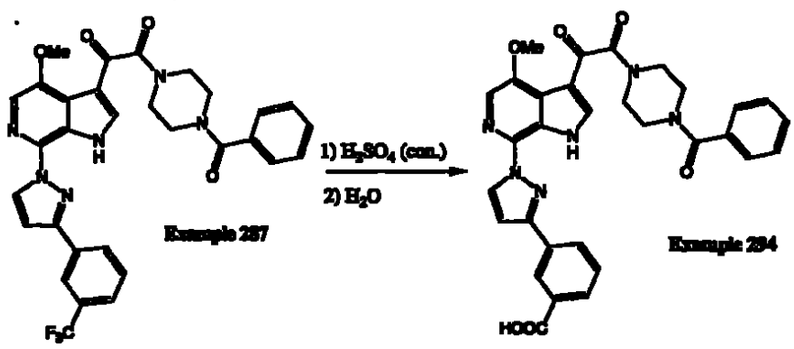
quenched with water (2ml) to form Example 292, which was purified using Shimadzu automated preparative HPLC System (2.1mg of Example 292 obtained). Example 292, 1-benzoyl-4-[(4-methoxy-7-(3-(4-hydroxylcarbonylphenyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{31}H_{27}N_6O_6$: 579.20; found 579.28. HPLC retention time: 1.72 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ8.71 (s, 1H), 8.29 (s, 1H), 8.15 (d, 2H, J = 8.00 Hz), 7.97 (d, 2H, J = 8.00 Hz), 7.80 (s, 1H), 7.45 (m, 5H), 6.90 (s, 1H), 4.05 (s, 3H), 4.02-3.49 (m, 8H).

EXAMPLE 293



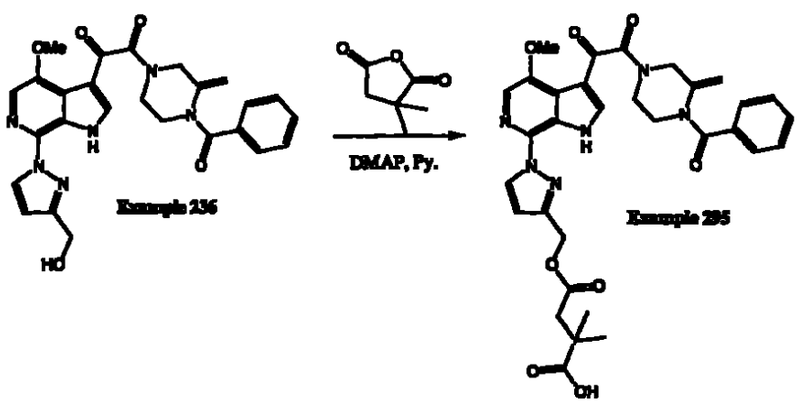
Example 288 (8mg) was dissolved in 0.2ml of concentrated at room temperature and the mixture was heated to 70°C for 6 hours. Then the mixture was quenched with MeOH (2ml) to form Example 293, which was purified using Shimadzu automated preparative HPLC System (1.1mg of Example 293 obtained). Example 293, 1-benzoyl-4-[(4-methoxy-7-(3-(4-methoxycarbonylphenyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{32}H_{29}N_6O_6$: 593.21; found 593.32. HPLC retention time: 1.84 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ8.74 (s, 1H), 8.29 (s, 1H), 8.16 (d, 2H, J = 8.00 Hz), 7.94 (d, 2H, J = 8.00 Hz), 7.79 (s, 1H), 7.44 (m, 5H), 6.89 (s, 1H), 4.05 (s, 3H), 3.96 (s, 3H), 3.90-3.40 (m, 8H).

EXAMPLE 294



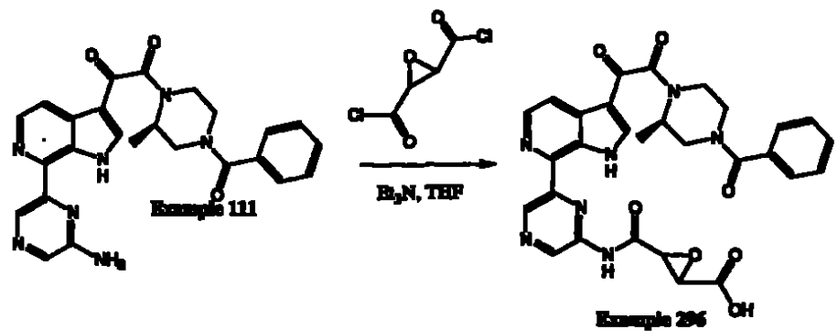
Example 287 (6mg) was dissolved in 0.2ml of concentrated at room temperature and the mixture was heated to 70°C for 6 hours. Then the mixture was quenched with water (2ml) to form Example 294, which was purified using Shimadzu automated preparative HPLC System (2.7mg of Example 294 obtained). Example 294, 1-benzoyl-4-[(4-methoxy-7-(3-(3-hydroxylcarbonylphenyl)-pyrazol-1-yl)-6-azaindol-3-yl)-oxoacetyl]piperazine; MS *m/z*: $(M+H)^+$ Calc'd for $C_{31}H_{27}N_6O_6$: 579.20; found 579.28. HPLC retention time: 1.74 minutes (column G). ^1H NMR (500 MHz, $CDCl_3$) δ8.76 (s, 1H), 8.56 (s, 1H), 8.30 (s, 1H), 8.10 (m, 2H), 7.77 (m, 1H), 7.80 (s, 1H), 7.45 (m, 5H), 6.87 (s, 1H), 4.04 (s, 3H), 4.00-3.40 (m, 8H).

EXAMPLE 295



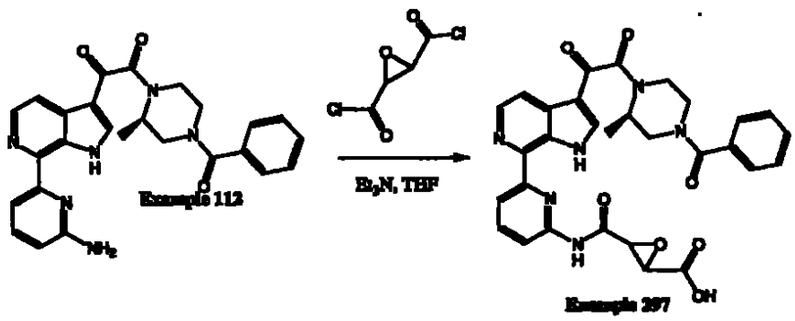
Example 136 (6mg), succinic anhydride (20mg) and DMAP (5ml) were dissolved in 5ml of anhydrous pyridine at room temperature and the mixture was heated to reflux for 10 hours. Then the mixture was quenched with MeOH and solvents were removed under vaccum to provide a residue, which was purified using Shimadzu automated preparative HPLC System to give Example 295 (2.4mg), 2,2-Dimethyl-succinic acid 4-(1-{3-[2-(4-benzoyl-3-methyl-piperazin-1-yl)-2-oxo-acetyl]-4-methoxy-1 H-pyrrolo[2,3-c]pyridin-7-yl}-1H-pyrazol-3-ylmethyl) ester; MS *m/z*: $(M+H)^+$ Calc'd for $C_{32}H_{35}N_6O_8$: 631.25; found 631.34. HPLC retention time: 1.64 minutes (column G).

EXAMPLE 296



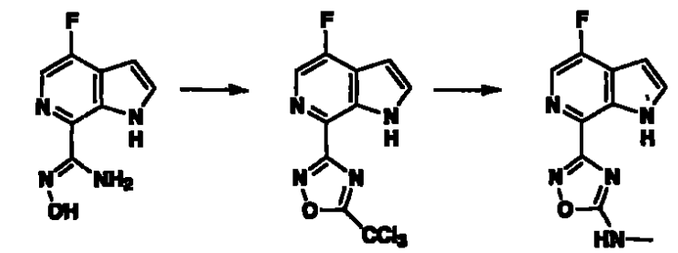
Example 111 (10mg), *trans*-epoxysuccinyl chloride (20mg) and Et_3N (0.2ml) were dissolved in 2ml of anhydrous THF at room temperature and the mixture was kept stirring for 10 hours. Then the mixture was quenched with water and solvents were removed under vaccum to provide a residue, which was purified using Shimadzu automated preparative HPLC System to give Example 296 (2mg), 3-(6-{3-[2-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-pyrrolo[2,3-c]pyridin-7-yl}-pyrazin-2-ylcarbamoyl)-oxirane-2-carboxylic acid; MS *m/z*: $(M+H)^+$ Calc'd for $C_{29}H_{26}N_7O_7$: 584.19; found 584.36. HPLC retention time: 1.44 minutes (column G).

EXAMPLE 297



Example 112 (10mg), *trans*-epoxysuccinyl chloride (20mg) and Et_3N (0.2ml) were dissolved in 2ml of anhydrous THF at room temperature and the mixture was kept stirring for 10 hours. Then the mixture was quenched with water and solvents were removed under vaccum to provide a residue, which was purified using Shimadzu automated preparative HPLC System to give Example 297 (5mg), 3-(6-{3-[2-(4-Benzoyl-2-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-pyrrolo[2,3-c]pyridin-7-yl}-pyridin-2-ylcarbamoyl)-oxirane-2-carboxylic acid; MS *m/z*: $(M+H)^+$ Calc'd for $C_{30}H_{27}N_6O_7$: 583.19; found 583.34. HPLC retention time: 1.31 minutes (column G).

PRECURSOR 4P

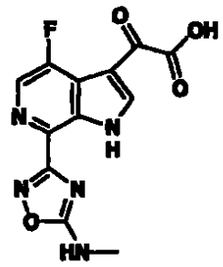


precursor 2p precursor 2u

Precursor 2p (200 mg, 1.0 mmol) was dissolved in trichloroacetic anhydride (1.2 mL) and heated at 80°C for 3h. MeOH (10 mL) was added and the mixture was stirred at rt for 30 min. The volatiles were removed in vacuo. The residue was diluted with AcOEt (25 mL) and washed with water (2 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was dissolved in DMF (1 mL) and treated with a 2M solution of $MeNH_2$ in MeOH (2 mL). The

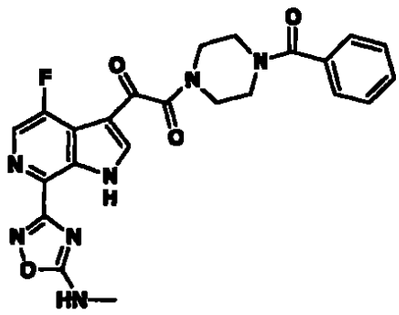
reaction mixture was stirred at rt for 18 h. LC/MS: (ES^+) m/z $(M+H)^+ = 234$. The volatiles were removed in vacuo and the crude (134 mg) was taken to next step without further purification.

PRECURSOR 4P



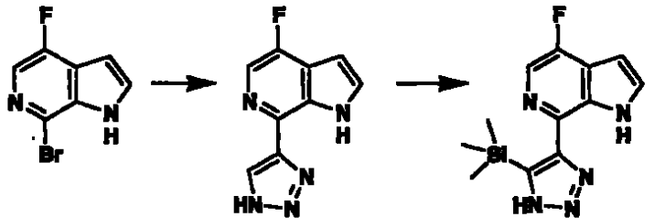
Precursor 4p was prepared from precursor 2n following the procedure described to prepare precursor 4m. LC/MS: (ES^+) m/z $(M+H)^+ = 306$. Taken to next step without further purification.

EXAMPLE 298



Example 298 was prepared from precursor 4p by treatment with EDC (434 mg, 2.3 mmol), HOBt (308 mg, 2.3 mmol) and benzoylpiperazine (304 mg, 1.36 mmol) in DMF (2 mL). The mixture was stirred at rt for 18 h and then concentrated in vacuo and purified using reverse phase HPCL to afford the title compound. LC/MS: (ES^+) m/z $(M+H)^+ = 478$; rt = 1.25 min.

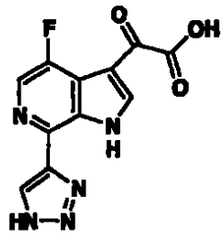
PRECURSORS 2V AND 2VV



Precursor 2v Precursor 2vv

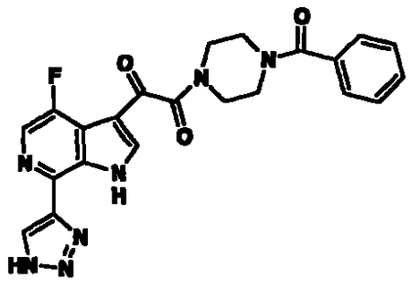
To a diethylether (10 mL) solution of trimethylsilyldiazomethane (2 M in hexane, 5.3 mL) was added *n*-BuLi (2.5 M in hexane, 4.2 mL) at 0°C. After stirring for 20 min, the resulting mixture was added into a diethylether (5 ml) solution of 4-fluoro-7-bromo-6-azaindole (340 mg, 2.1 mmol). The reaction was stirred at 0°C for 60 min and then, quenched with water (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated with ethyl acetate. The solid was filtered and dried in air to give precursor 2v as a white solid (35 mg). ^{1}HNMR (300MHz, CD_3OD): 8.43 (bs, 1H); 8.09-8.08 (m, 1H); 7.64-7.63 (m, 1H); 6.72-6.71 (m, 1H). *LC/MS*: (ES^+) m/z $(M+H)^+$ = 204. Rt = 0.50 min. The filtrate was concentrated and purified on silica gel column eluting with 5-10% of ethyl acetate/hexane to afford precursor 2vv as a yellow solid (422 mg). ^{1}HNMR (300MHz, $CDCl_3$): 8.09-8.08 (m, 1H); 7.47-7.45 (m, 1H); 6.69-6.67 (m, 1H); 0.45 (s, 9H). LC/MS: (ES^+) m/z $(M+H)^+$ = 276. Rt = 1.39min.

PRECURSOR 4Q



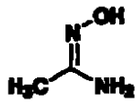
Precursor 4q was prepared following the procedure described before for compound 4m. LC/MS: (ES^+) m/z$(M+H)^+$ = 276. Rt = 0.42 min.

EXAMPLE 299



The title compound was prepared following the coupling procedure previously described before for precursor 5a ^{1}HNMR (300MHz, DMSO): 8.44(m, 1H); 8.33-8.31 (m, 2H); 7.44(m, 5H); 3.87-3.40(m, 8H). LC/MS: (ES^+) m/z$(M+H)^+$ = 448. Rt = 1.04min.

N-HYDROXY-ACETAMIDINE

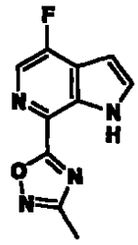


N-Hydroxy-acetamidine

Sodium ethoxide solution (32.5 mL, 21% w/v) was added over 1 h to a solution of hydrochloride (3.5 g, 0.05 mol) and phenolphthalein (5 mg) in ethanol (20 mL). After stirring for 3 hr at room temperature, acetonitrile (1.4 g) was added. The reaction was stirred for 2 h and then heated at 40°C for 48 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was kept at room temperature for 48 h, purified on silica gel column eluting with 9:1 dichloromethane : methanol to give N-Hydroxy-acetamidine (1.8 g, 73%). ^{1}HNMR (300MHz, DMSO): 8.60 (s, 1H); 5.51 (bs, 2H); 1.60 (s, 3H).

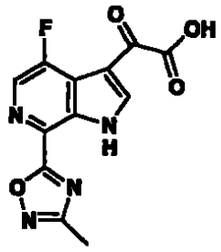
220

PRECURSOR 2Y



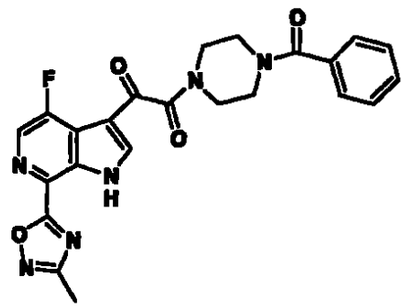
A solution of 4-fluoro-7-bromo-6-azaindole (100 mg, 0.46 mmol), N-Hydroxy-acetamidine (170 mg, 2.3 mmol), tetrakis(triphenylphosphine)palladium (200 mg, 0.17 mmol) and triethylamine (0.2 mL, 1.4 mmol) in toluene (2.5 mL) was heated at reflux under an atmosphere of carbon monoxide for 18 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was diluted with ethyl acetate (10 mL) and washed with water (2 x 25 mL). The organic layer was concentrated and purified on preparative HPLC to give precursor 2y (5 mg, 5%). ^{1}HNMR (300MHz, $CDCl_3$): 10.22 (bs, 1H); 8.32-8.31 (m, 1H); 7.55-7.53 (m, 1H); 6.81-6.79 (m, 1H); 2.55 (s, 3H). LC/MS: (ES^+) m/z$(M+H)^+$ = 219. Rt = 1.15 min.

PRECURSOR 4R



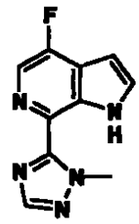
Precursor 4r was prepared following the procedure previously described for compound 4k LC/MS: (ES^+) m/z $(M+H)^+$ = 291. Rt = 0.87 min.

EXAMPLE 300



The title compound was prepared following the general coupling procedure described before for precursor 5a and using precursor 4k and benzoyl piperazine as the inputs. ^{1}HNMR (300MHz, $CDCl_3$): 10.92 (bs, 1H); 8.51-8.50 (m, 1H); 8.41-8.40 (m, 1H); 7.43 (m, 5H); 3.97-3.50 (m, 8H); 2.58 (s, 3H). LC/MS: (ES$^+$) m/z(m+H)$^+$ = 463. Rt = 1.24 min.

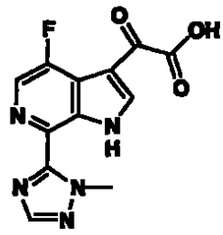
PRECURSOR 2Z



1-Methyl-1,2,4-triazole (249 mg, 3 mmol) was dissolved in anhydrous THF (3 mL) and cooled to -78°C. *n*-BuLi (2.5 M in hexane, 1.2 ml) was added via a syringe. After stirring for 10 min, $ZnCl_2$ (0.5 M in hexane, 6 mL) was added. The reaction mixture was stirred at -78°C for 20 min, then warmed to room temperature. The resulting mixture was transferred via a syringe into a pressure flask which contained a mixture of 4-fluoro-7-bromo-6-azaindole (215 mg, 1.0 mmol), tetrakis(triphenylphosphine)palladium (127 mg, 0.11 mmol) and dioxane (6mL). The reation mixture was heated at 120°C in the sealed flask for 15 h, and then cooled to room temperature. Ethyl acetate (100 mL) was added to quench the reaction. The resulting mixture was washed with water (2 x 20 mL). The organic layer was concentrated and purified on preparative HPLC. Final crystallization in

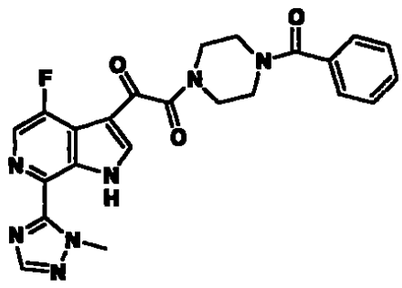
methanol/water gave **Precursor 2z** (80 mg, 37%). ^{1}HNMR (300MHz, $CDCl_3$): 11.10 (bs, 1H); 8.18-8.17 (m, 1H); 8.02-8.01 (m, 1H); 7.50-7.48 (m, 1H); 6.74-6.72 (m, 1H); 4.52 (s, 3H). LC/MS: (ES$^+$) m/z(M+H)$^+$ = 218. Rt = 1.23 min.

PRECURSOR 4S



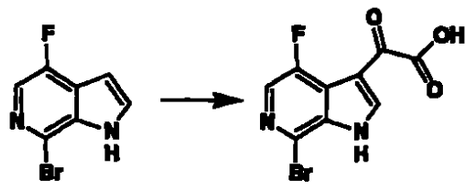
Precursor 4s was prepared following the procedure described before for **precursor 4m**. LC/MS: (ES$^+$) m/z(M+H)$^+$ = 293. Rt = 0.92 min.

EXAMPLE 301



The title compound was prepared following the example coupling procedure described before for **precursor 5a** and using **precursor 4s** and (benzoyl piperazine as inputs. ^{1}HNMR (300MHz, $CDCl_3$): 11.86 (bs, 1H); 8.37-8.36 (m, 1H); 8.32-8.31 (m, 1H); 8.02-8.01 (m, 1H); 7.42(m, 5H); 4.51 (s, 3H); 3.95-3.51 (m, 8H). LC/MS: (ES$^+$) m/z(M+H)$^+$ = 462 Rt = 1.32min.

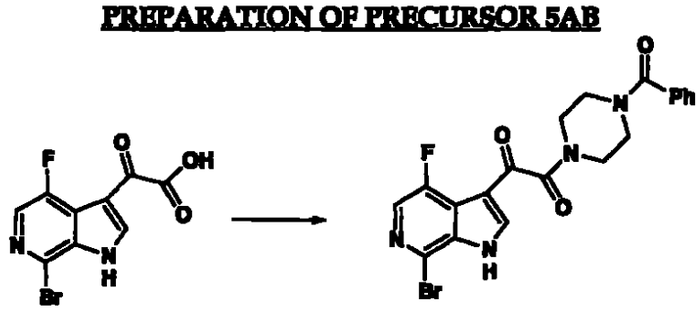
PREPARATION OF PRECURSOR 4T



Precursor 2i precursor 4t

To a solution of 1-ethyl-3-methyl imidazolium chloride (2.7g, 18.6mmol) and aluminum chloride (7.5g, 55.8mmol) was added precursor 2i (2.0g, 9.3mmol) followed by slow addition of ethyloxalylacetate (2.1ml, 18.6mmol) at room temperature. The reaction was then stirred at room temperature for 20h, and quenched by slow addition of ice water (20mL). A light brown solid precipitated out and was collected by filtration and dried in air to provide compound precursor 4t (2.2g, 82%). LC/MS: (ES^+) m/z $(M+H)^+$ = 289. Rt = 0.85min.

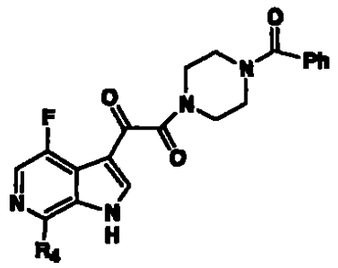
PREPARATION OF PRECURSOR 5AB



4t 5ab

A mixture of compound precursor 4t (500mg, 1.74 mmol), benzylpiperazine hydrochloride (395mg, 1.74 mmol), DEBPT (520mg, 1.74 mg) and diisopropylethylamine (0.61ml, 3.48mmol) in 3 ml of DMF was stirred at rt for 20h. The reaction mixture was diluted with EtOAc (50ml) and washed with water (50 ml). The aqueous layer was extracted with EtOAc (3 x 50ml). The organic extracts were combined and dried over Mg_2SO_4, filtered and concentrated to dryness. The residue was redissolved in EtOAc and precursor 5ab crystallized out as a pale brownish solid and was collected by filtration (221mg, 27%). ^{1}HNMR (d, MeOD): 8.4 (s, 1H), 8.1 (s, 1H), 7.5 (bs, 5H), 3.82-3.53 (m, 8H); MS m/z 461 (MH); Rt = 1.24 min.

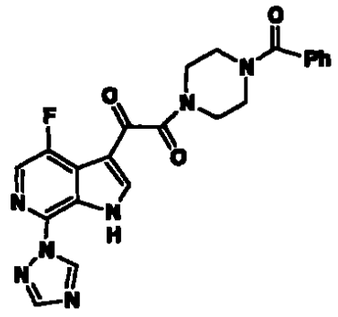
GENERAL PROCEDURE FOR PREPARING EXAMPLES 302-315



General procedure for the preparation of 7-N-linked heterocycles

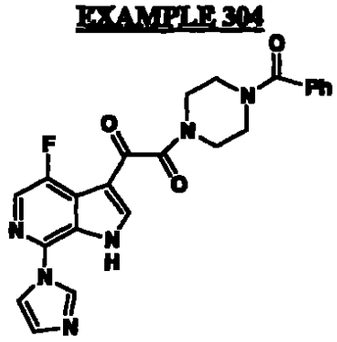
A mixture of precursor 5ab for examples 302-313 or 5ac for Examples 314-315, 15-30 equivalents of the corresponding amine, preferably 30 equivalents were used, 1 equivalent of copper powder and 1 equivalent of potassium carbonate was heated at 160°C for 4-7hr in a sealed tube. The reaction was cooled to room temperature, diluted with EtOAc and filtered through filter paper. The solvent was removed in vacuo and the residue was diluted with methanol and purified by preparative HPLC.

EXAMPLE 303



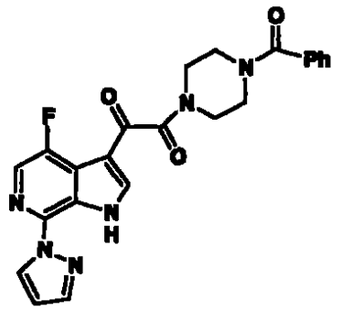
Example 303 was prepared from precursor 5ab and 1,2,4-triazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 11.15 (bs, 1H); 9.28 (s, 1H); 8.33-8.34 (m, 1H); 8.22 (s, 1H); 8.10 (s, 1H); 7.46-7.42 (m, 5H); 3.90-3.48 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 448. Rt = 1.21min.

EXAMPLE 304



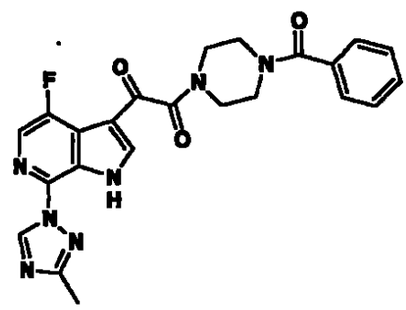
Example 304 was prepared from precursor 5ab and imidazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 13.35 (bs, 1H); 9.49 (s, 1H); 8.35-8.30 (m, 1H); 8.20 (s, 1H); 7.97 (s, 1H); 7.56-7.53 (m, 1H); 7.46-7.41 (m, 5H); 3.98-3.40 (m, 8H). LC/MS: (ES$^+$) m/z $(M+H)^+$ = 447. Rt =1.25min.

EXAMPLE 305

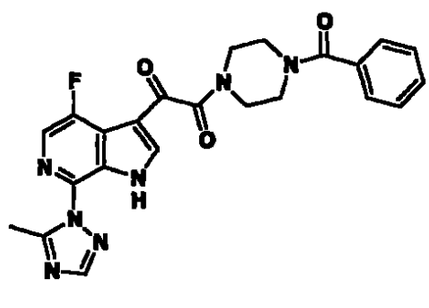


Example 305 was prepared from precursor 5ab and pyrazole following the procedure described above. ^{1}H NMR (500MHz, $CDCl_3$): 11.52 (bs, 1H); 8.65-8.64 (m, 1H); 8.27-8.26 (m, 1H); 8.05-8.04 (m, 1H); 7.81-7.80 (m, 1H); 7.50- 7.35 (m, 5H); 6.54- 6.53 (m, 1H); 4.01- 3.47 (m, 8H). LC/MS: (ES$^+$) m/z $(M+H)^+$ = 447. Rt = 1.25min. Compound of example 222 was prepared from precursor 5i and morpholine following the procedure described above. ^{1}H NMR (300MHz, CD_3OD_3): 8.38 (s, 1H); 7.86-7.84 (m, 1H); 4.14-3.25 (m, 16H). LC/MS: (ES$^+$) m/z $(M+H)^+$ = 466. Rt = 0.988min.

EXAMPLES 306 and 307



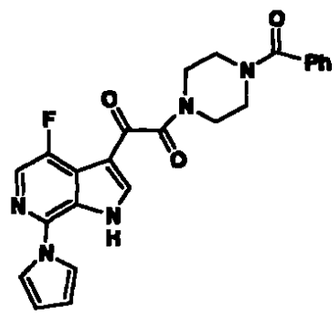
Example 306



Example 307

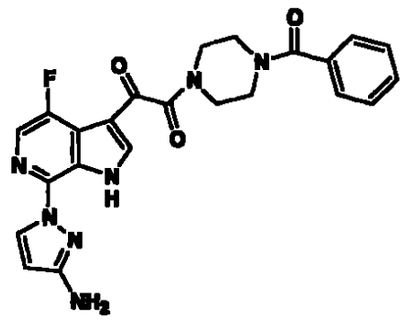
Examples 306 and 307 were prepared from precursor 5ab using the general procedure previously described above using 3-methyltriazole. Example 306: ^{1}HNMR (500MHz, $CDCl_3$): 9.14 (s, 1 H); 8.32 (s, 1 H); 8.06 (s, 1 H); 7.42 (m, 5 H); 3.75-3.85 (m, 4 H); 3.55-3.70 (m, 4 H); 2.57 (s, 3 H). LC/MS: (ES^+) m/z $(M+H)^+$ = 462; rt = 1.27 min. Example 307: ^{1}HNMR (500MHz, $CDCl_3$): 8.29 (s, 1 H); 8.17 (s, 1 H); 8.05 (s, 1 H); 7.42 (m, 5 H); 4.75-4.85 (m, 4 H); 4.55-5.70 (m, 4 H); 3.02 (s, 3 H). LC/MS: (ES^+) m/z $(M+H)^+$ = 462; rt = 1.27 min.

EXAMPLE 308



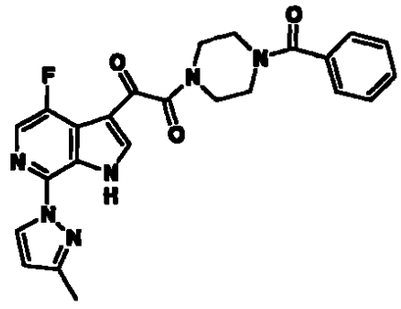
Example 308 was prepared from precursor 5ab and pyrrole following the procedure described above. ^{1}H NMR (300MHz, CD_3OD_3): 8.33-8.29 (m, 2H); 7.49-7.40 (m, 5H); 7.38-7.37 (m, 2H); 6.42-6.41 (m, 2H); 3.91-3.40 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 446. Rt = 1.34min.

EXAMPLE 309



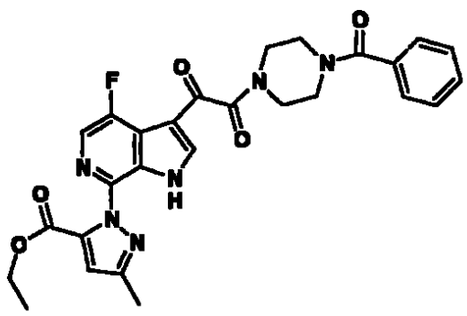
The title compound was prepared from precursor 5ab using the general procedure previously described using 3-aminopyrazole. ^{1}HNMR (300MHz, DMSO):12.42 (bs, 1H); 8.34-8.33 (m, 1H); 8.31-8.30 (m, 1H); 8.04-8.03 (m, 1H); 7.44 (bs, 5H); 5.93-5.92 (m,1H); 3.80-3.16 (m, 8H). LC/MS: (ES$^+$) m/z $(M+H)^+$ = 462. Rt = 1.26min.

EXAMPLE 310



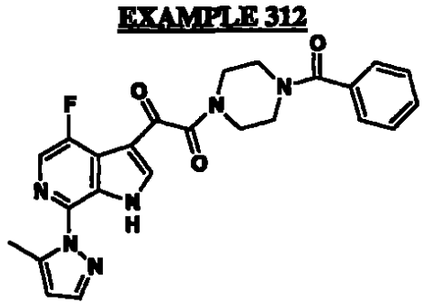
The title compound was prepared from precursor 5ab according to the general procedure previously described using 3-methylpyrazole. ^{1}HNMR (500MHz, $CDCl_3$): 11.59 (bs, 1H); 8.53-8.52 (m, 1H); 8.27-8.26 (m, 1H); 8.02-8.01 (m, 1H); 7.46-7.42 (m, 5H); 6.32-6.31 (m,1H); 3.82-3.48 (m, 8H); 2.43 (s, 3H). LC/MS: (ES$^+$) m/z $(M+H)^+$ = 461. Rt = 1.50min.

EXAMPLE 311



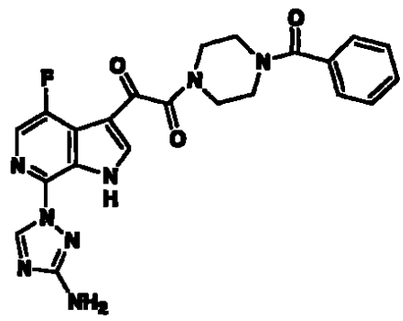
The title compound was prepared from precursor 5ab according to the general procedures previously described. ^{1}HNMR (500MHz, $CDCl_3$): 11.92 (bs, 1H); 8.28-8.27 (m, 1H); 8.08-8.07 (m, 1H); 7.47-7.42 (m, 5H); 6.73-6.72 (m,1H); 4.45-4.38 (m, 2H); 4.0-3.49 (m, 8H); 2.84 (s, 3H); 1.44-1.37 (m, 3H). LC/MS: (ES^+) m/z $(m+H)^+$ = 533. Rt = 1.67min.

EXAMPLE 312



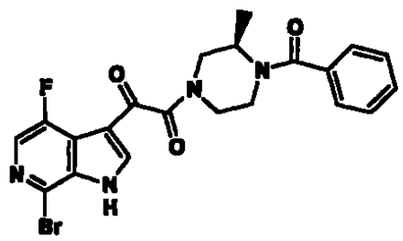
Example 312 was prepared from precursor 5ab according to the general procedure previously described using 3-methylpyrazole. ^{1}HNMR (300MHz, $CDCl_3$): 11.61 (bs, 1H); 8.23-8.22 (m, 1H); 8.06-8.05 (m, 1H); 7.67-7.66 (m, 1H); 7.42 (m, 5H); 6.25 (m, 1H); 3.89-3.48 (m, 8H); 2.82 (s, 3H). LC/MS: (ES^+) m/z $(M+H)^+$ = 461. Rt = 1.41min.

EXAMPLE 313



Example 313 was prepared from precursor 5ab according to the general procedure previously described using 3-amino-1,2,4-triazole. ^{1}HNMR (500MHz, $CDCl_3$): 11.12 (bs, 1H); 8.89-8.88 (m, 1H); 8.29-8.28 (m, 1H); 8.03-8.02 (m, 1H); 7.58-7.51 (m, 5H), 3.87-3.50 (m, 8H). LC/MS: (ES^+) m/z $(M+H)^+$ = 463. Rt = 1.16min.

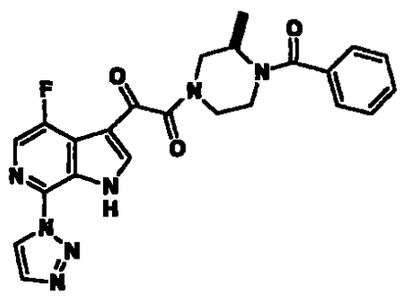
PRECURSOR 5AC



Precursor 5ac was prepared from precursor 4t following the procedure described for precursor 5ab using 1-benzoyl-3-(R)-methylpiperazine instead of benzylpiperazine.

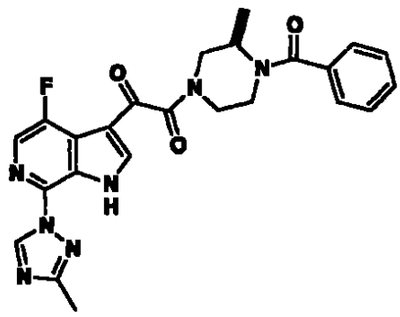
LC/MS: (ES^+) m/z $(M+H)^+$ = 474-475. Rt = 1.20min.

EXAMPLE 314

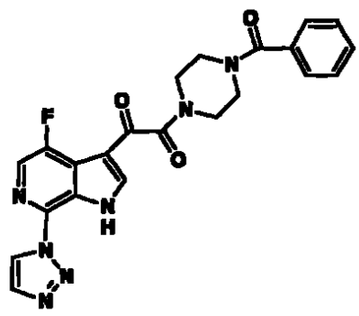


Example 314 was prepared from Precursor 5ac following the general procedure described above for 7-N-linked heterocycles. ^{1}HNMR (500MHz, $CDCl_3$): 8.75 (s, 1H); 8.36 (m, 1H); 8.08 (m, 1H); 7.45-7.38 (m, 5H); 4.75-2.947 (series of multiplets, 7H); 1.37-1.30 (m, 3H).

EXAMPLE 315

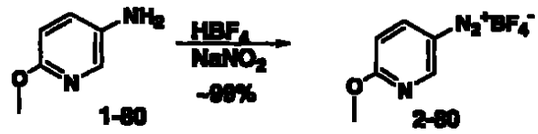


Example 315 was prepared from Precursor 5ac following the general procedure described above for 7-N-linked heterocycles. ^{1}HNMR (500MHz, $CDCl_3$): 9.15 (s, 1H); 8.32 (d, J=3.0 Hz, 1H); 8.16 (m, 1H); 7.92 (s, 1H); 7.45-7.38 (m, 5H); 4.72-2.94 (series of multiplets, 7H); 2.57 (s, 3H); 1.37-1.30 (m, 3H); LC/MS: (ES^+) m/z $(M+H)^+ = 476$. Rt = 1.29min.



Example 216

Synthetic Experimental Procedures for best preparation of Example 216 (Scheme 80)



1-80 2-80

FW = 223

5-Amino 2 methoxypyridine (50g, 0.4mol) was added to a stirring mixture of absolute ethanol (280 ml) and HBF_4 (48% in water, 172 ml) and cooled to 0°C. Sodium nitrite (129g) was dissolved in water (52 ml) and added portion-wise over 1h). The stirring was continued at 0°C for 2hr. The reaction mixture was diluted with ether (1L). The solid product was collected by filtration and washed with 500 ml of 50:50 EtOH/ether and subsequently several times with ether until the product was slightly pinkish in color. The pale pink solid 90g (~100% yield) was kept in a dessicator over P_2O_5.

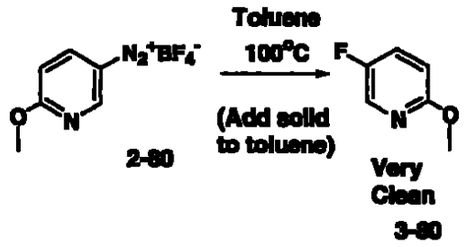
The same procedure was followed to perform the reaction on larger scale:

(1) (200g, 1.6 mol); HBF_4 (688 ml); $NaNO_2$ (116 g); EtOH (1.12 L); H_2O (208 ml)

The reaction was run 4 times (total 800 grams (1-80)). The product was dried over P_2O_5 for 48 hr. (only 24hr for first batch).

A total of 1,293 g of (2-80) was obtained, (91% yield).

Ref: J. Heterocyclic Chem., 10, 779, 1973 (for above reactions, including analytical data)



The decomposition of the diazonium salt was run in 3 batches of:

206g, 219g and 231g using 1.3L, 1.4L and 1.6L of anhydrous toluene respectively.

The toluene was preheated under nitrogen to 100°C (internal temperature) in a 2L 3-neck round bottom flask provided with a mechanical stirrer. The solid was added solid portion-wise via a scoop through a powder funnel which was attached to an adapter with slight outward positive nitrogen flow. During addition, the temperature was maintained between 99-102°C (set at 100°C) and stirred vigorously. Total addition time was 60 min. for the smaller two batches and 70 min. for the last one. After the addition was finished, each stirring reaction was heated at 110°C for 1hr. The heating mantle was removed and stirring was stopped. The reactions were allowed to stand for 2hr (ambient temp achieved). **Safety Note: The reaction contains BF3 so working with the reaction hot exposes vapors which caused skin irritation with some people. No incidents were noted at ambient temperature (6 different people).** The hot toluene from the reaction was poured into a 4L Erlenmeyer (a dark brown oil and residue remained in the flask). The residue was washed with 50 ml of toluene and poured into the original toluene extracts.

Add 1.5L of 1N NaOH to toluene layer, extract and wash with ~100 ml of sat aq. NaCl.

Combine NaCl with NaOH layer, re-extract with 150 ml of toluene, wash with 50ml of sat NaCl.

Combine toluene layers.

Add 1L of 1N NaOH to residue in reaction flask and swirl to dissolve as much residue as possible then add 500ml Et2O and pour into Erlenmeyer.

Add ~500ml more of 1 N NaOH to reaction flask and swirl ~500ml of Et2O.

Combine dark Et2O and NaOH washings in erlenmyer flask.

Et2O/NaOH mixture was poured through powder funnel containing plug of glass wool to collect dark viscous solid. (Add ~500ml more ether to wash) into 6L sep funnel.

Extract. Wash ether layer with ~200ml of H_2O and then 100ml of sat NaCl.

Combine all washings with original NaOH aq. Layer and re-extract with 500ml of ether. Wash with 100ml H_2O and 100ml of NaCl.

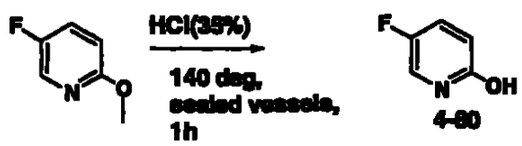
Combine ether extracts. Toluene and ether extracts were checked by LC/MS clean product.

The ether was concentrated on a rotovap and the residue was combined with the toluene extracts to make a homogeneous solution which is taken to next step as is.

The other two rxns were combined and worked up in the same way.

All aqueous layers were checked by LC/MS = no product.

Ref: J. Heterocyclic Chem., 10, 779, 1973 (for above reactions, including analytical data)



3-80 4-80

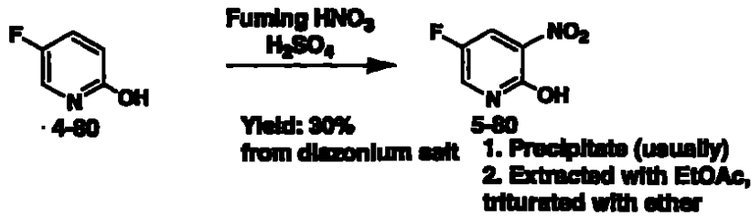
A total of 4.6L of toluene solution containing 3-80 was placed in several sealed tubes and treated with 900ml of 35% HCl at 145°C for 2hr. LC/MS showed no starting material, only 4. The toluene solution was decanted and discarded. The aqueous

phase was washed with EtOAc and concentrated down to remove volatiles to afford a brown solid containing the desired fluoro-hydroxypyridine 4-80.

A total of 244g of this solid was collected and taken to next step as is (it was not completely dry).

Note: We have subsequently run this by decanting the toluene layer first prior to heating to reduce volumes. Same reaction was carried out using HBr (48% in H2O) at 100°C for 6h with similar result to the literature procedure 49% yield.

Ref: J. Heterocyclic Chem., 10, 779, 1973 (for above reactions, including analytical data)



The solid from above containing (4-80) was divided in 4 batches and treated with H_2SO_4 and fuming HNO_3 as shown below. The amounts used were:

	batch 1	batch 2	batch 3	batch 4
(1)	25g	54g	75g	90g
fuming HNO_3	20.8ml	45ml	62.4ml	75ml
H_2SO_4 (for addition)	5.6ml+	12ml+	16.8ml+	20ml+
(for soln)	56ml	120ml	168ml	200ml

Compound 4-80 was dissolved in sulfuric acid (the larger amounts indicated above) at rt and then heated to 65°C. A preformed solution of fuming nitric acid and sulfuric acid (the smaller amount indicated above) was added dropwise. The temperature was kept between 65°C and 80°C (rxn is exothermic and although the bath is at 65°C, temperature goes higher, usually 75, sometimes 80°C). After the addition was complete, the reaction mixture was heated at 65°C for an additional hr. The reaction mixture was then cooled to rt and poured in a flask containing ice) (20g of ice/gr

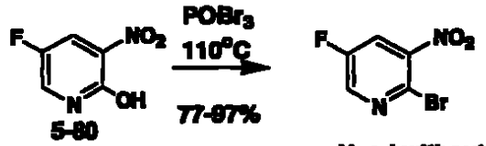
compound, evolution of gas occurred). A solid precipitated out and it was collected by filtration (^{1}HNM" showed 4-80 and something else (discarded)).

The aqueous layer was extracted with AcOEt several times (3-5) and concentrated on a rotary evaporator under vacuum to afford a solid that was triturated with ether to afford 5-80 as a bright yellow solid. A total of 117g of desired product was collected in the first crop (27% yield from diazonium salt). A portion did not crystallize: this oil was triturated with MeOH and Et_2O to afford 3.6g of 5-80; another precipitation from the mother liquid afforded an additional 6.23g of the desired product 5-80

Total:117.0+3.6+6.23 = 126.83. 30.4%). Yield for 3 steps (decomposition of diazonium salt; deprotection and nitration).

Analytical data from Notebook: 53877-115: ^{1}HNMR(δ, MeOD): 8.56-8.27 (dd, J= 7.5, 3.3 Hz, 1H), 8.01 (d, J=3.3 Hz, 1H); *LC/MS*$(M+1)^+$= 158.9; rt = 0.15 min.

Note: A portion of the aqueous acidic solution was taken and neutralized with Na_2CO_3 until effervescence stopped and then it was extracted with AcOEt ⇒ A different product was obtained. No desired product in these extracts.



5-80

Used without purification

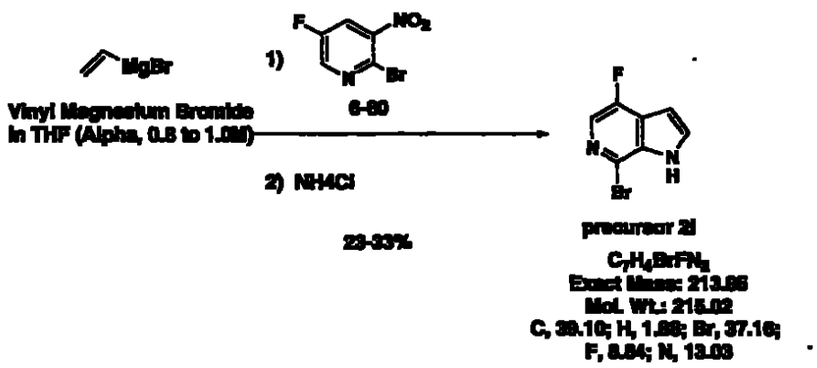
6-80

A total of 117g of 5-80 was divided in 4 batches of 30g x 3 and 27g x 1 and treated with $POBr_3$ (3 equiv.; 163g x 3 and 155 g x 1) and a catalytic amount of DMF (15 ml) at rt (DMF was added carefully ⇒ gas evolution). After 5 min. at room temperature, the solutions were heated at 110°C for 3hr. *LC/MS* showed starting material had been consumed. The reaction mixtures were allowed to cool to rt. The reaction flasks were placed in an ice bath; and then ice was added very slowly and carefully portionwise into the flask, gas evolution was due to HBr formation; the liquid and black solid that formed was poured into a beaker with ice. EtOAc was added and the mixture was then extracted several times with EtOAc. The organic

layer was washed with saturated aq. $NaHCO_3$; H_2O and brine; dried over Na_2SO_4 and filtered. The product was dried in the pump overnight to provide 123g of 6-80 as a brown solid (77% yield).

Note: Reaction is completed within 1h.

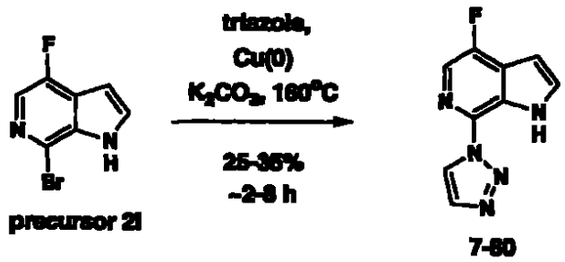
^{1}HNMR(δ, $CDCl_3$):8.52 (m, 1H), 7.93 (m, 1H).



800 ml of vinyl magnesium bromide (1M in THF, Aldrich) was cooled below -60°C with vigorous stirring under N_2. 2-bromo-5-fluoro-3-nitro pyridine (43.3g, 0.196 mol) in 200ml THF was added dropwise via addition funnel at such a rate that the temp was kept below -60°C. This took ~ 1.25 hr. The reaction mixture was warmed to --40 to -50°C and stirred for 1 hr more. Then 1L of saturated aqueous NH_4Cl was added slowly and cautiously. At first, foaming occurred and considerable solid was present, but this essentially dissolved as the addition was completed and the material warmed to rt. The layers were separated and the aqueous layer extracted 3 times with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford ~ 50g of a black gummy solid. HPLC indicated 57-58% product. To this was added CH_2Cl_2 and the solid was collected by filtration and washed with CH_2Cl_2 to afford 12.5g of product as a brown solid. The reaction was repeated on exactly the same scale and worked up in the same manner. From CH_2Cl_2 trituration there was obtained 12.4g of Precursor 2i (HPLC ~ 97% pure). The crude was recovered and allowed to stand in dichloromethane. Upon standing 3.6g of additional product separated and was recovered by filtration.

Total yield = 29.5g (35%).

^{1}HNMR(δ, $CDCl_3$): 8.69(bs, 1H), 7.92 (d, J= 1.8 Hz, 1H), 7.41 (m, 1H), 6.77 (m,1H); LC/MS$(M+1)^+$ = 216.-217.9; rt = 1.43 min.



precursor 2I

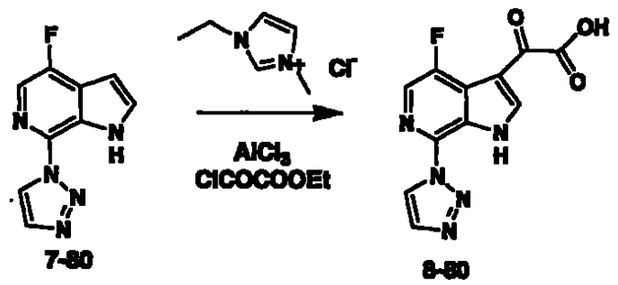
7-80

Chromatographed, ~1:1 isomer ratio

Reaction was carried in a 250ml flask (foaming occurred upon heating and the big size flask is more convenient). A mixture of precursor 2I (3g, 13.95mmol), 1,2,3-triazole (15g, 217.6 mmol, 15eq), K_2CO_3 (1.9g, 13.95mmol, 1eq) and Cu(0)(0.9g, 13.9mmol, 1eq) was heated at 160°C for 7 hr (from rt to 160°C total 7 hr) under N_2 (depending on the Cu(0) lot, reaction time may vary from 2hr to 7hr). The resulting mixture was diluted with MeOH, filtered through filter paper (to remove the copper). Washed with MeOH (20 ml) and water (30 ml).

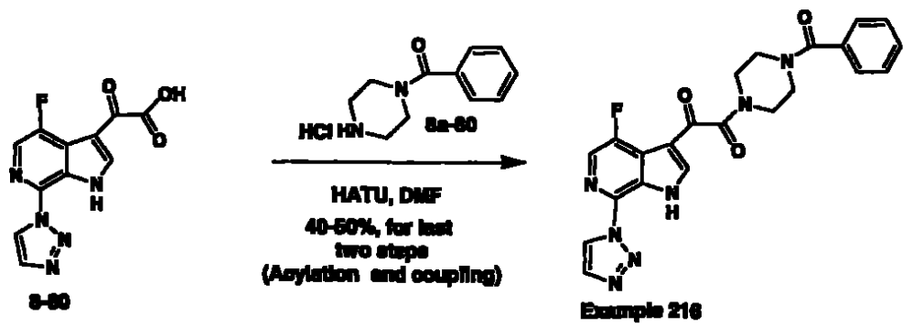
The filtrate was concentrated (remove solvent in rotovap) and diluted with ethylacetate. The aqueous layer was extracted with ethylacetate. The combined organic layer was dried over sodium sulfate, filtered and concentrated. The residue was dissolved in MeOH (20 ml), 7-80 (750mg) crystallized from the methanol as a white solid and was collected by filtration. (Slow gradient volume, silica gel hex /AcOEt (0→18%) of the mother liquids usually affords 5-10% more of 7-80.

^{1}HNMR (δ, $CDCl_3$): 10.47 (bs, 1H), 8.76 (s, 1H), 7.94 (s, 1H), 7.89 (s, 1H), 7.53 (m, 1 H), 6.78 (m, 1H); LCMS$(M+1)^+$= 204; rt = 1.29 min.



Chromatographed, ~1:1 isomer ratio

Ethyl methylimidazolium chloride (4.3g, 29.6 mmol, 3eq) was placed in a 250ml flask. $AlCl_3$ (11.8g, 88.6mmol, 9eq) was added into the flask in one portion. A liquid suspension was formed (some of $AlCl_3$ remained as solid). After stirring for 5-10 min. compound (1) (2.0g, 9.85mmol) was added in one portion followed by slow addition (via a syringe) of ethyl chlorooxalacetate (3.3 ml, 29.6 mmol, 3eq). The reaction was stirred at room temperature for 20 hr. LCMS indicated compound 8-80:compound 7-80 = 6:2. (Compound I has strong UV absorption) The reaction was quenched by carefully adding ice water (~75 ml) at 0°C. A yellow solid precipitated at this point. The resulting suspension was filtered and the solid was washed with water. MeOH and ethyl acetate (to remove unreacted SM) and the solid was dried in air. (LCMS purity 70% ~ 80%) 2g of solid containing 8-80 was obtained and taken to the next step without further purification. LCMS$(M+1)^+$= 276; rt =0.97 min.



A mixture of compound 8-80 (4.9g, 17.8 mmol) & N-benzoylpiperazine hydrochloride 8a-80 (HCl salt; 6.0g, 26.7mmol, 1.5eq) in DMF (30 ml) was stirred at RT overnight (16 hr). A slurry was formed. An additional 20ml of DMF was added into the slurry. Then HATU (12.2g, 26.7mmol, 1.5eq) was added followed by

DMAP (4.3g, 35.6 mmol, 2eq). The reaction mixture was stirred for 30 min. LCMS indicated the starting material 8-80 was completely converted to product (EXAMPLE 216). The resulting mixture was filtered and the solid washed with water. The filtrate was concentrated in vacuo. Water was added to the residue and the solid was collected by filtration. The solids were combined and washed with water, MeOH and EtOAc. Then the solid was dried in air. LCMS & HPLC showed BMS-585248, >99% pure. The solid product was further purified by precipitation and crystallization in 5~10% $CH_3OH/CHCl_3$.

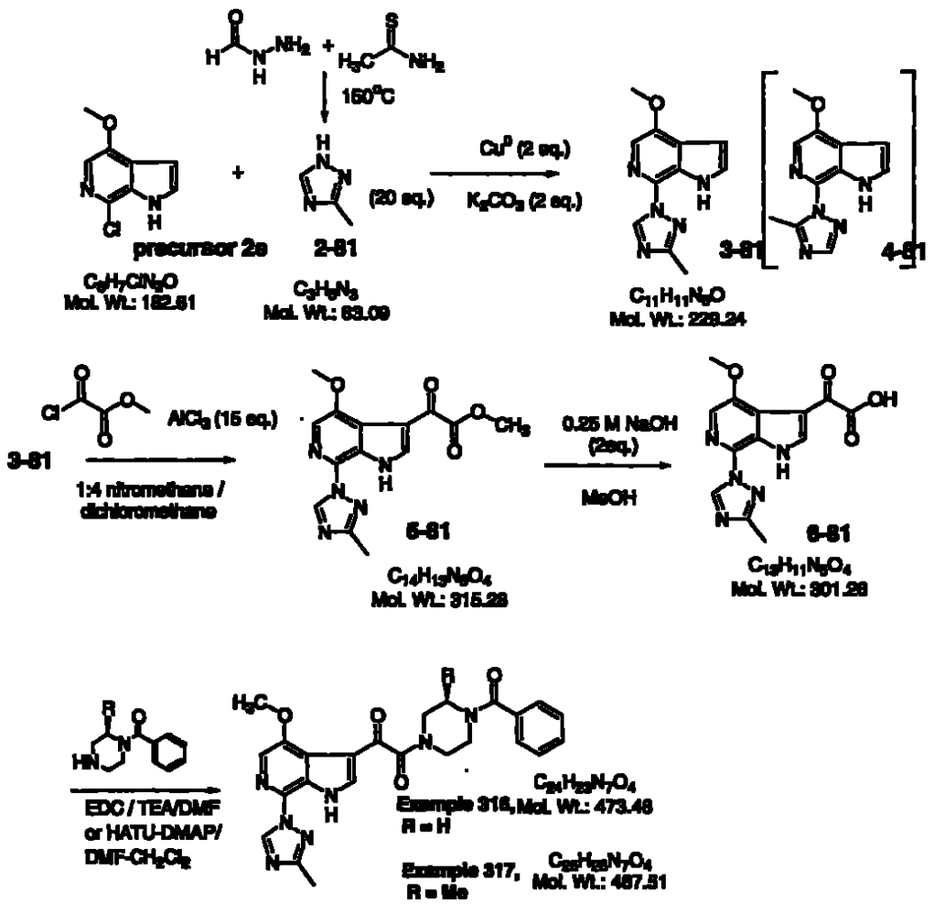
Purification of Example 216

Crude compound of Example 216 obtained as above (15.3g) was dissolved in 10% $MeOH/CHCl_3$ (600 ml). A light brown suspension was formed, filtered through filter paper and washed with MeOH a twice. The brownish solid was discarded (~1.2g). Example 216 was crystallized in the filtrate, the solid was collected by filtration and the white solid was dried in air. The filtrate was used to repeat the crystallization several times. The solid obtained from each filtration was analyzed by HPLC. All the pure fractions were combined. The not so pure fractions were resubjected to crystallization with MeOH & $CHCl_3$. A total of 12.7g of Example 216 was obtained from recrystallization and precipitation. The mother liquid was concentrated and purified on silica gel column (EtOAc, then $CHCl_3$/MeOH (0-2%)) to provide 506mg of product) as a white solid.

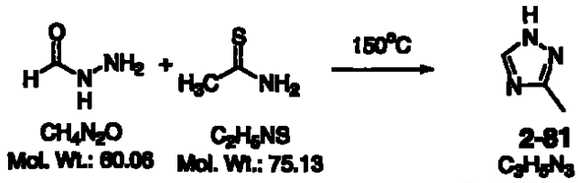
^{1}HNMR (d, DMSO) 13.1 (bs, 1H), 9.0 (s, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.4 (bs, 5H), 3.7 (bs, 4H), 3.5 (bs, 4H); MS m/z 448 (MH). Anal: Calc for $C_{22}H_{18}FN_7O_3$; C 59.05, H 4.05, N 21.91, F 4.24. Found; C 57.28, H 4.14, N 21.22; F 4.07%.

Scheme 81 is a preferred method for making compounds of Formula I and Ia where R^2 is methoxy. This is specifically exemplified for the preparation of compound Example 316 and 317.

Scheme 81



Preparation of 3-methyl-1,2,4-triazole (2-81)

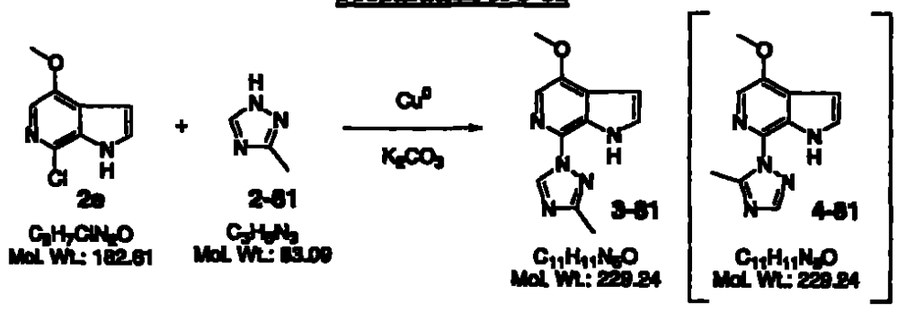


Procedure: A solid mixture of formic hydrazide (68 g, 1.13 mol) and thioacetamide (85 g, 1.13 mol) in a 500mL-RBF was heated with stirring at 150°C (oil bath temp.) for 1.5 hrs with a gentle stream of nitrogen, removing H_2S and water (about 18 mL of liquid collected) formed during the reaction. The reaction mixture was distilled under reduced pressure, collecting 60.3 g (0.726 mol, Y. 63.3%) of the title compound at

102°C / 0.35-1 mmHg as white solid after removing a liquid forerun. : ^{1}H NMR ($CDCl_3$) δppm 2.51 (3H, s, 3-Me), 8.03 (1H, s, 5-H), 9.5 (1H, br, NH); TLC Rf (10% MeOH/CH_2Cl_2) = 0.3 (phosphomolybdate-charring, white spot).

Reference: Vanek, T.; Velkova, V.; Gut, Jiri *Coll. Czech. Chem. Comm.* 1985, *49*, 2492.

Preparation of 3-81



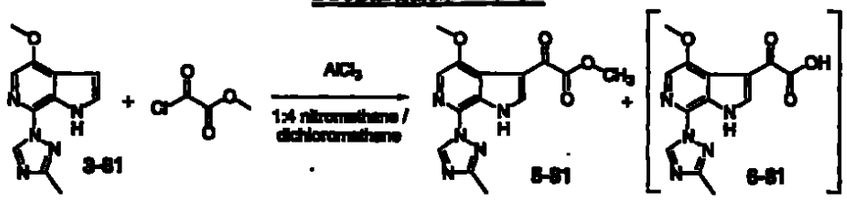
Procedure: A 500 mL round bottom flask was loaded with 4-methoxy-7-chloro-6-azaindole precursor 2e (9.1 g, 50 mmol; dried *in vacuo*), potassium carbonate (13.8 g, 100 mmol, 2 eq.), copper powder (6.35 g, 100 mmol, 2 eq.), and 3-methyl-1,2,4-triazole (83 g, 1.0 mol, 20 eq.). The solid mixture was heated to melt at 170-175°C (external oil bath temperature) under gentle stream of anhydrous nitrogen for 12 h, by which time HPLC analysis indicates the amount of the peak for the starting material becomes 5-30% and the desired product peak becomes about 45% with isomeric by-product peak becomes 15%. As the reaction mixture cools, MeOH (150 mL) was added slowly to the stirred warm mixture. Upon cooling, the insoluble material (copper powder) was filtered through a Celite pad, and rinsed with methanol. The filtrate was concentrated *in vacuo* to a thick paste which was diluted with water (1 L) and extracted with EtOAc (3x150mL). The EtOAc extracts were dried ($MgSO_4$), filtered and concentrated to obtain about 8 g of crude residue which was crystallized by dissolving in hot CH_3CN (50 mL), followed by diluting with water (100 mL) and cooling at 0°C to collect 1.45 g (12.7%) of the title compound as white solid. The filtrate was purified by C-18 reverse phase silica gel (YMC ODS-A 75 μm) eluted with 15-30% CH_3CN/H_2O. Appropriate fractions were combined and the aqueous solution after removing CH_3CN by rotary evaporator was lyophilized to give additional 1.15 g of the title compound 3-81. The crude aqueous layer was further

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extracted with EtOAc several times. The ethyl acetate extracts were dried (MgSO4), filtered, concentrated, and crystallized from MeOH to give additional 200 mg of the title compound 3-81. The total yield: 2.8 g (12.2 mmol, Y. 24.5%); MS m/z 230 (MH), HRMS (ESI) m/z calcd for $C_{11}H_{12}N_5O$ (M+H), 230.1042, found 230.1038 (Δ - 1.7 ppm); ^1H NMR ($CDCl_3$) δppm 2.54 (3H, s, CH_3), 4.05 (3H, s, OCH_3), 6.73 (1H, s, H-3), 7.40 (1H, s, H-2), 7.56 (1H, s, H-5), 9.15 (1H, s, triazole-H-5); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ ppm 14.2 (triazole-Me), 56.3 (OMe), 100.5 (C-3), 116.9 (C-5), 123.5, 127.2, 127.5 (C-2), 129.5 (C-7), 141.2 (C-5'), 149.5 (C-4), 161.8 (C-3'); Anal. Calcd for $C_{11}H_{11}N_5O$: C 57.63, H 4.83, N 30.55, found C 57.37, H 4.64, N 30.68.

The structure was confirmed by a single X-ray crystallographic analysis using crystals obtained from C-18 column fractions. A portion of C-18 column fractions containing a mixture of the desired 3-methyl-1,2,4-triazolyl analog 3-81 and isomeric 5-methyl-1,2,4-triazolyl analog 4-81 was further purified by C-18 reverse phase column eluting with 8-10% CH_3CN/H_2O. Appropriate fractions were extracted with CH_2Cl_2, and slow evaporation of the solvent gave crystalline material of the isomeric 7-(5-methyl-1,2,4-triazolyl)-4-methoxy-6-azaindole (4-81): MS m/z 230 (MH), ^1H NMR ($CDCl_3$) δppm 3.05 (3H, s, CH_3), 4.07 (3H, s, OCH_3), 6.74 (1H, q, J=2.4, H-2), 7.37 (1H, t, J=2.4, H-3), 7.65 (1H, s, H-5), 8.07 (1H, s, triazole-H-3). The structure was confirmed by a single X-ray crystallographic analysis.

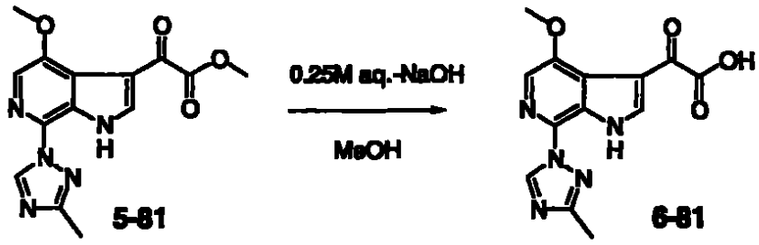
Preparation of 5-81



Procedure: $AlCl_3$ (40 g, 0.3 mol, 15 eq.) was dissolved in a solution of CH_2Cl_2 (100 mL) and nitromethane (20 mL) under dry nitrogen. To this solution was added compound 3-81 (4.58 g, 0.02 mol) under stirring and under N_2, followed by methyl chlorooxoacetate (9.8 g, 0.08 mol, 4 eq.). The mixture was stirred under N_2 at room temperature for 1.5 h. The mixture was added drop-wise to a cold and stirred

solution of 20% aqueous ammonium acetate solution (750 mL). The mixture was stirred for 20 min and the resultant precipitate was filtered, washed thoroughly with water and dried *in vacuo* to obtain 4.7 g (0.015 mol, Y. 75%) of the title compound 5-81 as white solid: MS m/z 316 (MH); HRMS (ESI) m/z calcd for $C_{14}H_{14}N_5O_4$ (M+H), 316.1046; found 316.1041 (Δ -1.6 ppm); ^{1}H NMR ($CDCl_3$, 500 MHz) δppm 2.58 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.76 (1H, s, H-5), 8.34 (1H, d, J=3Hz, H-2), 9.15 (1H, s, triazole-H-5), 11.0 (1H, bra, NH). More title compound 5-81 and hydrolyzed acid 6-81 can be obtained from the filtrate by acid-base extraction with EtOAc.

Preparation of 6-81

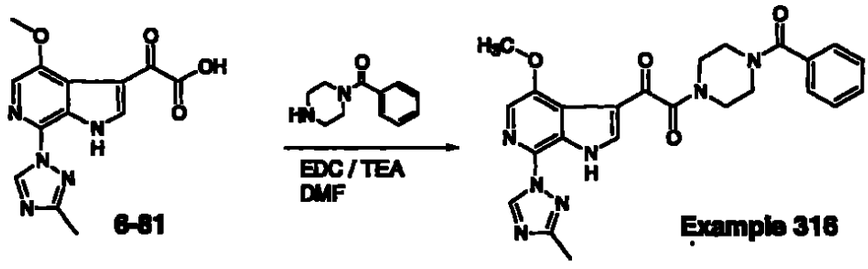


Procedure: To a suspension of the methyl ester 5-81 (2.2 g, 7.0 mmol) in MeOH (50 mL) was added 0.25M NaOH solution in water (56 mL, 14 mmol, 2 eq.) at room temperature and the mixture stirred for 15 min by which time HPLC indicated the hydrolysis was complete. The mixture was concentrated *in vacuo* quickly to remove MeOH, and to the residual solution was added water (100 mL) and 1N HCl (14 mL) with stirring to neutralize the mixture. The resultant fine precipitate was filtered, washed with water and dried *in vacuo* to obtain 1.98 g (6.58 mmol, Y. 94%) of the title compound 6-81 as off-white solid: MS m/z 302 (MH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 2.50 (3H, s, overlapped with DMSO peaks), 3.98 (3H, s, CH_3O), 7.87 (1H, s, H-5), 8.29 (1H, d, J=3.5Hz, H-2), 9.25 (1H, s, triazole-H-5), 12.37 (1H, s, NH).

Alternative procedure: To a suspension of the methyl ester 5-81 (10.7 g, 34 mmol) in MeOH (150 mL) was added 0.25M NaOH solution in water (272 mL, 68 mmol, 2 eq.) at room temperature and the mixture stirred for 20 min by which time HPLC indicated the hydrolysis was complete. The mixture was concentrated *in vacuo*

quickly to remove MeOH, and the residual solution was extracted with EtOAc to remove any neutral impurities. To the aqueous phase was added 1N HCl (68 mL, 68 mmol) to neutralize the product. The resultant mixture was frozen and lyophilized to obtain 14.1 g (33.7 mmol, Y. 99.2%) of the title compound **6-81**, containing 2 mole equivalents of NaCl as off-white solid. This material was used in the subsequent reaction without further purification. The sodium salt of the title compound **6-81** was obtained by C-18 reverse phase column chromatography after sodium bicarbonate treatment: HPLC >97% (AP, uv at 254nm); HRMS (Na salt, ESI $^-$) m/z calcd for $C_{13}H_{10}N_5O_4$ (M-H), 300.0733; found 300.0724 (Δ -3 ppm); ^{1}H NMR (Na salt, DMSO-d_6, 500 MHz) δ ppm 2.37 (3H, s, Me), 3.83 (3H, s, CH_3O), 7.56 (1H, s, H-5), 8.03 (1H, s, H-2), 9.32 (1H, s, triazole-H-5); ^{13}C NMR (Na salt, DMSO-d_6, 125.7 MHz) δ ppm 13.8 (triazole-Me), 57.2 (OMe), 114.8 (C-3), 120.0 (C-5), 125.1, 143.5 (C-5'), 149.8 (C-4), 160.0 (C-3'), 171.7, 191.3.

Preparation of Example 316



6-81 **Example 316**

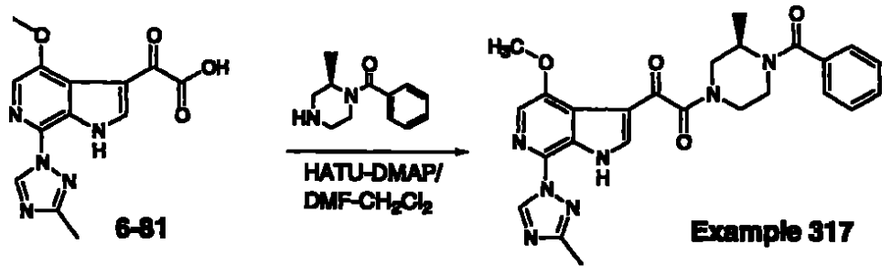
Procedure: To a solution of the acid **6-81** (3.01 g, 10 mmol) and benzoylpiperazine hydrochloride (3.39 g, 15 mmol) in DMF (50 mL) was added triethylamine (10.1 g, 100 mmol, 10 eq.), followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 5.75 g, 30 mmol) under N_2 and the mixture stirred at room temperature for 22 h after sonication and at 40°C for 2 h. The mixture was concentrated *in vacuo* to remove DMF and TEA, and to the residual solution was added water (200 mL) under stirring and sonication. The precipitates formed were collected, washed with water and dried *in vacuo* to obtain 2.8 g (5.9 mmol, Y. 59%) of the title compound **Example 316** as off-white solid. The filtrate was extracted with CH_2Cl_2 (x2). The CH_2Cl_2 extracts were dried (Na_2SO_4), filtered and concentrated to gum which was triturated with Et_2O to obtain a solid. This solid was

suspended and tritrated with MeOH to obtain 400 mg of the title compound Example 316 as off-white solid. Total yield: 3.2 g (6.8 mmol, Y. 68%): MS m/z 474 (MH); HRMS (ESI) m/z calcd for $C_{24}H_{24}N_7O_4$ (M+H) 474.1890, found 474.1884 (Δ -1.2 ppm); ^{1}H NMR (DMSO-*d6*) δ ppm 2.50 (3H, s, overlapped with DMSO peaks), 3.43 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 3.99 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.88 (1H, s, indole-H-5), 8.25 (1H, s, indole-H-2), 9.25 (1H, s, triazole-H-5), 12.40 (1H, s, NH); ^{13}C-NMR (DMSO-*d6*) δ ppm 13.78, 40.58, 45.11, 56.78, 114.11, 120.95, 122.71, 123.60, 126.98, 128.34, 129.6, 135.43, 138.52, 142.10, 149.15, 161.29, 166.17, 169.22, 185.42; UV (MeOH) λmax 233.6 nm (ε 3.43x10^4), 314.9 nm (ε 1.73x10^4); Anal: Calc for $C_{24}H_{24}N_7O_4.1/5H_2O$; C 60.42, H 4.94, N 20.55, Found; C 60.42, H 5.03, N 20.65; KF (H_2O) 0.75%.

This reaction can also be performed by use of HATU and DMAP to provide more consistent yield of the title compound: To a suspension of the acid 6-81 (15.6 mmol) and HATU [O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophos phonate] (8.90 g, 23.4 mmol; 1.5 eq.) in DMF (60 mL) and CH_2Cl_2 (60 mL) was added a mixture of DMAP (5.72 g, 46.8 mmol, 3 eq.) and benzoylpiperazine hydrochloride (5.30 g, 23.4 mmol; 1.5 eq.) in DMF (60 mL) at room temperature and the mixture was stirred under nitrogen atmosphere for 4 hrs. The mixture was concentrated *in vacuo* to remove CH_2Cl_2 and most of DMF, and to the residual solution was added water under stirring and sonication. The precipitates formed were collected, washed with water and dried *in vacuo* to obtain 5.38 g (11.4 mmol, Y. 72.8%) of the title compound Example 316 as off-white solid: HPLC >95% (AP, uv at 254nm).

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Preparation of Example 317

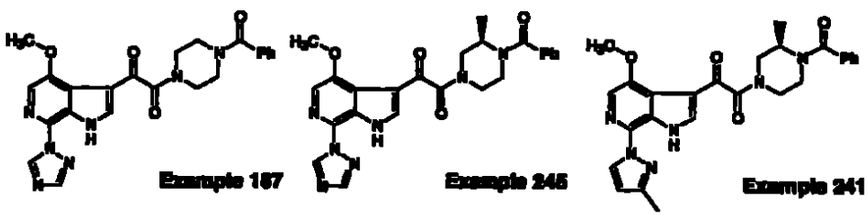


6-81 Example 317

Procedure: To a solution of the acid **6-81**, containing 2 mole equivalent of NaCl (4.1 g, 9.8 mmol) in CH_2Cl_2 (30 mL) and DMF (30 mL) was added at -10°C under anhydrous nitrogen HATU [O-(7-azabenzotriazol-1yl)-N,N,N',N'-tetrmethyluronium hexafluorophosphate] (5.59 g, 14.7 mmol; 1.5 eq.), and stirred at –10°C for 30min. To this mixture was added a solution of 2-(R)-methyl-N-benzoylpiperazine trifluoroacetate (4.7 g, 14.7 mmol; 1.5 eq.) and dimethylaminopyridine (3.5 g, 29 mmol; 3 eq.) in DMF (30 mL) and CH_2Cl_2 (30 mL) and the mixture stirred at room temperature · overnight, by which time HPLC analysis indicated reaction was essentially complete. The mixture was concentrated *in vacuo* to remove valatiles and DMF, and to the residue was added water (~150 mL) under stirring and sonication. The precipitates formed were collected, washed with water and dried *in vacuo* to obtain 4.3 g of the title compound **Example 317** as off-white solid. This was dissolved in 20% MeOH in CH_2Cl_2 (about 250 mL), removing any insoluble material, and the filtrate was concentrated *in vacuo* to remove more volatile CH2Cl2. The resultant precipitate was collected , washed with MeOH and then with Et_2O to obtain 3.5 g (7.18 mmol, Y. 73.2%; AP >99%) of the title compound **Example 317** as off-white solid: LC/MS m/z 488 (MH); ^{1}H NMR (DMSO-*d6*) δ ppm 1.15, 1.22 (3H, 2d, J = 7Hz), 2.50 (3H, s, overlapped with DMSO peaks), 3-4.3 (8H, m, CH_2N), 3.98, 4.00 (3H, s, CH_3O), 7.45 (5H, m, Ar-Hs), 7.89 (1H, s, indole-H-5), 8.19, 8.26 (1H, 2s, indole-H-2), 9.24, 9.25 (1H, 2s, triazole-H-5), 12.40 (1H, br.s, NH); Anal: Calc for $C_{25}H_{25}N_7O_4$; C 61.59, H 5.16, N 20.11, Found; C 61.69, H 5.27, N 20.10; KF (H_2O) <0.1%.

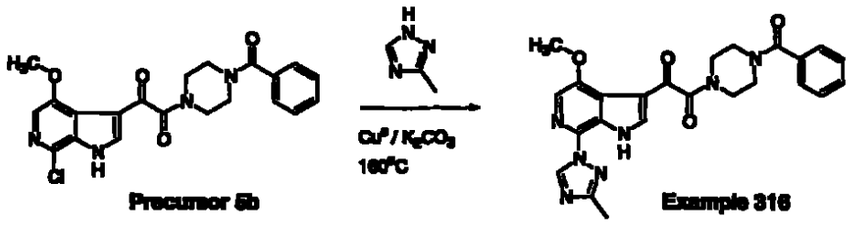
NOTES:

The following compounds, Examples 187, 245, and 241, were also prepared by the method described above using appropriate azoles (1,2,4-triazole for Example 187, and Example 245; 3-methylpyrazole for Example 241.



Preparation of Example 316

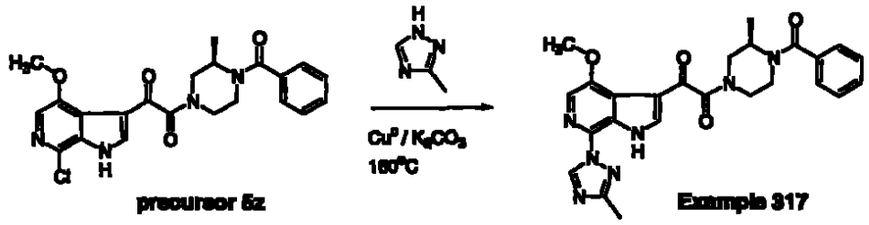
Alternate Preparation of Example 316



A mixture of compound precursor 5b (150 mg, 0.35 mmol), 3-methyl-1,2,4-triazole (581 mg, 7 mmol; 20 eq.; prepared by the method described in *Coll. Czech. Chem. Comm.* 1985, *49*, 2492), copper powder (45 mg, 0.7 mmol; 2 eq.), potassium carbonate (97 mg, 0.7 mmol; 2 eq.) was flushed with anhydrous nitrogen and heated in a sealed tube at 160°C for 11 h. Upon cooling, to the mixture was added MeOH, and the insoluble material was filtered. The filtrate was concentrated *in vacuo* and purified by C-18 reverse phase column (Prep. System eluting with MeOH-water containing 0.1% TFA) to obtain 19 mg (0.040 mmol, Y. 11%) of the title compound Example 216 as amorphous powder (TFA salt): MS m/e 474 (MH); ^{1}H NMR (DMSO-d6) δ ppm 2.50 (3H, s, overlapped with DMSO peaks), 3.44 (4H, br, CH_2N),

3.68 (4H, br, CH_2N), 4.00 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.89 (1H, s), 8.25 (1H, s), 9.24 (1H, s), 12.41 (1H, s, NH).

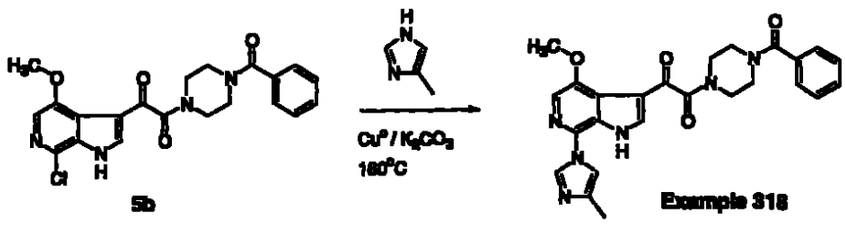
Alternate Preparation of Example 317



precursor 5z Example 317

A mixture of compound 5z (220 mg, 0.5 mmol), 3-methyl-1,2,4-triazole (830 mg, 10 mmol; 20 eq.; prepared by the method described in *Coll. Czech. Chem. Comm.* 1985, *49*, 2492), copper powder (63.5 mg, 1 mmol; 2 eq.), potassium carbonate (138 mg, 1 mmol; 2 eq.) was flushed with anhydrous nitrogen and heated in a sealed tube at 160°C for 11 h. Upon cooling, to the mixture was added MeOH, and the insoluble material was filtered. The filtrate was concentrated *in vacuo* and purified by C-18 reverse phase column (Prep. System eluting with gradient 0-70% MeOH-water containing 0.1% TFA) to obtain 24 mg (0.049 mmol, Y. 9.8%) of the title compound Example 317 as amorphous powder (TFA salt): MS m/e 488 (MH); ^{1}H NMR (CD_3OD) δ ppm 1.30, 1.35 (3H, 2d, J=7Hz), 2.54 (3H, s, CH_3), 3-4.5 (8H, m, CH_2N), 4.04, 4.05 (3H, 2s, CH_3O), 7.46, 7.47 (5H, 2s, Ar-Hs), 7.85, 7.86 (1H, 2s), 8.28, 8.31 (1H, 2s), 9.22 (1H, s).

Preparation of Example 318

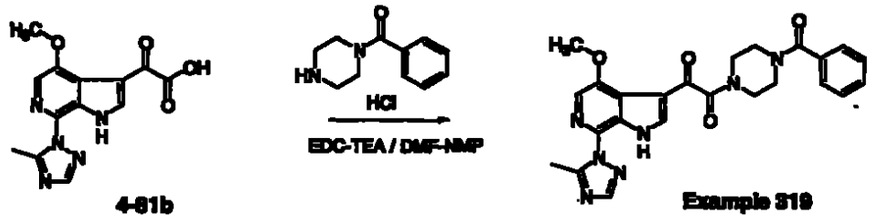


5b Example 318

A mixture of compound 5b (150 mg, 0.35 mmol), 4-methylimidazole (517 mg, 6.2 mmol; 18 eq.; Aldrich), copper powder (26 mg, 0.42 mmol; 1.2 eq.), potassium carbonate (57 mg, 0.42 mmol; 1.2 eq.) was flushed with anhydrous nitrogen and

heated in a sealed tube at 160°C for 6 h. Upon cooling, to the mixture was added MeOH, and the insoluble material was filtered. The filtrate was concentrated *in vacuo* and purified by C-18 reverse phase column eluting with 15% CH_3CN-water containing 0.1% TFA to obtain 32 mg (0.068 mmol, Y. 19%) of the title compound Example 318 as amorphous powder (TFA salt). H-NMR indicates contamination of about 30% of the isomeric product, 5-methylimidazolyl analog: MS (ES) m/e 473 (MH); ^1H NMR (CD_3OD) δ ppm 2.25 (s), 2.51 (3H, s, CH_3), 3.63 (4H, br, CH_2N), 3.9 (4H, br, CH_2N), 4.13 (3H, s, CH_3O), 4.15 (s), 7.50 (5H, br. s, Ar-Hs), 7.60 (s), 7.89 (1H, s), 8.03 (1H, s), 8.11 (s), 8.43 (1H, s), 9.35 (s), 9.42 (1H, s).

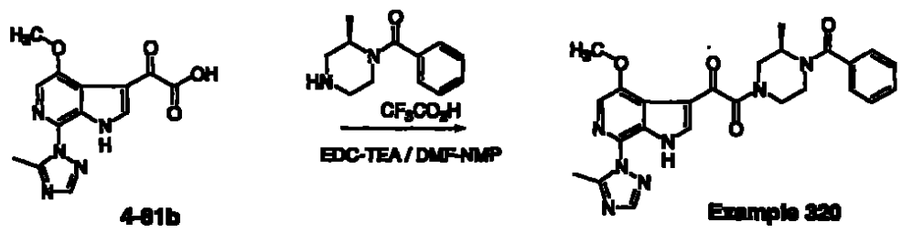
Preparation of Example 319



4-81b Example 319

A mixture of precursor 4-81b (30 mg, 0.11 mmol; prepared from 7-(5-methyl-1,2,4-triazolyl)-4-methoxy-6-azaindole by the method used for the best mode-preparation of Example 316), benzoylpiperazine hydrochloride (39 mg, 0.17 mmol), triethylamine (200 mg, 1.9 mmol; 18 eq.), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 77 mg, 0.45 mmol) in 1:1 DMF-NMP (1 mL) was stirred under N_2 at room temperature for 20 h. The mixture was concentrated *in vacuo* to remove DMF and to the residue was added water and the mixture stirred to form precipitates which were collected and dried to obtain 14 mg (0.030 mmol, Y. 27%) of the title compound Example 319 as amorphous powder: MS m/e 474 (MH); ^1H NMR (DMSO-d6) δ ppm 2.67 (3H, s, CH_3), 3.44 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.02 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.98 (1H, s), 8.21 (1H, s), 8.24 (1H, s), 12.57 (1H, s, NH).

Preparation of Example 320

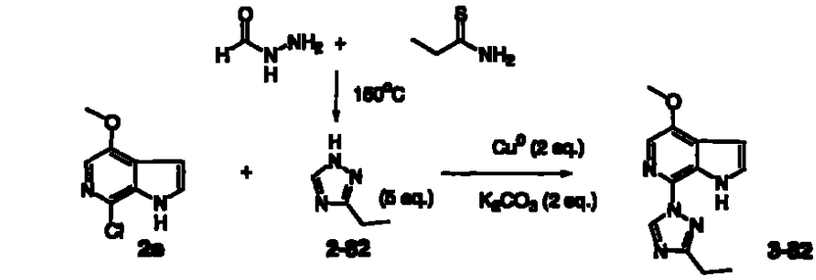


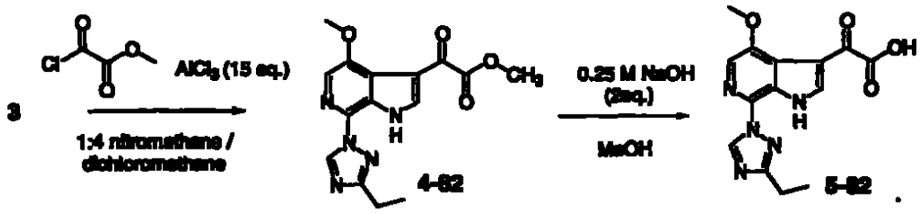
4-81b Example 320

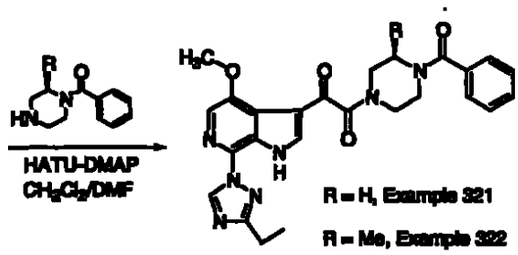
A mixture of compound **4-81b** (30 mg, 0.11 mmol; prepared from 7-(5-methyl-1,2,4-triazolyl)-4-methoxy-6-azaindole by the method used for the best mode-preparation of **Example 316**), 2R-methyl-1-benzoylpiperazine trifluoroacetate (54 mg, 0.17 mmol), triethylamine (200 mg, 1.9 mmol; 18 eq.), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 77 mg, 0.45 mmol) in 1:1 DMF-NMP (1 mL) was stirred under N_2 at room temperature for 20 h. More EDC (20 mg) was added to the mixture and stirred for additional 6 h. The mixture was concentrated *in vacuo* to remove DMF and to the residue was added water and the product was extracted with EtOAc twice. The EtOAc extracts were dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography eluting with 5%MeOH-CH_2Cl_2 to obtain 10 mg (0.021 mmol, Y. 19%) of the title compound **Example 320** as amorphous powder: MS m/e 488 (MH); ^1H NMR ($CDCl_3$) δ ppm 1.33, 1.36 (3H, 2d, J=7Hz), 3.00 (3H, s, CH_3), 3-4.6 (8H, m, CH_2N), 4.05 (3H, s, CH_3O), 7.38-7.44 (5H, m, Ar-Hs), 7.81 (1H, s), 8.02 (1H, s), 8.16, 8.17, 8.18, 8.19 (1H, 4s), 11.10 (1H, s, NH).

Preparation of Example 321 and Example 322

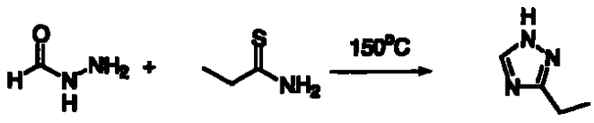
Scheme 82







Preparation of 3-methyl-1,2,4-triazole (2-82)

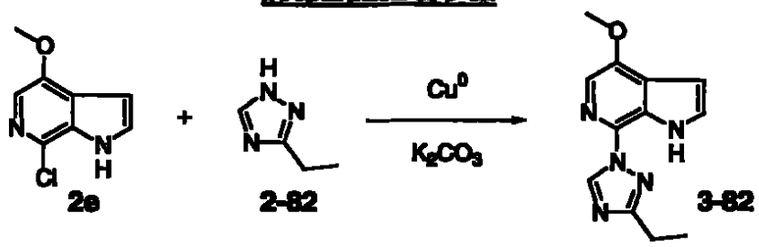


Procedure: A solid mixture of formic hydrazide (6.0 g, 0.1 mol; Aldrich) and thiopropionamide (8.92 g, 0.1 mol; TCI) was heated with stirring at 150°C (oil bath temp.) for 2 hrs with a gentle stream of nitrogen. It was cooled and stored at room temperature overnight. The solid reaction mixture was suspended in 20%

EtOAc/CH_2Cl_2, removing insoluble solid and the filtrate was concentrated. The residue was purified by column chromatography, eluting first with 50-80% EtOAc/CH_2Cl_2, removing by-products, and then with 10% MeOH/CH_2Cl_2, collecting 5.4 g (0.056 mol, Y. 56 %) of the title compound as a solid: MS (ESI -) m/z 96 (M-H); ^{1}H NMR ($CDCl_3$) δppm 1.37 (3H, t, J=7.5 Hz), 2.88 (2H, q, J=7.5 Hz), 8.06 (1H, s, 5-H), 9.4 (1H, br, NH).

Reference: Vanek, T.; Velkova, V.; Gut, Jiri *Coll. Czech. Chem. Comm.* 1985, *49*, 2492.

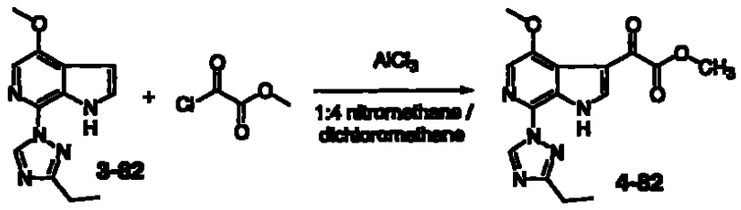
Preparation of 3-82



Procedure: A mixture of 4-methoxy-7-chloro-6-azaindole **2e** (910 mg, 5.0 mmol), potassium carbonate (1.38 g, 10 mmol, 2 eq.), copper powder (635 mg, 10 mmol, 2 eq.), and 3-ethyl-1,2,4-triazole (2.4 g, 25 mmol, 5 eq.) in a sealed tube was heated at 145-150°C (external oil bath temperature) for 52 h, by which time HPLC analysis indicated no more reaction progressed. After cooling, MeOH was added, the insoluble material (copper powder) was filtered through a Celite pad, and rinsed with methanol. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% EtOAc/CH_2Cl_2) to obtain 450 mg of the products as an about 4:1 mixture of two regio-isomers. This was further separated by C-18 reverse phase silica gel (YMC, ODS-A 75 μm) eluted with 15% CH_3CN/H_2O containing 0.1% TFA. The fractions containing the major isomer were concentrated in vacuo to remove acetonitrile and the aqueous solution was extracted with CH2Cl2 after neutralizing with aqueous sodium bicarbonate to obtain the title compound **3-82** (305 mg, 1.25 mmol; Y. 25%): HPLC >97% (AP at 254nm); MS (LC/MS) m/z 244 (M+H); ^{1}H NMR ($CDCl_3$) δppm 1.43 (3H, t, J=7.5 Hz; CH_3), 2.91 (2H, q, J=7.5 Hz;

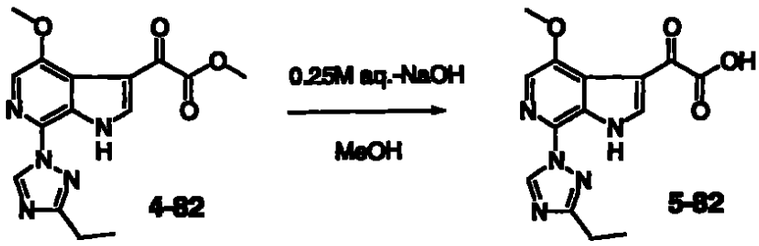
CH_2), 4.05 (3H, s, OCH_3), 6.71 (1H, dd, J=6, 2.4 Hz, H-3), 7.57 (1H, t, J=3 Hz, H-2), 7.57 (1H, s, H-5), 9.16 (1H, s, triazole-H-5), 10.3 (1H, br, NH).

Preparation of 4-82



Procedure: $AlCl_3$ (2.50 g, 18.8 mmol, 15 eq.) was dissolved in a solution of CH_2Cl_2 (8 mL) and nitromethane (2 mL) under dry nitrogen. To this solution was added compound 3-82 (305 mg, 1.26 mmol) under stirring and under N_2, followed by methyl chlorooxoacetate (612 mg, 5.0 mol, 4 eq.). The mixture was stirred under N_2 at room temperature for 1.5 h. The mixture was added drop-wise to a cold and stirred solution of 20% aqueous ammonium acetate solution (120 mL). The mixture was stirred for 30 min and the resultant precipitate was filtered, washed thoroughly with water and dried *in vacuo* to obtain 320 mg (0.97 mmol, Y. 77%) of the title compound 5-82 as a solid: HPLC purity 97% (AP at 254nm); LC/MS m/z 330 (M+H); ^{1}H NMR (DMSO-d_6) δppm 1.35 (3H, t, J=7.5 Hz, CH_3), 2.85 (2H, q, J=7.5 Hz, CH_2), 3.89 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 7.90 (1H, s, H-5), 8.35 (1H, s, H-2), 9.25 (1H, s, triazole-H-5), 12.4 (1H, bm, NH).

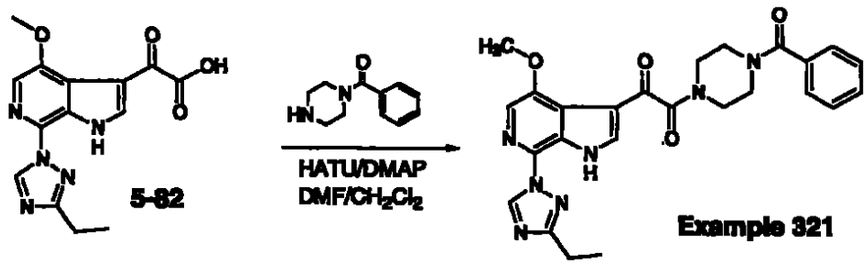
Preparation of 5-82



Procedure: To a suspension of the methyl ester 4-82 (315 mg, 0.957 mmol) in MeOH (8 mL) was added 0.25M NaOH solution in water (7.6 mL, 1.9 mmol, 2 eq.) at room temperature and the mixture stirred for 15 min by which time HPLC

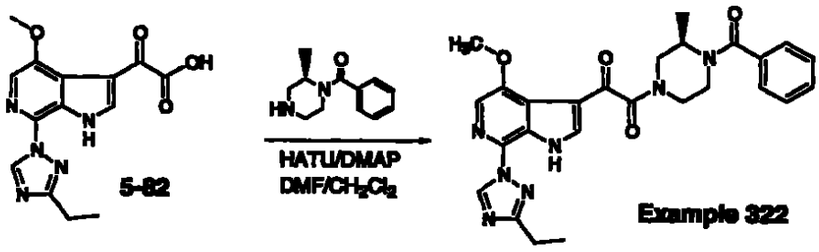
indicated the hydrolysis was complete. The mixture was concentrated *in vacuo* quickly to remove MeOH, and to the residual solution was added water (~10 mL) and 1N HCl (2 mL) with stirring to neutralize the mixture. The resultant fine precipitate was filtered, washed with water and dried *in vacuo* to obtain 285 mg (0.904 mmol, Y. 94%) of the title compound **5-82** as off-white solid: HPLC purity >96% (AP at 254nm); LC/MS m/z 316 (M+H); ^{1}H NMR (DMSO-d_6) δ ppm 1.35 (3H, t, J=7.5 Hz, Me), 2.85 (2H, q, J=7.5 Hz, CH_2), 3.97 (3H, s, CH_3O), 7.88 (1H, s, H-5), 8.30 (1H, d, J=3 Hz, H-2), 9.24 (1H, s, triazole-H-5), 12.28 (1H, s, NH).

Preparation of Example 321



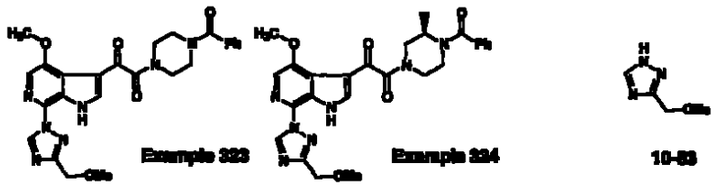
Procedure: A mixture of the acid **5-82** (126 mg, 0.4 mmol) and HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphonate, 228 mg, 0.6 mmol; 1.5 eq.) in a mixture of CH_2Cl_2 (2 mL) and DMF (2 mL) was stirred for 30min under N_2. To this mixture was added a mixture of benzoylpiperazine hydrochloride (136 mg, 0.60 mmol; 1.5 eq.) and DMAP (dimethylaminipyridine, 147 mg,1.2 mmol; 3 eq.) in DMF (2 mL), and the mixture ws stirred at room temperature under N_2 for 15 min, by which time HPLC indicated the reaction was complete. The mixture was quickly concentrated *in vacuo* to remove DMF and all volatile materials, and to the residue was added water (50 mL) under stirring and sonication. The precipitates formed were collected, washed with water and dried *in vacuo* to obtain 160 mg (0.328 mmol, Y. 82%) of the title compound **Example 321** as off-white solid: HPLC purity 100% (AP, at 254nm); LC/MS m/z 488 (M+H); ^{1}H NMR (DMSO-*d6*) δ ppm 1.35 (3H, t, J=7.5 Hz, Me), 2.85 (2H, q, J=7.5 Hz, CH_2), 3.43 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.00 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.89 (1H, s, indole-H-5), 8.26 (1H, s, indole-H-2), 9.25 (1H, s, triazole-H-5), 12.32 (1H, br.s, NH).

Preparation of Example 322



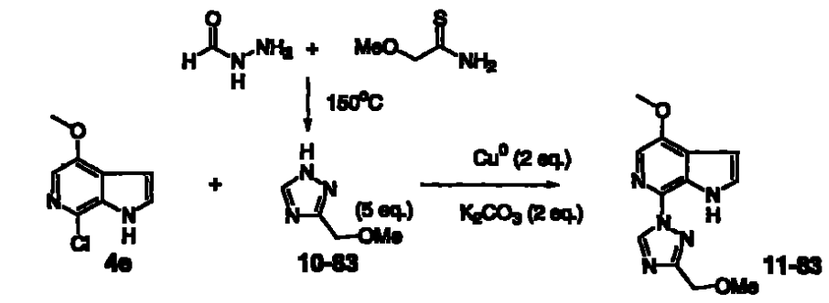
Procedure: A mixture of the acid **5-82** (79 mg, 0.25 mmol) and HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphonate, 142 mg, 0.375 mmol; 1.5 eq.) in a mixture of CH_2Cl_2 (1 mL) and DMF (1 mL) was stirred for 30min under N_2. To this mixture was added a mixture of benzoylpiperazine hydrochloride (136 mg, 0.60 mmol; 1.5 eq.) and DMAP (dimethylaminipyridine, 92 mg, 0.75 mmol; 3 eq.) in DMF (1 mL), and the mixture was stirred at room temperature under N_2 for 15 min, by which time HPLC indicated the reaction was complete. The mixture was quickly concentrated *in vacuo* to remove all solvents, CH_2Cl_2 and DMF, and to the residue was added water (~25 mL) under stirring and sonication. The resultant gum were further washed with water and collected by decantation. The residual gum was dried *in vacuo*. The solution of this gum in isopropanol was concentrated in vavuo to remove any residual water. Addition of anhydrous diethyl ether and trituration gave 90 mg (0.18 mmol, Y. 72%) of the title compound **Example 322** as off-white solid: HPLC purity ~95% (AP, at 254nm); LC/MS m/z 502 (M+H); ^{1}H NMR (DMSO-*d6*) δ ppm 1.15, 1.22 (3H, 2d, J=6.6 Hz, Me), 1.35 (3H, t, J=7.5 Hz, Me), 2.85 (2H, q, J=7.5 Hz, CH_2), 2.9-4.4 (7H, m, CH_2N, CHN), 3.99, 4.00 (3H, 2s, CH_3O), 7.45 (5H, br. s, Ph-Hs), 7.89 (1H, s, indole-H-5), 8.20, 8.25 (1H, 2s, indole-H-2), 9.24, 9.25 (1H, 2s, triazole-H-5), 12.29, 12.32 (1H, 2br.s, NH).

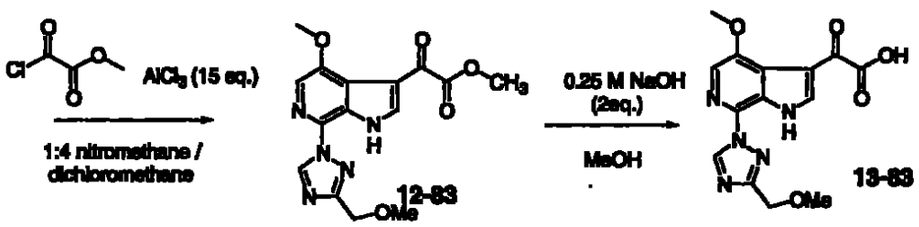
The following compounds, **Example 323**, and **Example 324**, were prepared by the method described above using 3-(methoxymethyl)-1,2,4-triazole (**10-83**).

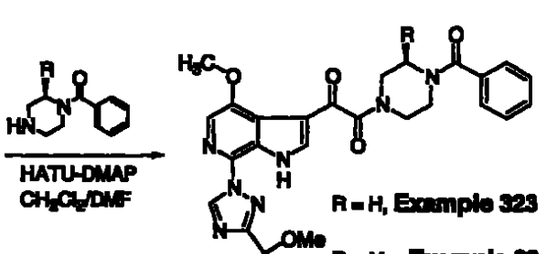


Synthetic Scheme

Scheme 83

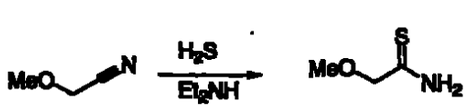






5

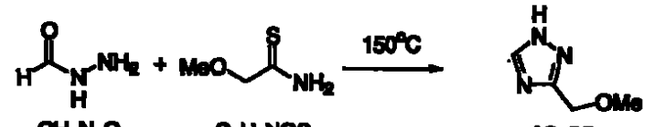
Preparation of 3-methoxymethyl-1,2,4-triazole (10-83)



C3H7NOS
Mol. Wt.: 105.16

Procedure: To a mixture of methoxyacetonitrile (25 g, 0.35 mol: Aldrich) and diethylamine (1 g, 8.6 mmol) was condensed H_2S (50 mL), and the mixture was sealed, and heated at 50°C for 14 hrs. After cooling volatile materials were evaporated and the residue was dissolved in water, extracted with EtOAc several times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc:CH_2Cl_2=1:10) to obtain 13 g (0.12 mol, Y. 35%) of the title compound as a dark oil: GC/MS m/z 105 (M); ^{1}H NMR ($CDCl_3$) δppm 3.43 (3H, s, CH_3), 4.26 (2H, s, CH_2).

Preparation of 3-methoxymethyl-1,2,4-triazole (10-83)



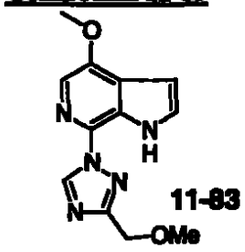
CH_4N_2O
Mol. Wt.: 60.06

C_3H_7NOS
Mol. Wt.: 105.16

10-83
$C_4H_7N_3O$
Mol. Wt.: 113.12

Procedure: A solid mixture of formic hydrazide (4.58 g, 0.0763 mol) and methoxythioacetamide (8.92 g, 0.1 mol) was heated with stirring at 150°C (oil bath temp.) for 2 hrs with a gentle stream of nitrogen. It was cooled and stored at room temperature overnight. The solid reaction mixture was suspended in 20% EtOAc/CH2Cl2, removing insoluble solid and the filtrate was concentrated. The residue was purified by column chromatography, eluting first with 50-80% EtOAc/CH_2Cl_2, removing by-products, and then with 10% MeOH/CH_2Cl_2, collecting 3.8 g (0.034 mol, Y. 44 %) of the title compound **10-83** as a solid: ^{1}H NMR ($CDCl_3$) δppm 3.48 (3H, s, MeO), 4.67 (2H, s, CH_2), 8.10 (1H, s, 5-H).

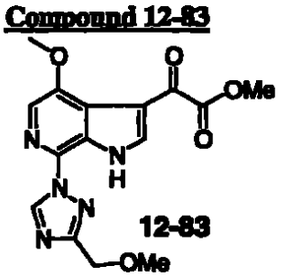
Compound 11-83



11-83

Y. 9 %: HPLC >98% (AP at 254nm); MS (LC/MS) m/z 260 (M+H); ^{1}H NMR ($CDCl_3$) δppm 3.53 (3H, s, MeO), 4.06 (3H, s, 4-OCH_3), 4.69 (2H, s, CH_2), 6.73 (1H, dd, J=3, 2.4 Hz, H-3), 7.40 (1H, t, J=2.7 Hz, H-2), 7.58 (1H, s, H-5), 9.16 (1H, s, triazole-H-5), 10.2 (1H, br, NH).

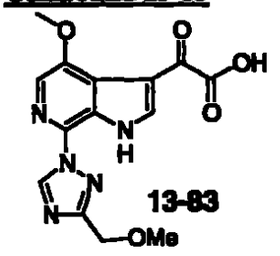
Compound 12-83



12-83

Y. 78 %: HPLC 100 % (AP at 254nm); MS (LC/MS) m/z 346 (M+H); ^{1}H NMR (CD_3OD) δppm 3.51 (3H, s, MeO), 3.94 (3H, s, MeO), 4.05 (3H, s, MeO), 4.71 (2H, s, CH_2), 7.87 (1H, s), 8.35 (1H, s), 9.33 (1H, s, triazole-H-5).

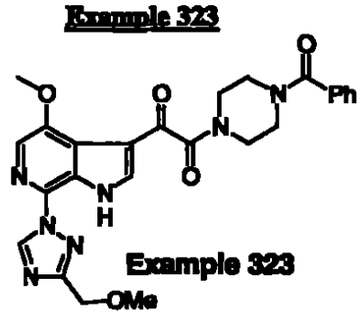
Compound 13-83



13-83

Y. 97 %: HPLC 98 % (AP at 254nm); MS (LC/MS) m/z 332 (M+H); ^{1}H NMR ($CDCl_3$) δppm 3.49 (1H, s, OH), 3.55 (3H, s, MeO), 4.10 (3H, s, MeO), 4.72 (2H, s, CH_2), 7.84 (1H, s, H-5), 9.13 (1H, d, J=3.3 Hz), 9.21 (1H, s, triazole-H-5), 11.15 (1H, br, NH).

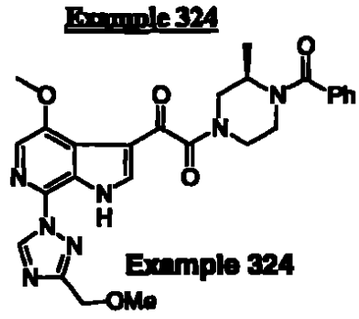
Example 323



Example 323

Y. 79 %: HPLC 100 % (AP at 254nm); MS (LC/MS) m/z 504 (M+H); ^{1}H NMR (DMSO-d_6) δppm 3.39 (3H, s, MeO), 3.42 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.01 (3H, s, 4-MeO), 4.61 (2H, s, CH_2), 7.46 (5H, s, Ph-Hs), 7.92 (1H, s), 8.27 (1H, s), 9.36 (1H, s, triazole-H-5), 12.42 (1H, br.s, NH).

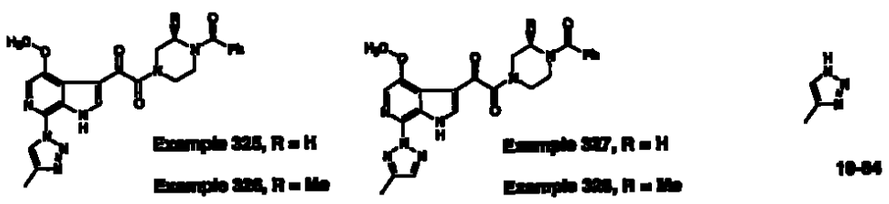
Example 324



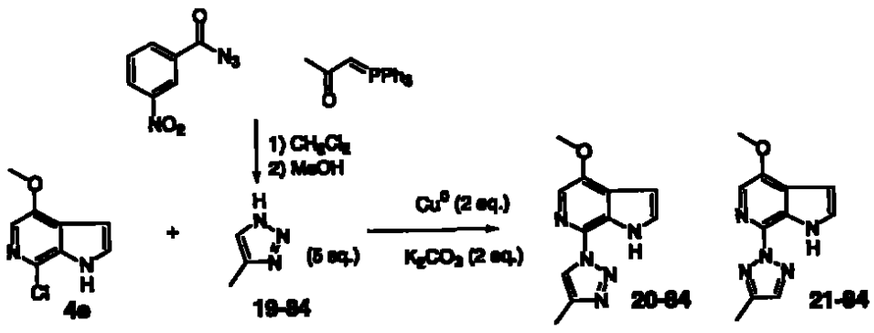
Example 324

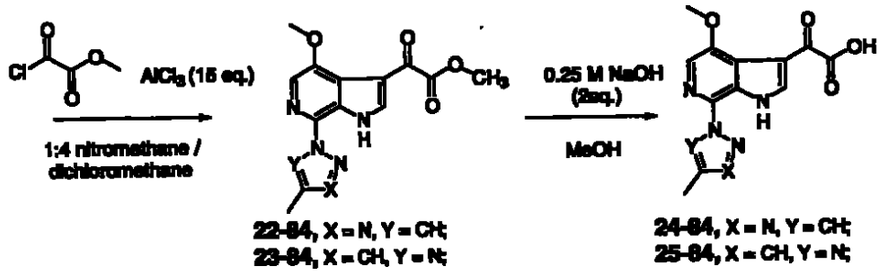
Y. 69 %: HPLC >97 % (AP at 254nm); MS (LC/MS) m/z 518 (M+H); ^{1}H NMR (DMSO-d_6) δppm 1.15, 1.22 (3H, 2d, J=7 Hz, Me), 2.9-4.4 (7H, m, CH_2N, CHN), 3.39 (3H, s, MeO), 4.00, 4.01 (3H, 2s, CH_3O), 4.61 (2H, s, CH_2), 7.4-7.5 (5H, m, Ph-Hs), 7.92 (1H, s, indole-H-5), 8.21, 8.29 (1H, 2s, indole-H-2), 9.35, 9.36 (1H, 2s, triazole-H-5), 12.4 (1H, br, NH).

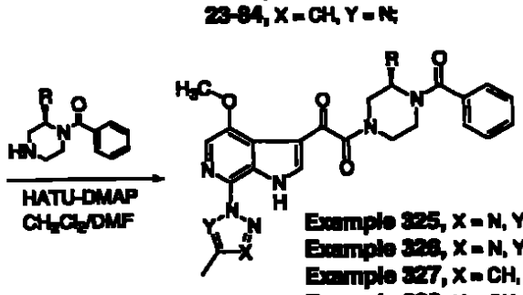
The following compounds, Examples 325, 326, 327, and 328, were prepared by the method described above using 4-methyl-1,2,3-triazole (19-84).



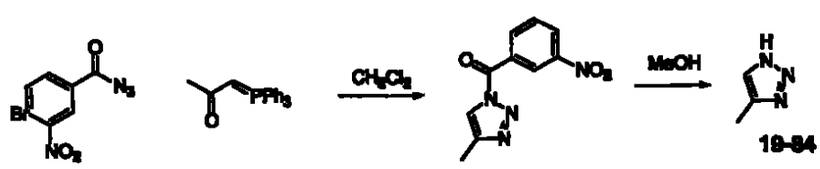
Scheme 84







Preparation of 4-methyl-1,2,3-triazole (19-84)

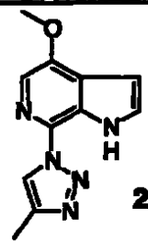


Procedure:

This compound 19-84 was prepared by the method described in M. Begtrup *J. Chem Soc., Perkin Transactions II*, 1976, 736.

A mixture of m-nitrobenzoyl azide (38.4 g, 0.200 mol; prepared from m-nitrobenzoyl chloride and sodium azide following the procedure described in *Org. Syn.* Coll. Vol. IV, 1963, p. 715) and 1-triphenylphosphoranylidene-2-propanone (63.6 g, 0.200 mol: Aldrich) in CH_2Cl_2 (300 mL) was stirred at room temperature for 2 hrs. The mixture was concentrated in vacuo to obtain a solid. This solid was dissolved in MeOH, and the solution was stirred at room temperature for 30 min, and the precipitates formed were removed. The filtrate was concentrated *in vacuo*, and the residue was extracted with water (500 mL) containing TFA (17 mL). This solution was washed once with a small amount of CH_2Cl_2 to remove the most of triphenylphosphine, and the aqueous phase neutralized with NaHCO3 to pH 7 and extracted five times with CH_2Cl_2 (total of 500 mL). The combined extracts were dried over Na2SO4, concentrated to obtain 7.6 g (0.091 mol, Y. 46%) of the title compound 19-84 as a yellow oil: ^{1}H NMR ($CDCl_3$) δppm 2.37 (3H, s, Me), 7.50 (1H, s, 5-H), 10.41 (1H, br, NH).

Compound 20-84

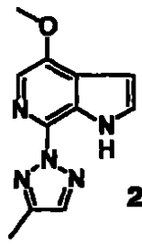


20-84

Yield 5-9 %: HPLC purity 100% (RT 1.89min, AP at 254nm); MS (LC/MS) m/z 230 (M+H); ^{1}H NMR ($CDCl_3$) δppm 2.47 (3H, s, Me), 4.07 (3H, s, 4-OCH_3), 6.74 (1H, t, J=2.7 Hz, H-3), 7.42 (1H, t, J=2.7 Hz, H-2), 7.62 (1H, s, H-5), 8.41 (1H, s, triazole-H-5), 10.3 (1H, br, NH).

The structure was confirmed by a single X-ray crystallographic analysis.

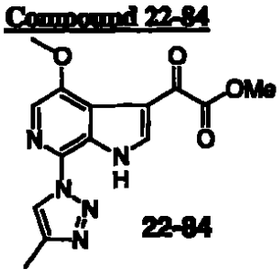
Compound 21-84



21-84

Yield 11-14 %: HPLC purity 100% (RT 1.36min, AP at 254nm); MS (LC/MS) m/z 230 (M+H); ^{1}H NMR ($CDCl_3$) δppm 2.48 (3H, s, Me), 4.06 (3H, s, 4-OCH_3), 6.74 (1H, dd, J=3, 2.4 Hz, H-3), 7.39 (1H, t, J=3 Hz, H-2), 7.68 (1H, s, H-5), 7.72 (1H, br, triazole-H-5), 10.25 (1H, br, NH).

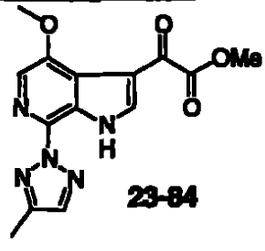
Compound 22-84



22-84

Yield 79 %: HPLC purity 94% (AP at 254nm); MS (LC/MS) m/z 316 (M+H); ^{1}H NMR ($CDCl_3$) δppm 2.49 (3H, s, Me), 3.96 (3H, s, OMe), 4.07 (3H, s, OMe), 7.81 (1H, s, H-5), 8.38 (1H, d, J=3.3 Hz, H-2), 8.42 (1H, s, triazole-H-5), 11.07 (1H, br, NH).

Compound 23-84

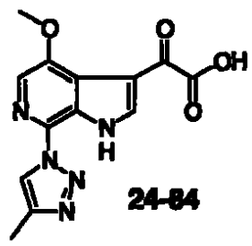


23-84

Yield 81 %: HPLC purity >95% (AP at 254nm); MS (LC/MS) m/z 316 (M+H); ^{1}H NMR ($CDCl_3$) δppm 2.49 (3H, s, Me), 4.00 (3H, s, OMe), 4.05 (3H, s, OMe), 7.72

(1H, s, H-5), 7.89 (1H, br.s, triazole-H-5), 8.33 (1H, d, J=3 Hz, H-2), 11 (1H, br, NH).

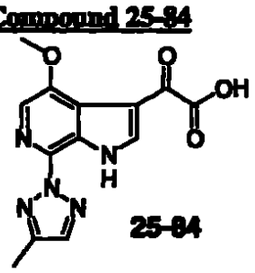
Compound 24-84



24-84

Yield 83 %: HPLC purity 98% (AP at 254nm); MS (LC/MS) m/z 302 (M+H); ^{1}H NMR (CD_3OD) δppm 2.46 (3H, s, Me), 4.06 (3H, s, OMe), 7.89 (1H, s, H-5), 8.39 (1H, d, J=3.3 Hz, H-2), 8.58 (1H, s, triazole-H-5).

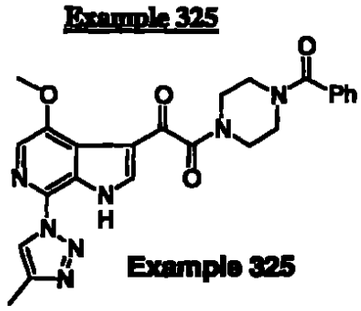
Compound 25-84



25-84

Yield 74 %: HPLC purity 100% (AP at 254nm); MS (LC/MS) m/z 302 (M+H); ^{1}H NMR (CD_3OD) δppm 2.50 (3H, s, Me), 4.05 (3H, s, OMe), 7.84 (1H, s), 7.90 (1H, s), 8.39 (1H, s).

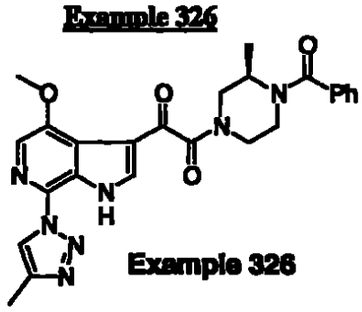
Example 325



Example 325

Y. 76 %: HPLC 98 % (AP at 254nm); MS (LC/MS) m/z 474 (M+H); ^{1}H NMR (DMSO-d_6) δppm 2.40 (3H, s, Me), 3.44 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.02 (3H, s, 4-MeO), 7.46 (5H, s, Ph-Hs), 7.96 (1H, s), 8.21 (1H, s), 8.68 (1H, s, triazole-H-5), 12.72 (1H, br.s, NH).

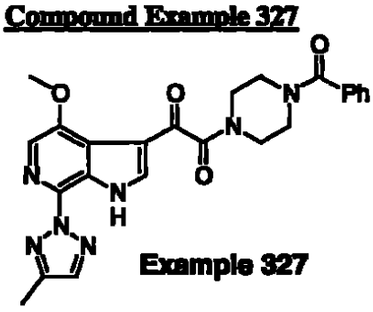
Example 326



Example 326

Y. 62 %: HPLC 97 % (AP at 254nm); MS (LC/MS) m/z 488 (M+H); ^{1}H NMR (DMSO-d_6) δppm 1.14, 1.21 (3H, 2d, J=7 Hz, Me), 2.40 (3H, s, Me), 2.9-4.4 (7H, m, CH_2N, CHN), 4.01, 4.02 (3H, 2s, CH_3O), 7.46 (5H, s, Ph-Hs), 7.96 (1H, s), 8.16, 8.23 (1H, 2s), 8.675, 8.68 (1H, 2d, J=2.5 Hz), 12.72 (1H, br.s, NH).

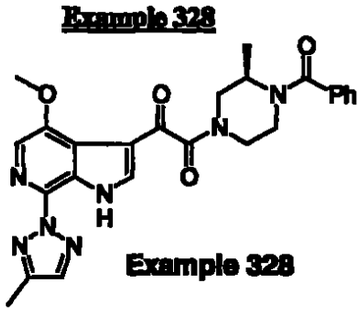
Compound Example 327



Example 327

Y. 73 %: HPLC 96 % (AP at 254nm); MS (LC/MS) m/z 474 (M+H); ^{1}H NMR (DMSO-d_6) δppm 2.45 (3H, s, Me), 3.44 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.01 (3H, s, 4-MeO), 7.46 (5H, s, Ph-Hs), 7.93 (1H, s), 8.04 (1H, s), 8.24 (1H, d, J=3Hz, H-2), 12.51 (1H, br.s, NH).

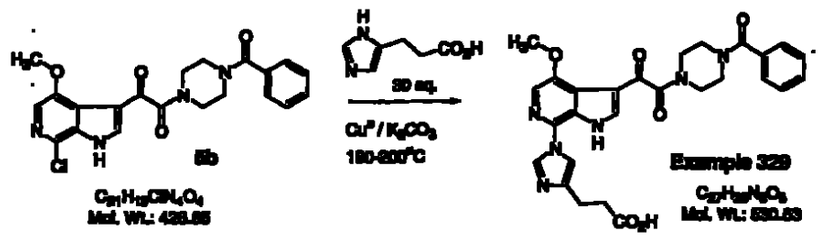
Example 328



Example 328

Y. 74 %: HPLC 99 % (AP at 254nm); MS (LC/MS) m/z 488 (M+H); ^{1}H NMR (DMSO-d_6) δppm 1.15, 1.22 (3H, 2d, J=7 Hz, Me), 2.45 (3H, s, Me), 2.9-4.4 (7H, m, CH_2N, CHN), 4.00, 4.01 (3H, 2s, CH_3O), 7.45 (5H, s, Ph-Hs), 7.92 (1H, s), 8.03 (1H, s), 8.18, 8.26 (1H, 2s), 12.5 (1H, br.s, NH).

Preparation of Example 329

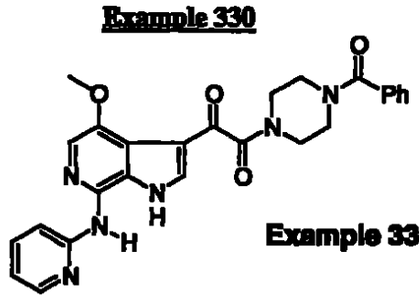


A mixture of compound 5b (128 mg, 0.3 mmol), imidazole-4-propionic acid (1.26 g, 9 mmol; 30 eq.; prepared from urocanic acid by catalytic hydrogenation using 10% Pd-C in acetic acid, following the procedure described in J. Altman, N. Shoef, M. Wilchek, and A. Warshawsky *J. Chem. Soc., Perkin Trans. I*, 1984, 59), copper powder (38 mg, 0.6 mmol; 2 eq.), potassium carbonate (83 mg, 0.6 mmol; 2 eq.) was flushed with anhydrous nitrogen and heated in a sealed tube at 190°-200°C (oil bath temp.) for 2 h. Upon cooling, to the mixture was added MeOH, and the insoluble material was filtered. The filtrate was concentrated *in vacuo* and purified by C-18 reverse phase column (YMC, eluting with 15% CH_3CN-water containing 0.1% TFA) to obtain 12 mg (0.023 mmol, Y. 7.5%) of the title compound Example 329 as amorphous powder (about 1:1 mixture of two regio-isomers): HPLC purity 96% (AP, at 254nm); MS (LC/MS) m/z 531 (M+H); ^{1}H NMR (CD_3OD) δ ppm 2.74, 3.00 (2H, 2t, J=7 Hz), 2.82, 3.11 (2H, 2t, J=7 Hz), 3.59 (4H, br, CH_2N), 3.79 (4H, br, CH_2N),

3.79, 4.10 (3H, 2s, CH_3O), 6.73 (s), 7.33 (s), 7.48 (5H, br. s, Ar-Hs), 7.93 (br.s), 8.00 (s), 8.10 (s), 8.40 (s), 8.77 (s), 9.43 (br.s).

The following compounds, Examples 330 and 331 were similarly prepared by following the above procedure.

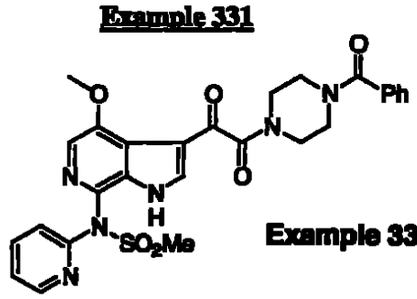
Example 330



Example 330

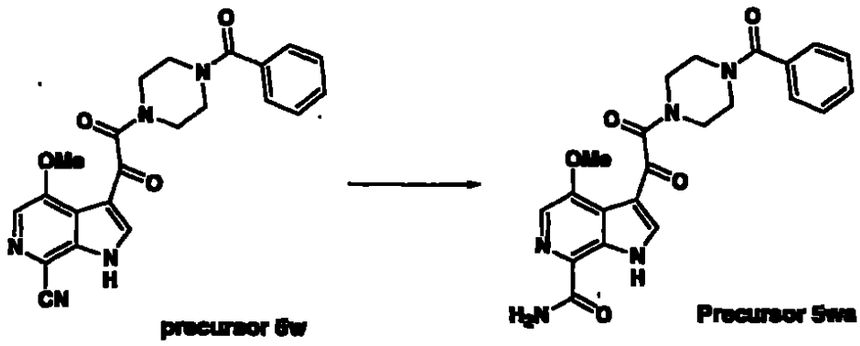
Y. 10 % (150°C, 7h): HPLC 93 % (AP at 254nm); MS (LC/MS) m/z 485 (M+H); ^{1}H NMR (CD_3OD, 500 MHz) δppm 3.63 (4H, br, CH_2N), 3.84 (4H, br, CH_2N), 4.05 (3H, s, 4-MeO), 7.32 (2H, m, pyr-Hs), 7.52 (5H, s, Ph-Hs), 7.71 (1H, s), 8.06 (1H, t, J=7.5 Hz, pyr-H), 8.48 (1H, d, J=4.5 Hz), 8.60 (1H, s).

Example 331

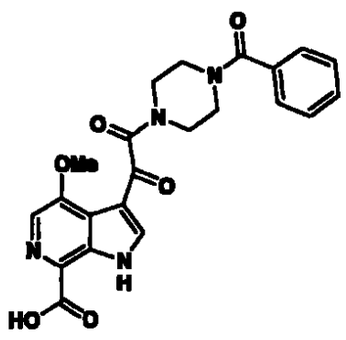


Example 331

Y. 10 % (150°C, 7h): HPLC 93 % (AP at 254nm); MS (LC/MS) m/z 563 (M+H); ^{1}H NMR ($CDCl_3$) δppm 2.76 (3h. S, Me), 3.55 (4H, br, CH_2N), 3.78 (4H, br, CH_2N), 4.09 (3H, s, 4-MeO), 6.71 (1H, t, J=7 Hz, pyr-H), 7.43 (5H, s, Ph-Hs), 7.68 (1H, t, J=7 Hz, pyr-H), 7.82 (1H, t, J=7 Hz, pyr-H), 7.91(1H, s), 8.15 (1H, s), 10.84 (1H, br, NH).



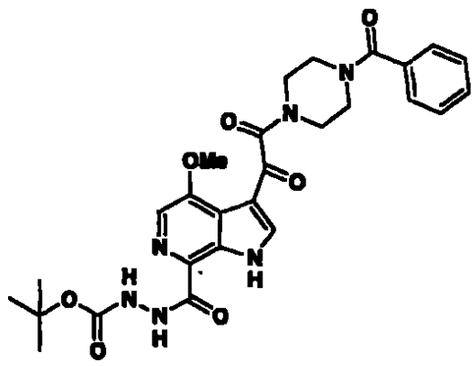
A mixture of precursor 5w (71.5 mg, 0.17 mmol) in MeOH (1.5 mL) was cooled to 0°C, and saturated with hydrogen chloride gas over the course of 10 min. The volatiles were then evaporated *via* blowing N_2 overnight to provide precursor 5wa. ^{1}H NMR: (DMSO-d_6) δ 12.45 (s, 1H), 8.12 (s, 2H), 8.07 (s, 1H), 7.65 (s, 1H), 7.45 (s, 5H), 4.04 (s, 3H), 3.80 – 3.30 (b m, 8H); LC/MS: (ES+) m/z $(M+H)^+$ = 436, HPLC R_t = 1.357 (Column G).



Precursor 5wb

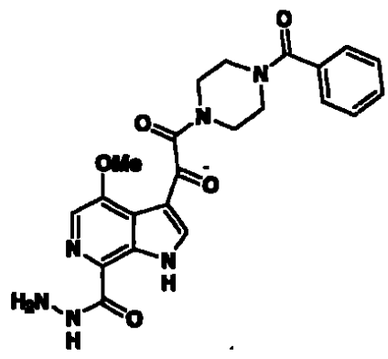
To a mixture of precursor 5wa (10 mg, 23 μmol) in acetic acid (0.4 mL) and acetic anhydride (0.75 mL) at 0°C, was added $NaNO_2$ (30 mg, 0.43 mmol). The reaction mixture was stirred at 0°C for 30 min, and allowed to warm to ambient temperature. After stirring for an additional 1.5 hr, the mixture was filtered and the residue dried under vacuum to give the desired compound 5wb an off-white solid. ^{1}H NMR:

(CD_3OD) δ 8.44 (s, 1H), 8.08 (s, 1H), 7.48 (b s, 5H), 4.14-3.27 (m, 8H), 4.14 (s, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 437, HPLC R_t = 0.750 (Column G).



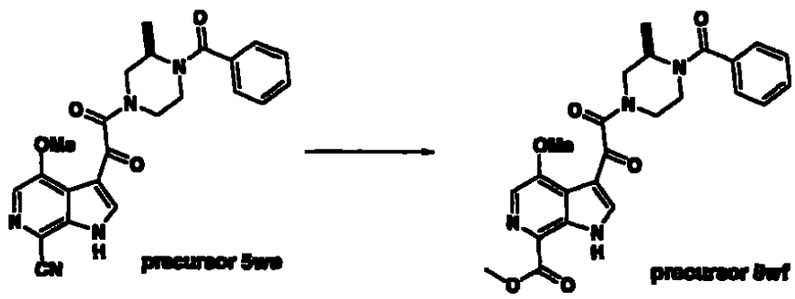
Precursor 5wc

A flask was charged with precursor **5wb** (2.6 mg, 6.0 μmol), DMF (0.5 mL), *tert*-butyl carbazate (1.2 mg, 8.9 μmol), DEPBT (5.4 mg, 18 μmol), and *N,N*-diisopropylethylamine (10 μL, 30 μmol). The reaction mixture was allowed to stir at ambient temperature overnight. The product **5wc** was separated using the following reverse phase preparative HPLC method: Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xerra Prep MS C18 5μm19x50mm, Fraction Collection: 4.38 – 4.59 min. ^1H NMR: (CD_3OD) δ 8.29 (s, 1H), 8.11 (s, 1H), 7.47 (b s, 5H), 4.11-3.28 (m, 8H), 4.10 (s, 3H), 1.50 (b s, 9H); LC/MS: (ES+) m/z $(M+H)^+$ = 551, HPLC R_t = 1.203 (Column G).

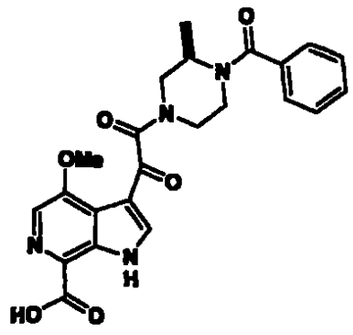


Precursor 5wd

To precursor 5we (57 mg, 0.104 mmol) was added a solution of HCl in 1,4-dioxane (4 *M*, 0.25 mL), and the reaction mixture was stirred overnight at room temperature. The deprotection afforded the desired product precursor 5wd cleanly. The excess reagent and solvent were evaporated *via* blowing N_2, and the product dried under vacuum. LC/MS: (ES+) m/z $(M+H)^+$ = 451, HPLC R_t = 0.803 (Column G).

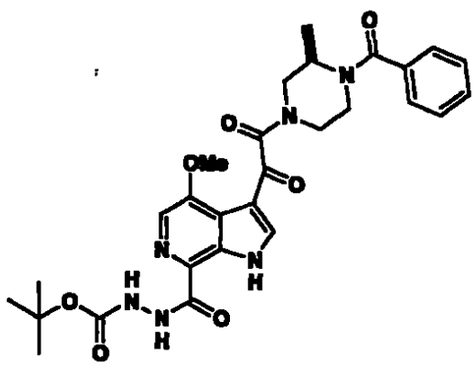


A solution of precursor 5we (106 mg, 0.25 mmol) in MeOH (2.5 mL) in a sealed tube at 0°C was flushed with N_2, and saturated with HCl gas for 10 min. The tube was closed and the reaction mixture was stirred at 70°C for 50 minutes. After cooling to ambient temperature, the volatiles were evaporated *in vacuo* to give precursor 5wf. ^{1}H NMR: (CD_3OD) δ 8.33, 8.30 (s, 1H), 8.13, 8.12 (s, 1H), 7.48-7.44 (m, 5H), 4.60-3.10 (b m, 7H), 4.12, 4.11 (s, 3H) 4.06 (s, 3H), 1.35,1.29 (d, *J* = 6.5, 7.0, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 465, HPLC R_t = 0.993 (Column G).



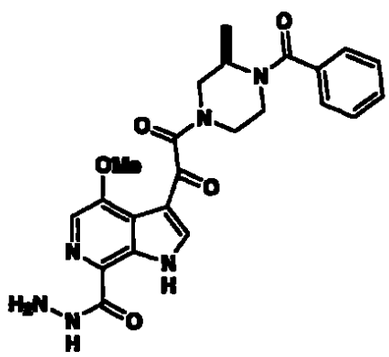
Precursor 5wg

To a solution of precursor 5wf (65 mg, 0.14 mmol) in MeOH (1 mL) was added NaOH (1.5 mL, 1 *N aq.*). The mixture was stirred for 2 hours, and upon which time HCl (1.5 mL, 1 *N aq.*) was added to quench the reaction. The volatiles were evaporated in vacuo to give precursor 5wg. ^{1}H NMR: (TFA solvate, CD_3OD) δ 8.54, 8.51 (s, 1H), 8.11 (b s, 1H), 7.57-7.48 (b s, 5H), 4.60-3.10 (b m, 7H), 4.17, 4.16 (s, 3H), 1.37,1.33 (d, J = 6.5, 6.0, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 451, HPLC R_t = 0.837 (Column G).



Precursor 5wh

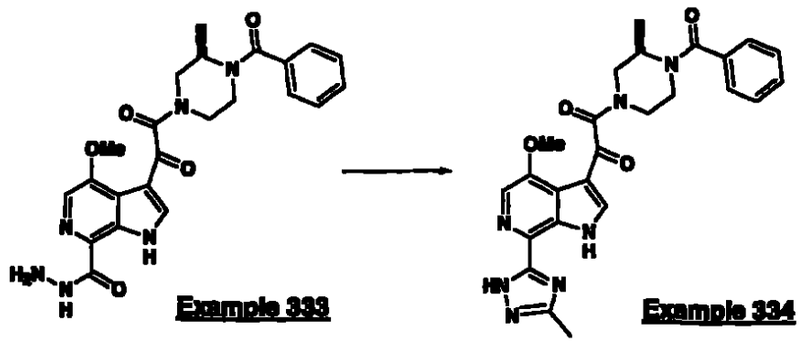
To a mixture of precursor 5wg (22 mg, 0.048 mmol) in DMF (1 mL) were added *tert*-butyl carbazate (14 mg, 0.11 mmol), DEPBT (53 mg, 0.18 mmol), and *N,N*-diisopropylethylamine (40 μL, 0.23 mmol). The reaction mixture was stirred overnight, and the desired compound precursor 5wh was isolated via preparative reverse phase HPLC using the following conditions: Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xerra Prep MS C18 5μm19x50mm, Fraction Collection: 4.37 – 4.98 min. ^{1}H NMR: (CD_3OD) δ 8.28, 8.26 (s, 1H), 8.08 (b s, 1H), 7.47-7.43 (m, 5H), 4.75-3.26 (m, 7H), 4.10 (s, 3H), 1.50 (b s, 9H), 1.36-1.27 (m, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 565, HPLC R_t = 1.207 (Column G).



Precursor 5wl

A mixture of precursor 5wh in a solution of HCl in 1,4-dioxane (0.2 mL, 4 *M*) was stirred for 3.5 hr at ambient temperature. The volatiles were evaporated *in vacuo*, and the crude mixture was purified via reverse phase preparative HPLC using the following method: Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xterra Prep MS C18 5μm19x50mm, Fraction Collection: 3.20 – 3.80 min. ^{1}H NMR: (CD_3OD) δ 8.74, 8.71 (s, 1H), 8.31, 8.28 (s, 1H), 7.47-7.44 (m, 5H), 4.46-3.35 (m, 7H), 4.18, 4.10 (s, 3H), 1.38-1.22 (m, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 465, HPLC R_t = 0.850 (Column G).

Example 333 and Example 334



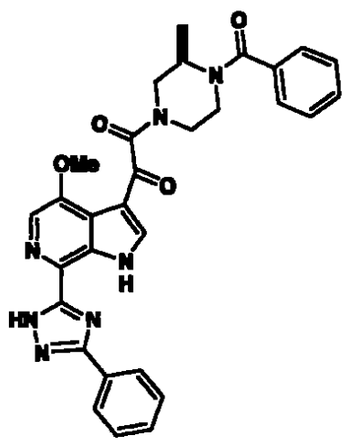
Example 333 **Example 334**

Thioacetamide (2 mg, 22 μmol) was added to Example 333 (10 mg, 20 μmol, HCl salt) in a round-bottom flask. The mixture was heated to 150°C for 20 minutes, after which it was cooled to ambient temperature, and diluted with MeOH. Purification of the desired compound Example 334 was performed via preparative reverse phase

HPLC using the following method: Start %B = 0, Final %B = 100, Gradient time = 6min, Flow Rate = 30mL/min, Column: Xerra Prep MS C18 5µm19x50mm, Fraction Collection: 3.47 – 3.86 min. ^{1}H NMR: (CD_3OD) δ 8.64, 8.62 (s, 1H), 8.04 (b s, 1H), 7.49-7.44 (m, 5H), 4.37-3.44 (m, 7H), 4.16, 4.14 (s, 3H), 2.63 (s, 3H), 1.36-1.32 (m, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 488, HPLC R_t = 0.973 (column G).

The following examples were prepared in a similar manner as above.

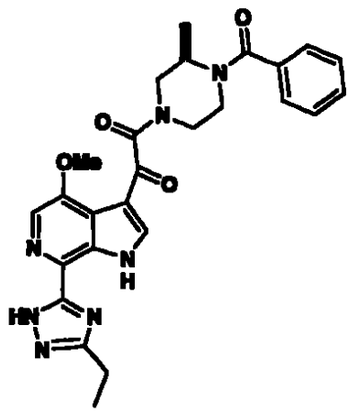
Example 335



Preparation of Example 335

^{1}H NMR: (CD_3OD) δ 8.60, 8.58 (s, 1H), 8.12 (d, J = 3, 1H), 7.71-7.67 (m, 1H), 7.59-7.54 (m, 4H), 7.50-7.46 (m, 5H), 4.37-3.44 (m, 7H), 4.16, 4.14 (s, 3H), 1.37, 1.33 (d, J = 6.5, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 550, HPLC R_t = 1.283(column G).

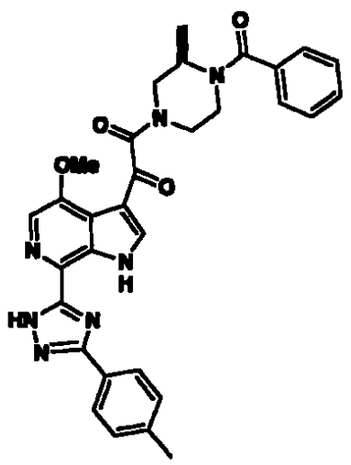
Example 336



Example 336

^{1}H NMR: (CD_3OD) δ 8.66, 8.64 (s, 1H), 8.04 (d, J = 3, 1H), 7.49-7.40 (m, 5H), 4.41-3.44 (m, 7H), 4.16, 4.14 (s, 3H), 3.00 (q, J = 7.5, 2H), 1.46 (t, J = 7.5, 3H), 1.36-1.32 (m, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 502, HPLC R_t = 1.007(column G).

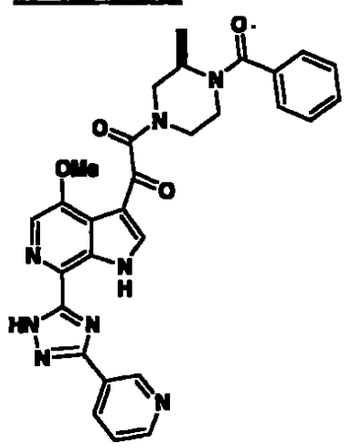
Example 337



Example 337

^{1}H NMR: (CD_3OD) δ 8.59, 8.57 (s, 1H), 8.11 (b d, 1H), 7.48-7.40 (m, 9H), 4.46-3.39 (m, 7H), 4.16, 4.14 (s, 3H), 2.45 (s, 3H), 1.40-1.29 (m, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 564, HPLC R_t = 1.363 (column G).

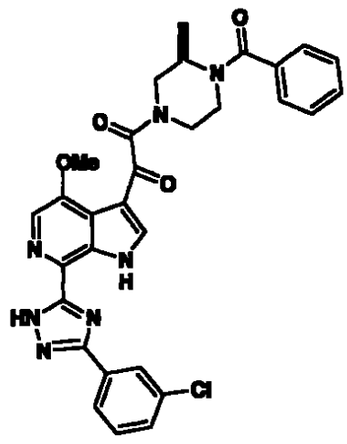
Example 338



Example 338

^{1}H NMR: (CD_3OD) δ 9.62 (s, 1H), 9.11 (s, 1H), 8.82 (d, J = 5.5, 1H), 8.47 (d, J = 8.5, 1H), 8.19 (s, 1H), 7.98 (s, 1H), 7.49-7.46 (m, 5H), 4.64-3.35 (m, 7H), 4.14, 4.13 (s, 3H), 1.37, 1.32 (d, J = 7, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 551, HPLC R_t = 1.090 (column G).

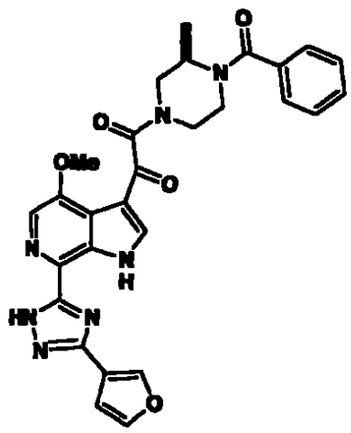
Example 339



Example 339

^{1}H NMR: (CD_3OD) δ 8.50 (s, 1H), 8.17 (b d, 1H), 7.53-7.45 (m, 9H), 4.64-3.35 (m, 7H), 4.14, 4.13 (s, 3H), 1.37, 1.32 (d, J = 6.5, 7, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 584, HPLC R_t = 1.427 (column G).

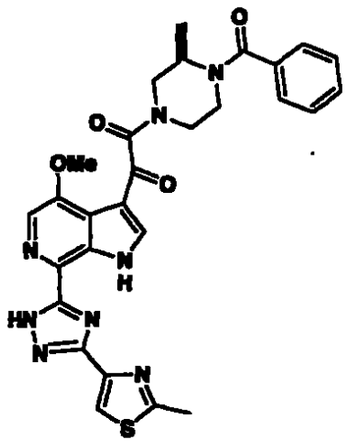
Example 340



Example 340

^{1}H NMR: (CD_3OD) δ 8.56, 8.55 (s, 1H), 8.36 (s, 1H), 8.10 (s, 1H), 7.72 (s, 1H), 7.48-7.45 (m, 5H), 7.09 (s, 1H), 4.64-3.44 (m, 7H), 4.15, 4.14 (s, 3H), 1.36-1.32 (m, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 540, HPLC R_t = 1.133 (column G).

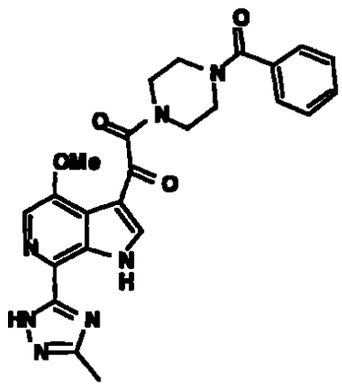
Example 341



Example 341

^{1}H NMR: (CD_3OD) δ 8.54, 8.51 (s, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 7.48-7.39 (m, 5H), 4.71-3.44 (m, 7H), 4.14, 4.13 (s, 3H), 2.85 (s, 3H), 1.37-1.29 (m, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 571, HPLC R_t = 1.450 (column G).

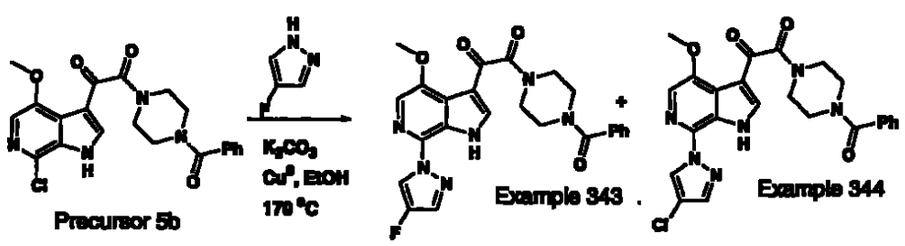
Example 342



Example 342

^{1}H NMR: (CD_3OD) δ 8.64 (s, 1H), 8.04 (s, 1H), 7.48 (s, 5H), 4.16 (s, 3H), 3.92-3.39 (m, 8H), 2.64 (s, 3H); LC/MS: (ES+) m/z $(M+H)^+$ = 474, HPLC R_t = 0.903 (column G).

Examples 343 and 344

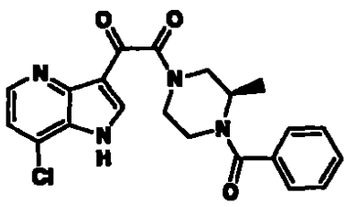


Precursor 5b (60 mg, 0.14 mmol), 4-fluoropyrazole (0.30 mL) (prepared as described in Molines, H.; Wakselman, C. *J. Org. Chem.* 1989, *54*, 5618-5620), copper(0) (8.0 mg, 0.13 mmol), K_2CO_3 (15 mg, 0.11 mmol) and EtOH (0.30 mL) were combined in a sealed tube flushed with nitrogen and heated at 170 °C with microwave irradiation for 1.5h. The reaction was cooled, filtered and concentrated. The residue was purified by preparative HPLC under the standard conditions described above to provide (6.6 mg,0.014 mmol) of Example 343 as a yellow solid and Example 344 (3.1 mg, 0.006 mmol) as a greenish solid.

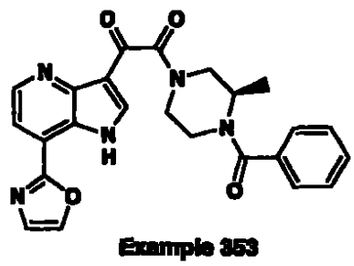
Example 343: ^{1}H NMR (500 MHz, CD_3OD) δ 8.56 (d, J = 4.3 Hz, 1H), 8.27 (s, 1H), 7.82-7.79 (m, 2H), 7.47 (br s, 5H), 4.03 (s, 3H), 3.97-3.45 (m, 8H). MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{21}FN_6O_2$: 477.16; found 477.16. HPLC retention time: 1.45 minutes (column G).

Example 344: ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.16 (br s, 1H), 8.59 (s 1H), 8.19 (s, 1H), 7.78-7.62 (m, 2H), 7.43 (br s, 5H), 4.04 (s, 3H), 3.987-3.40 (m, 8H). MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{21}ClN_6O_2$: 493.13; found 493.12. HPLC retention time: 1.59 minutes (column G).

Example 353



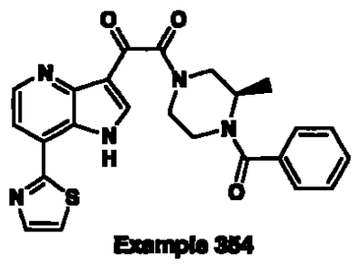
Precursor 5mn



Example 353

Example 353 was prepared from the corresponding 7-chloro precursor 5mn and 2-tributyl stannyl oxazole via the standard Stille coupling conditions described above. The 7-chloro precursor was prepared similarly to precursor 5d except that 2-(R) methyl piperazine benzamide (precursor 17b) was utilized. Example 353, 4-azaindole-7-(2'-oxazole): ^{1}H NMR (500 MHz, CD_3OD) δ 8.68 (s, 0.5H), 8.67 (s, 0.5H), 8.45 (s, 0.5H), 8.43 (s, 0.5H), 8.18 (s, 1H), 7.86 (d, J = 4.9 Hz, 0.5H), 7.85 (d, J = 4.9 Hz, 0.5H), 7.55 (s, 1H), 7.50-7.40 (m, 5H), 4.45-3.06 (m, 7H), 1.48 (d, J = 6.7 Hz, 1.5H) 1.24 (d, J = 6.7 Hz, 1.5H). MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{22}N_5O_4$: 444.16; found 444.23. HPLC retention time: 0.90 minutes (column G).

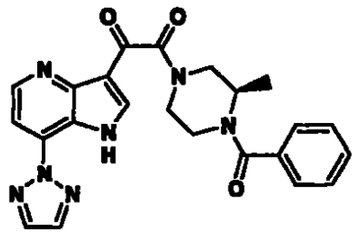
Example 354



Example 354

Example 354 was prepared from the corresponding 7-chloro precursor 5mm and 2-tributyl stannyl thiazole via the standard Stille coupling conditions described above. The 7-chloro precursor was prepared similarly to precursor 5d except that 2-(R) methyl piperazine benzamide (precursor 17b) was utilized. Example 354: 4-azaindole-7-(2'-thiazole): ^{1}H NMR (500 MHz, CD_3OD) δ 8.80 (s, 0.5H), 8.74-8.71 (m, 1.5H), 8.35 (d, J = 3.5 Hz, 0.5H), 8.35 (d, J = 3.5 Hz, 0.5H), 8.26 (d, J = 3.5 Hz, 0.5H), 8.25 (d, J = 3.5 Hz, 0.5H), 8.14 (d, J = 3.1 Hz, 0.5H), 8.14 (d, J = 3.1 Hz, 0.5H), 7.50-7.42 (m, 5H), 4.48-3.08 (m, 7H), 1.36 (d, J = 6.7 Hz, 1.5H) 1.32 (d, J = 6.7 Hz, 1.5H). MS *m/z*: $(M+H)^+$ calcd for $C_{24}H_{22}N_5O_3S$: 460.14; found 460.20. HPLC retention time: 0.94 minutes (column G).

Example 355

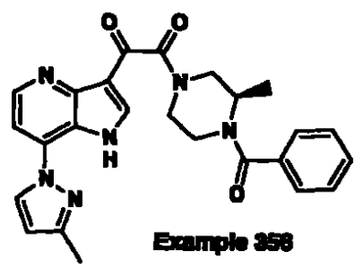


Example 355

Example 355 was prepared via the procedure used for Example 205 from the corresponding 7-chloro precursor 5mm and 1,2,3,triazole. The 7-chloro precursor was prepared similarly to precursor 5d except that 2-(R) methyl piperazine benzamide (precursor 17b) was utilized. Example 355, 4-azaindole-7-(2'-triazole) : ^{1}H NMR (500 MHz, CD_3OD) δ 8.79-8.76 (m, 1H), 8.78 (s, 0.5H), 8.70 (s, 0.5H), 8.44 (d, J = 5.9 Hz, 0.5H), 8.43 (d, J = 5.9 Hz, 0.5H), 8.38 (s, 1H), 8.38 (s, 1H), 7.51-

7.42 (m, 5H), 4.50-3.21 (m, 7H), 1.37 (d, J = 6.7 Hz, 1.5H) 1.32 (d, J = 6.7 Hz, 1.5H). MS m/z: $(M+H)^+$ calcd for $C_{23}H_{22}N_7O_3$: 444.17; found 444.26. HPLC retention time: 0.90 minutes (column G).

Example 356



Example 356

Example 356 was prepared via the procedure used for Example 205 from the corresponding 7-chloro precursor 5mm and 3-methyl pyrazole. The 7-chloro precursor was prepared similarly to precursor 5d except that 2-(R) methyl piperazine benzamide(precursor 17b)was utilized. Example 356,4-azaindole-7-(3'-methyl-2'-pyrazole): ^{1}H NMR (500 MHz, CD_3OD) δ 8.73-8.71 (m, 1H), 8.70 (s, 0.5H), 8.63 (s, 0.5H), 8.64-8.60 (m, 1H), 8.06 (s, 0.5H), 8.04 (s, 0.5H), 7.52-7.42 (m, 5H), 6.68 (s, 0.5H), 6.67 (s, 0.5H), 4.61-3.21 (m, 7H), 2.51 (s, 3H), 1.35 (d, J = 6.5 Hz, 1.5H) 1.32 (d, J = 6.5 Hz, 1.5H). MS m/z: $(M+H)^+$ calcd for $C_{25}H_{25}N_6O_3$: 457.19; found 457.33. HPLC retention time: 1.04 minutes (column G).

Biology

- "μM" means micromolar;
- "mL" means milliliter;
- "μl" means microliter;
- "mg" means milligram;

The materials and experimental procedures used to obtain the results reported in Tables 1-5 are described below.

Cells:

- Virus production-Human embryonic Kidney cell line, 293, propagated in Dulbecco's Modified Eagle Medium (Life Technologies, Gaithersburg, MD) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO).
- Virus infection- Human epithelial cell line, HeLa, expressing the HIV-1 receptors CD4 and CCR5 was propagated in Dulbecco's Modified Eagle Medium (Life Technologies, Gaithersburg, MD) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO) and supplemented with 0.2 mg/mL Geneticin (Life Technologies, Gaithersburg, MD) and 0.4 mg/mL Zeocin (Invitrogen, Carlsbad, CA).

Virus-Single-round infectious reporter virus was produced by co-transfecting human embryonic Kidney 293 cells with an HIV-1 envelope DNA expression vector and a proviral cDNA containing an envelope deletion mutation and the luciferase reporter gene inserted in place of HIV-1 nef sequences (Chen et al, Ref. 41). Transfections were performed using lipofectAMINE PLUS reagent as described by the manufacturer (Life Technologies, Gaithersburg, MD).

Experiment

1. Compound was added to HeLa CD4 CCR5 cells plated in 96 well plates at a cell density of 5 X 10^4 cells per well in 100 µl Dulbecco's Modified Eagle Medium containing 10 % fetal Bovine serum at a concentration of <20 µM.

2. 100 µl of single-round infectious reporter virus in Dulbecco's Modified Eagle Medium was then added to the plated cells and compound at an approximate multiplicity of infection (MOI) of 0.01, resulting in a final volume of 200 µl per well and a final compound concentration of <10 µM.

3. Samples were harvested 72 h after infection.

4. Viral infection was monitored by measuring luciferase expression from viral DNA in the infected cells using a luciferase reporter gene assay kit (Roche Molecular Biochemicals, Indianapolis, IN). Infected cell supernatants were removed and 50 µl of Dulbecco's Modified Eagle Medium (without phenol red) and 50 µl of luciferase assay reagent reconstituted as described by the manufacturer (Roche Molecular Biochemicals, Indianapolis, IN) was added per well. Luciferase activity was then quantified by measuring luminescence using a Wallac microbeta scintillation counter.

5. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.

6. An EC_{50} provides a method for comparing the antiviral potency of the compounds of this invention. The effective concentration for fifty percent inhibition (EC_{50}) was calculated with the Microsoft Excel Xlfit curve fitting software. For each compound, curves were generated from percent inhibition calculated at 10 different concentrations by using a four parameter logistic model (model 205). The EC_{50} data for the compounds is shown in Tables 2-4. Table 1 is the key for the data in Tables 2-4.

Cytoxicity assays were conducted with the same HeLa using methodology well known in the art. This method has been described in the literature (S Weislow, R Kiser, DL Fine, J Bader, RH Shoemaker and MR Boyd: New soluble-formazan assay for HIV-1 cytopathic effects: application to high-flux screening of synthetic and natural products for AIDS-antiviral activity. Journal of the National Cancer Institute. 81(8):577-586, 1989.

Cells were incubated in the presence of drug for six days, after which cell viability was measured using a dye reduction assay (MTT) and determined as a CC50. This assay measures the intracellular reducing activity present in actively respiring cells.

Results

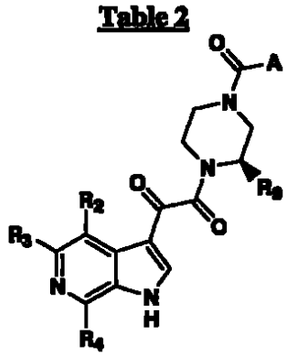
Table 1. Biological Data Key for EC_{50}s

Compounds* with EC_{50} >5μM	Compounds with EC_{50} >1 μM but <5μM	Compounds with EC50 >50nM but not yet tested at higher concentrations	Compounds with EC50 < 1 μM
Group C	Group B	Group A'	Group A

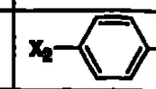
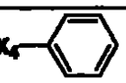
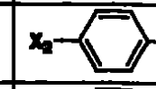
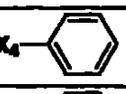
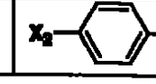
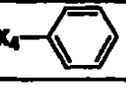
*Some of these compounds may have been tested at a concentration lower than their EC_{50} but showed some ability to cause inhibition and thus should be evaluated at a higher concentration to determine the exact EC_{50}.

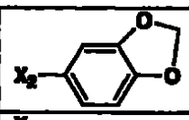
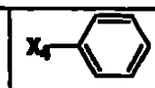
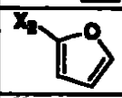
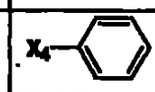
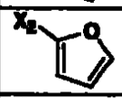
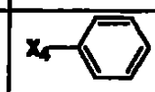
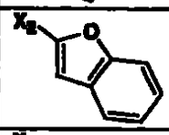
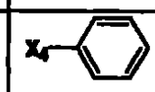
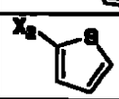
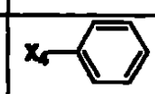
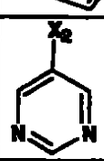
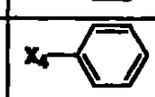
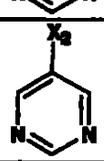
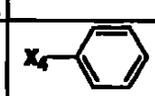
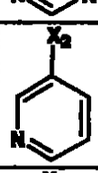
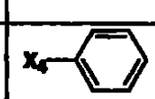
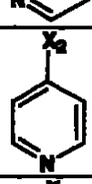
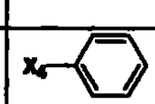
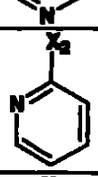
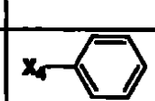
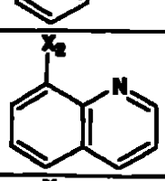
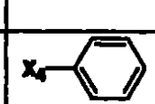
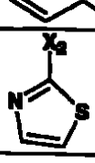
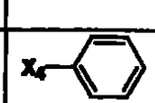
In Tables 2-5, X_2, X_4 etc. indicates the point of attachment.

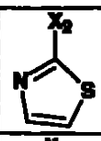
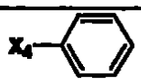
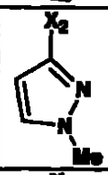
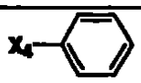
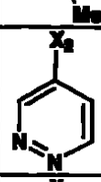
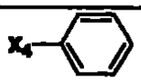
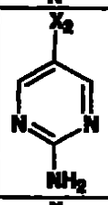
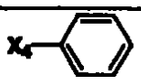
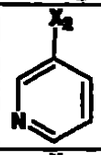
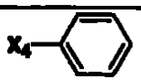
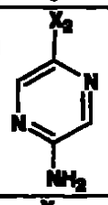
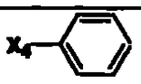
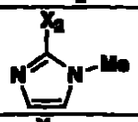
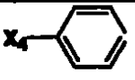
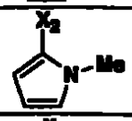
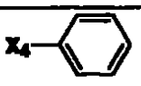
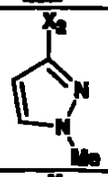
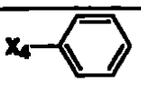
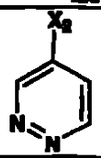
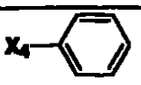
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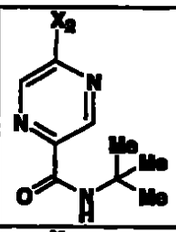
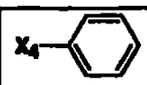
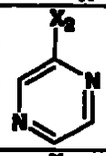
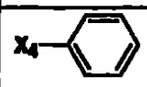
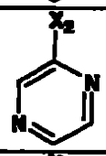
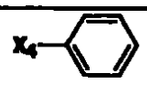
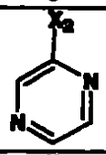
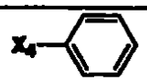
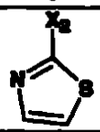
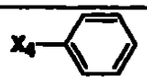
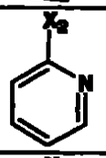
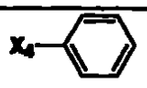
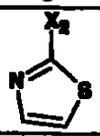
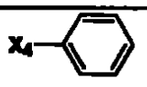
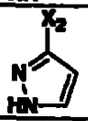
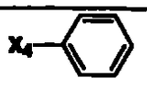
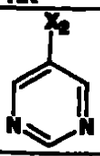
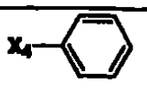
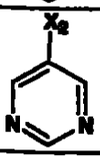
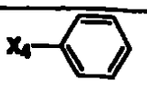


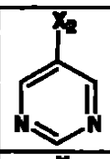
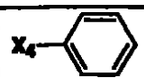
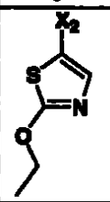
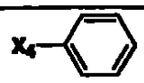
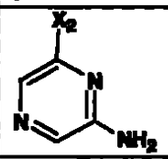
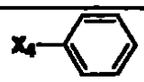
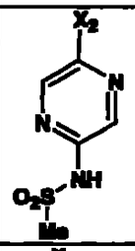
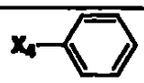
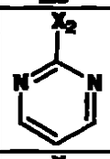
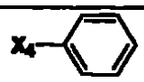
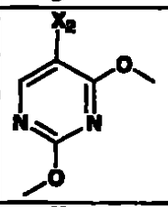
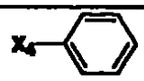
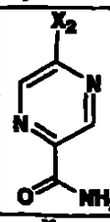
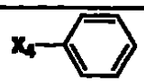
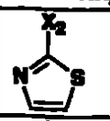
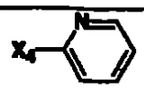
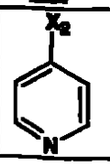
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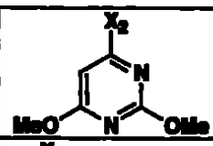
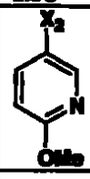
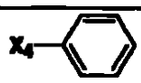
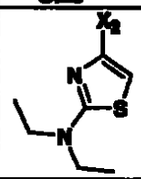
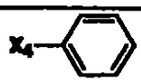
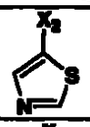
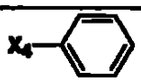
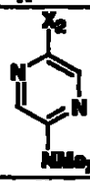
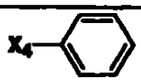
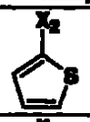
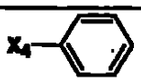
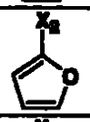
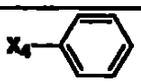
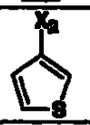
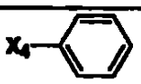
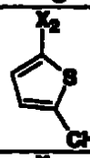
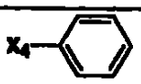
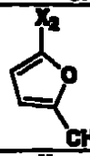
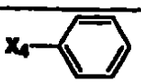
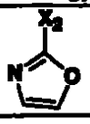
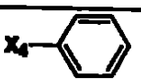
Table Entry (Example Number.)	R2	R3	R4	R9	A	EC_{50} Group from Table 1
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2 (Example 2)	H	H		CH_3		A
4 (Example 4)	H	H		H		A

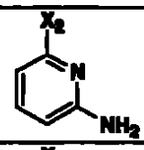
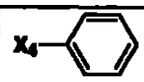
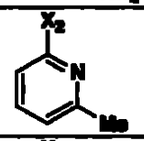
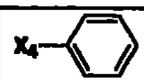
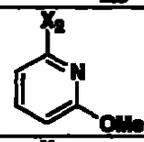
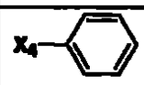
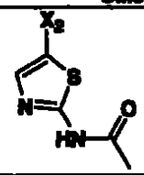
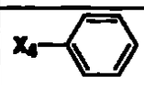
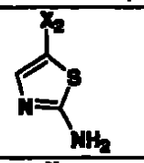
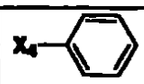
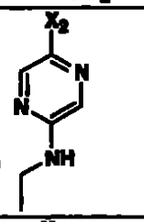
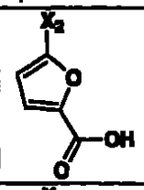
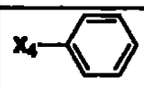
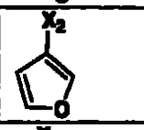
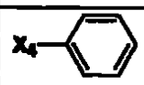
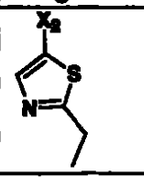
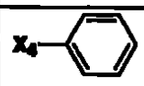
5 (Example 5)	H	H		CH_3		A
6 (Example 6)	H	H		CH_3		A
7 (Example 7)	H	H		H		A
8 (Example 8)	H	H		H		A
9 (Example 9)	H	H		CH_3		A
10 (Example 16)	H	H		CH_3		A
11 (Example 17)	H	H		H		A
12 (Example 18)	H	H		CH_3		A
13 (Example 10)	H	H		H		A
14 (Example 19)	H	H		H		A
15 (Example 11)	H	H		H		A'
16 (Example 20)	H	H		CH_3		A

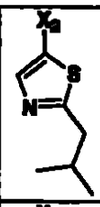
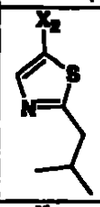
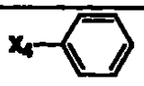
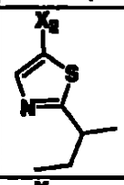
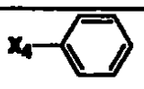
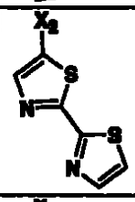
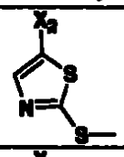
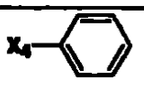
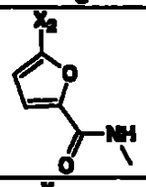
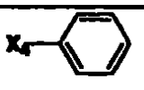
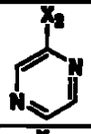
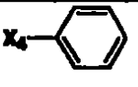
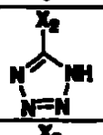
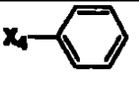
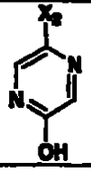
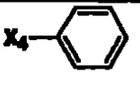
17 (Example 21)	H	H		H		A
18 (Example 22)	OMe	H		H		A
19 (Example 23)	OMe	H		H		A
20 (Example 24)	OMe	H		H		A
21 (Example 25)	OMe	H		H		A
22 (Example 26)	OMe	H		H		A
23 (Example 27)	OMe	H		H		A
24 (Example 28)	OMe	H		H		A
25 (Example 29)	F	H		H		A
26 (Example 30)	F	H		H		A

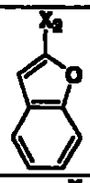
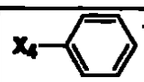
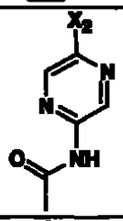
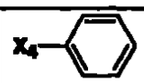
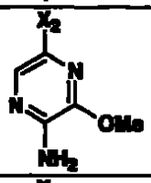
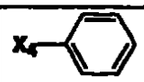
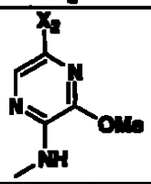
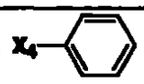
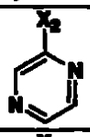
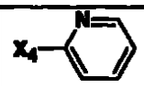
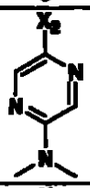
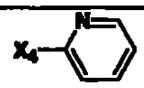
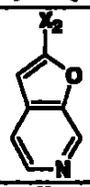
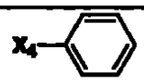
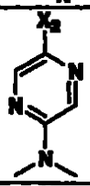
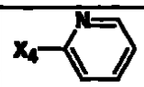
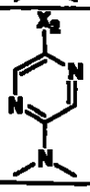
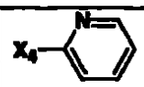
27 (Example 15)	OMe	H		H		A
28 (Example 32)	OMe	H		H		A
29 (Example 33)	H	H		Me		A
30 (Example 34)	H	H		H		A
31 (Example 35)	OMe	H		H		A
32 (Example 36)	OMe	H		H		A
33 (Example 37)	F	H		Me		A
34 (Example 38)	F	H		H		A
35 (Example 39)	OMe	H		H		A
36 (Example 40)	OMe	H		H		A
37 (Example 41)	F	H		Me		A

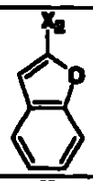
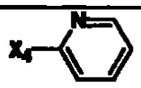
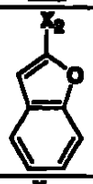
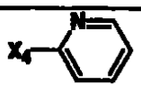
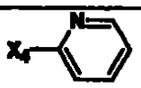
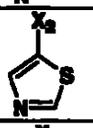
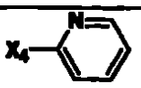
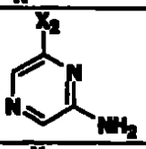
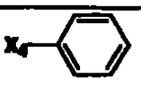
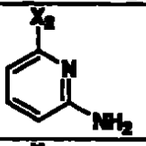
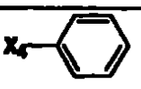
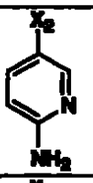
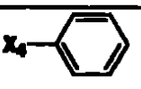
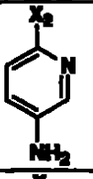
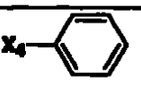
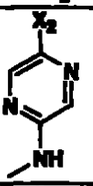
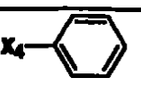
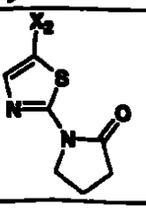
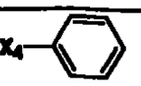
38 (Example 42)	F	H		H		A
41 (Example 45)	OMe	H		H		A
42 (Example 46)	OMe	H		H		A
43 (Example 47)	OMe	H		H		A
45 (Example 49)	OMe	H		H		A
46 (Example 13)	OMe	H		H		A
47 (Example 55)	OMe	H		H		A
48 (Example 50)	OMe	H		H		A
49 (Example 14)	OMe	H		H		A

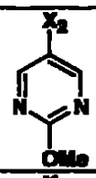
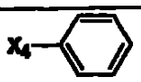
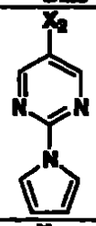
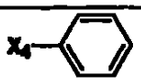
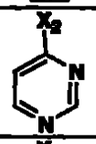
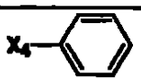
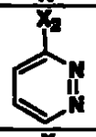
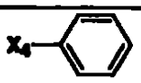
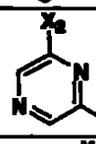
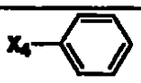
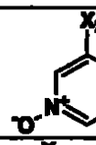
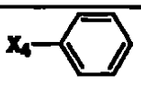
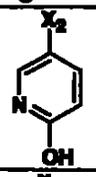
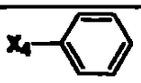
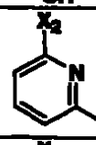
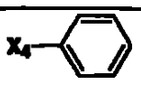
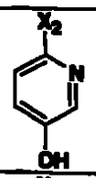
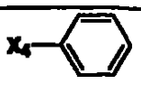
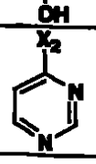
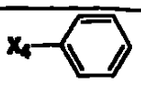
50 (Example 68)	OMe	H		H		A
51 (Example 69)	OMe	H		H		A
52 (Example 70)	OMe	H		H		A
53 (Example 71)	OMe	H		H		A
54 (Example 72)	OMe	H		H		A
55 (Example 82)	OMe	H		H		A
56 (Example 73)	OMe	H		H		A
57 (Example 83)	OMe	H		H		A
58 (Example 84)	OMe	H		H		A
59 (Example 85)	OMe	H		H		A
60 (Example 74)	OMe	H		H		A

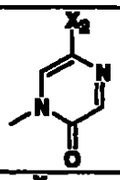
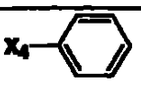
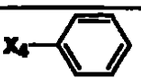
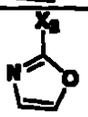
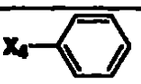
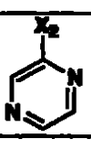
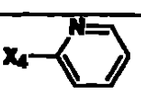
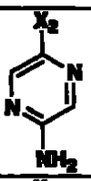
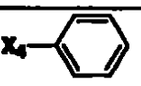
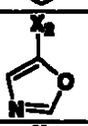
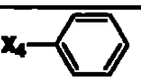
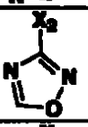
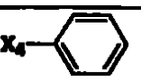
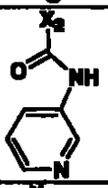
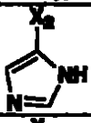
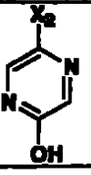
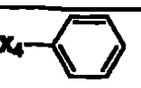
61 (Example 75)	OMe	H		H		A
62 (Example 76)	OMe	H		H		A
63 (Example 77)	OMe	H		H		A
64 (Example 78)	OMe	H		H		A
65 (Example 80)	OMe	H		H		A
66 (Example 79)	OMe	H		H		A
67 (Example 87)	OMe	H		H		A
68 (Example 81)	OMe	H		H		A
69 (Example 88)	OMe	H		H		A

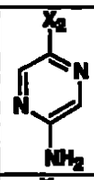
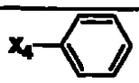
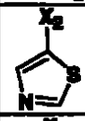
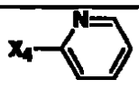
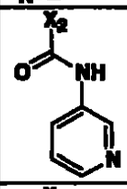
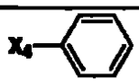
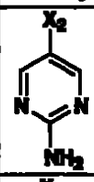
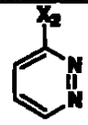
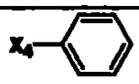
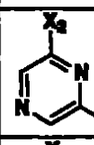
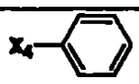
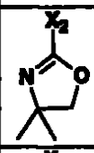
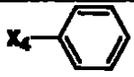
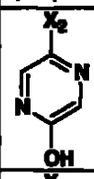
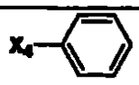
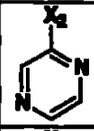
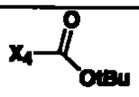
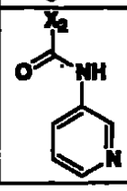
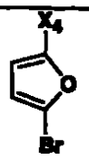
70 (Example 89)	H	H		H		A
71 (Example 90)	OMe	H		H		A
72 (Example 91)	OMe	H		H		A
72 (Example 92)	OMe	H		H		A
73 (Example 93)	OMe	H		H		A
74 (Example 94)	OMe	H		H		A
75 (Example 95)	F	H		H		A
76 (Example 96)	Cl	H		H		A
77 (Example 97)	OMe	H		H		A

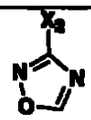
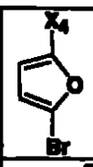
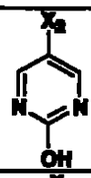
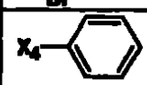
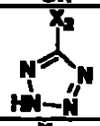
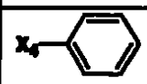
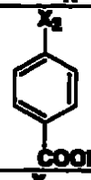
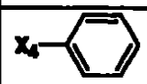
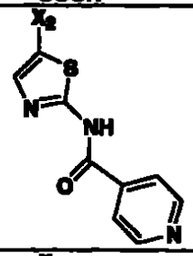
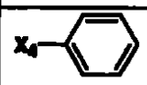
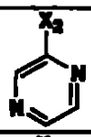
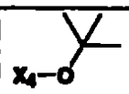
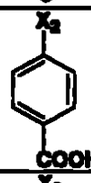
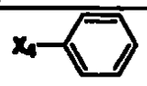
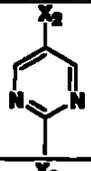
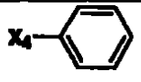
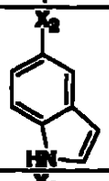
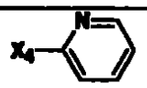
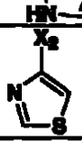
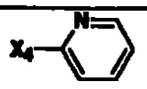
78 (Example 98)	OMe	H		H		A
79 (Example 99)	OMe	H		H		A
80 (Example 100)	OMe	H		H		A
81 (Example 101)	OMe	H		H		A
82 (Example 102)	OMe	H		H		A
83 (Example 103)	OMe	H		H		A
84 (Example 104)	OMe	H		H		A
85 (Example 105)	H	H		(R)-Me		A
86 (Example 106)	H	H		(S)-Me		A

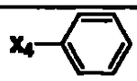
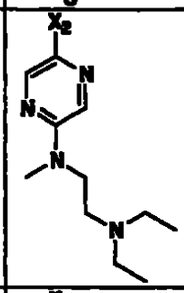
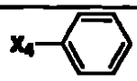
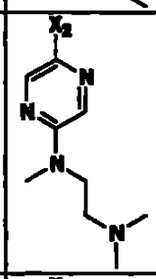
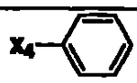
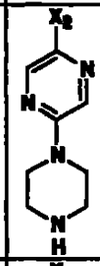
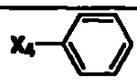
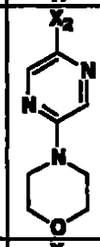
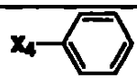
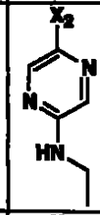
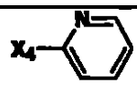
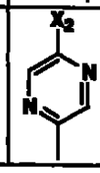
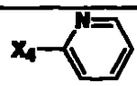
87 (Example 107)	H	H		(R)-Me		A
88 (Example 108)	H	H		(S)-Me		A
89 (Example 109)	H	H		(R)-Me		A
90 (Example 110)	H	H		(S)-Me		A
91 (Example 111)	H	H		(R)-Me		A
92 (Example 112)	H	H		(R)-Me		A
93 (Example 113)	H	H		(R)-Me		A
94 (Example 114)	H	H		(R)-Me		A
95 (Example 115)	OMe	H		H		A
96 (Example 116)	OMe	H		H		A

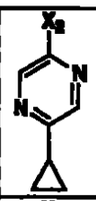
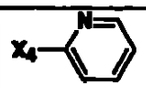
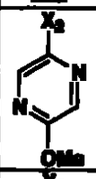
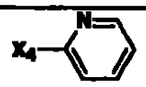
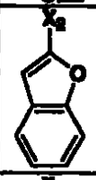
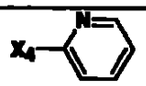
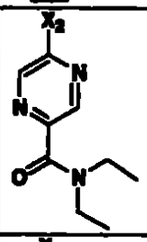
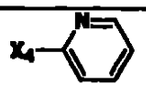
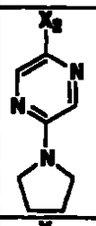
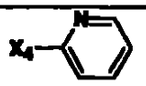
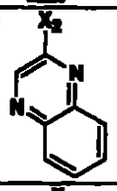
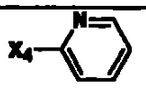
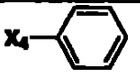
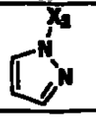
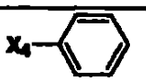
97 (Example 117)	OMe	H		H		A
98 (Example 118)	OMe	H		H		A
99 (Example 119)	OMe	H		H		A
100 (Example 120)	OMe	H		H		A
101 (Example 121)	H	H		(R)-Me		A
102 (Example 121-2)	H	H		(R)-Me		A
103 (Example 122)	H	H		(R)-Me		A
104 (Example 123)	H	H		(R)-Me		A
105 (Example 124)	H	H		(R)-Me		A
106 (Example 125)	F	H		H		A

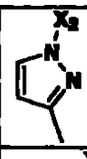
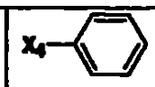
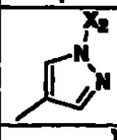
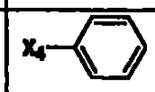
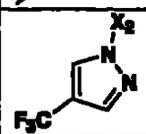
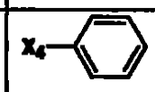
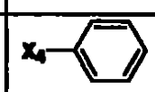
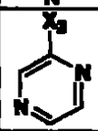
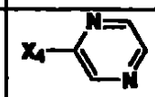
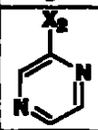
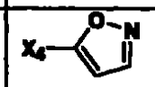
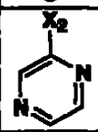
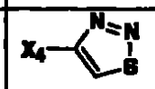
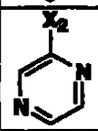
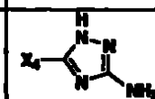
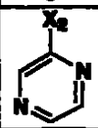
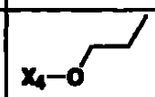
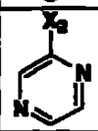
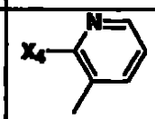
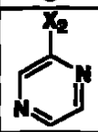
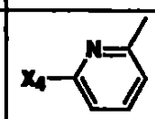
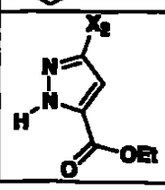
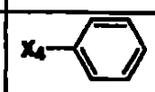
107 (Example 138)	OMe	H		H		A
108 (Example 139)	Br	H		(R)-Me		A
109 (Example 140)	F	H		H		A
110 (Example 141)	F	H		(R)-Me		A
111						
112 (Example 143)	Cl	H		H		A
113 (Example 144)	Cl	H		H		A
114 (Example 145)	F	H		H		A
115 (Example 146)	F	H		H		A
116 (Example 147)	F	H		H		A
117 (Example 148)	F	H		H		A
118 (Example 149)	Cl	H		H		A

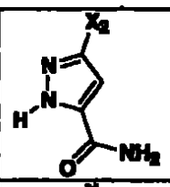
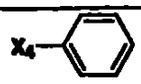
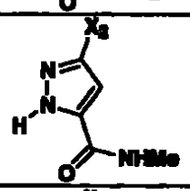
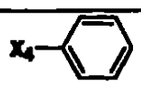
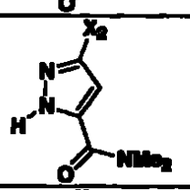
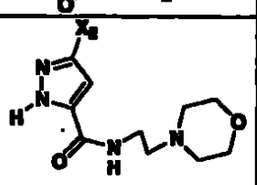
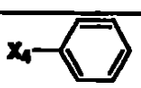
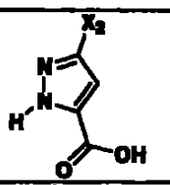
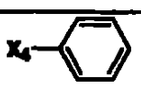
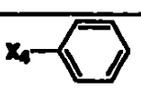
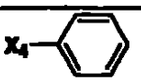
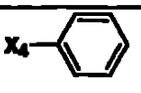
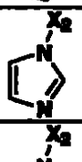
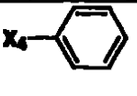
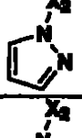
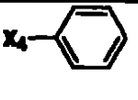
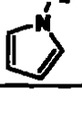
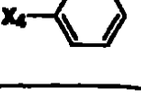
119 (Example 150)	H	H		(R)-Me		A
120 (Example 151)	OMe	H		H		A
121 (Example 152)	Cl	H		H		A
122 (Example 153)	H	H		(R)-Me		A
123 (Example 154)	F	H		H		A
124 (Example 155)	OMe	H		H		A
125 (Example 156)	OMe	H		H		A
126 (Example 157)	H	H		(R)-Me		A
127 (Example 165)	Cl	H		H		A
128 (Example 166)	F	H		H		

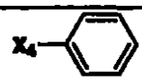
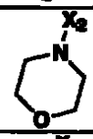
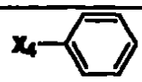
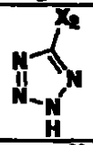
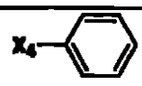
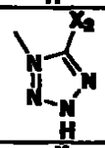
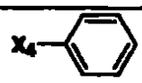
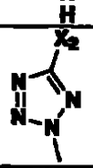
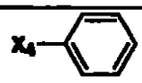
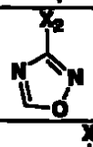
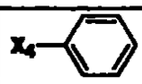
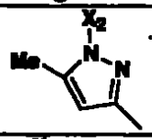
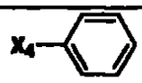
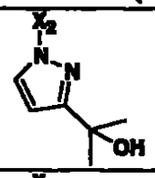
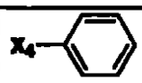
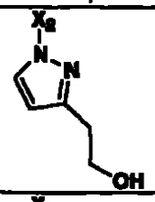
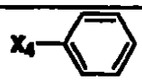
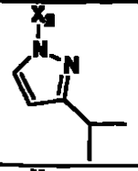
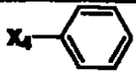
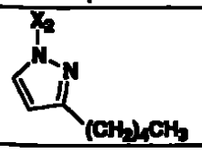
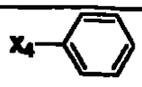
129 (Example 167)	F	H		H		
130 (Example 162)	H	H		(R)-Me		A
131 (Example 163)	Cl	H		H		A
132 (Example 164)	H	H		(R)Me		A
133 (Example 169)	OMe	H		H		
134 (Precursor 5t)	OMe	H		H		A
135 (Example 170)	H	H		(R)-Me		A
136 (Example 171)	OMe	H		H		A
137 (Example 172)	OMe	H		H		A
138 (Example 173)	OMe	H		H		A

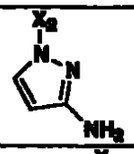
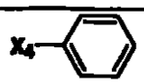
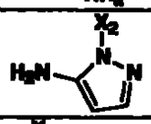
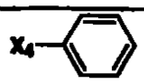
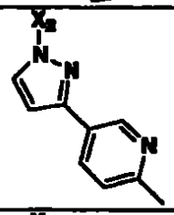
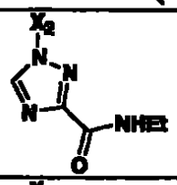
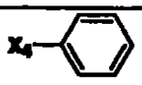
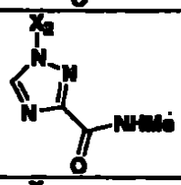
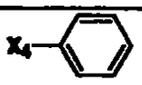
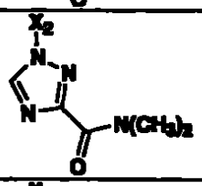
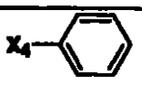
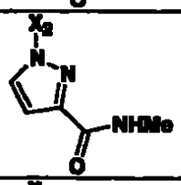
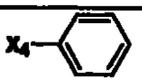
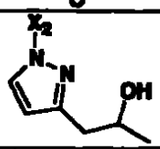
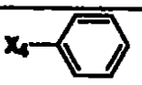
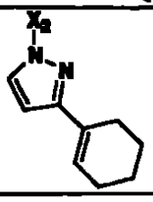
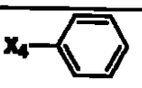
139 (Example 174)	OMe	H		H		A
140 (Example 175)	OMe	H		H		A
141 (Example 176)	OMe	H		H		A
142 (Example 177)	OMe	H		H		A
143 (Example 178)	OMe	H		H		A
144 (Example 179)	OMe	H		H		A
145 (Example 180)	OMe	H		H		A

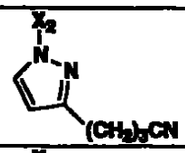
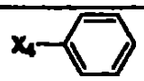
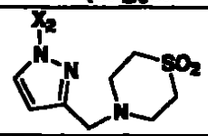
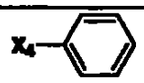
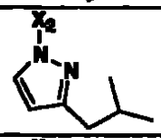
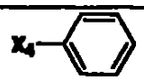
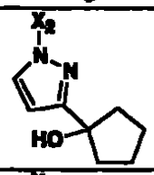
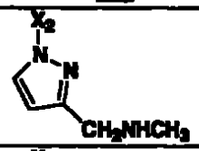
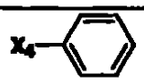
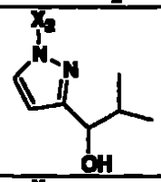
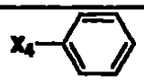
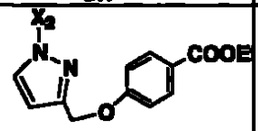
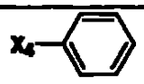
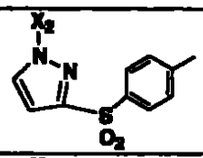
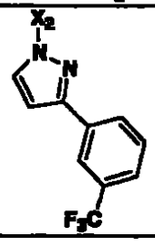
146 (Example 181)	OMe	H		H		A
147 (Example 182)	OMe	H		H		A
148 (Example 183)	OMe	H		H		A
149 (Example 184)	OMe	H		H		A
150 (Example 185)	OMe	H		H		A
151 (Example 186)	OMe	H		H		A
152 (Example 187)	OMe	H		H		A
153 (Example 188)	OMe	H		H		A
154 (Example 189)	OMe	H		H		A

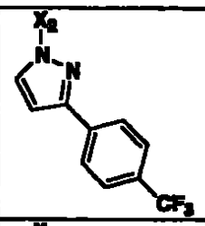
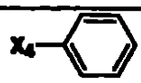
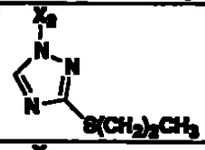
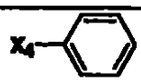
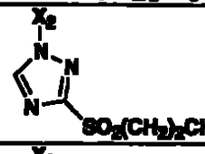
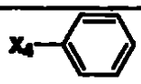
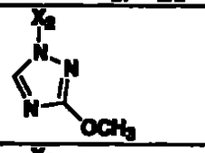
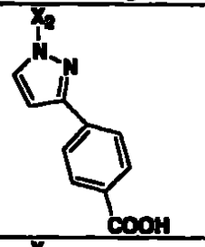
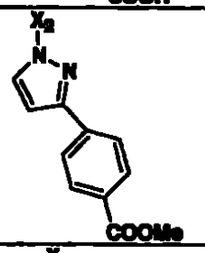
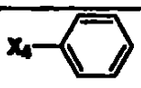
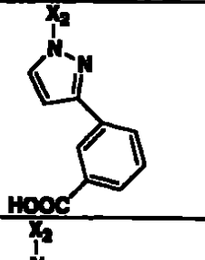
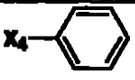
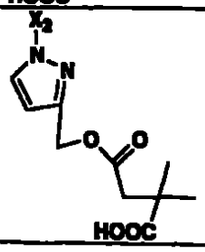
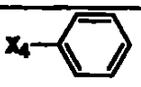
155 (Example 190)	OMe	H		H		A
156 (Example 191)	OMe	H		H		A
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158 (Example 193)	OMe	H		H		A
159 (Example 195)	OMe	H		H		A
160 (Example 196)	OMe	H		H		A
161 (Example 197)	OMe	H		H		A
162 (Example 198)	OMe	H		H		A
163 (Example 199)	OMe	H		H		A
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166 (Example 209)	F	H		H		A

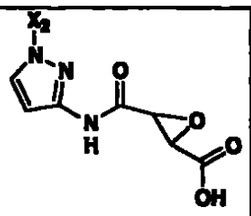
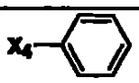
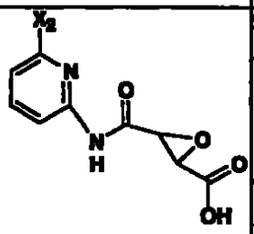
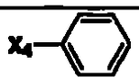
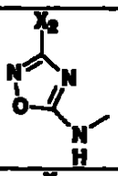
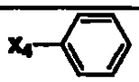
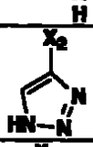
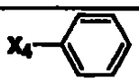
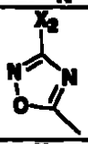
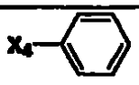
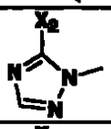
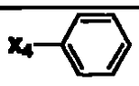
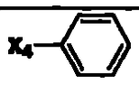
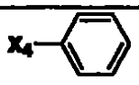
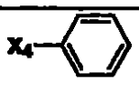
167 (Example 210)	F	H		H		A
168 (Example 211)	F	H		H		A
169 (Example 212)	F	H		H		A
170 (Example 213)	F	H		H		A
171 (Example 214)	F	H		H		A
172 (Example 215)	F	H		H		A
173 (Example 216)	F	H		H		A
174 (Example 217)	F	H		H		A
175 (Example 218)	F	H		H		A
176 (Example 219)	F	H		H		A
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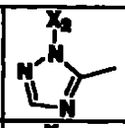
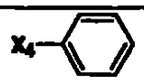
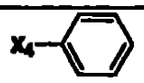
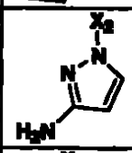
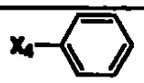
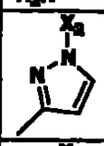
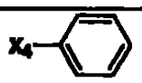
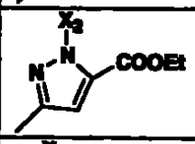
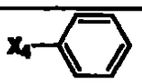
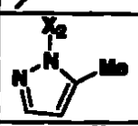
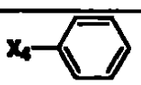
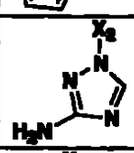
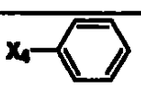
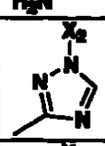
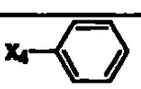
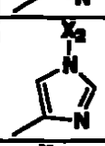
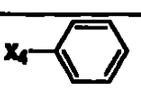
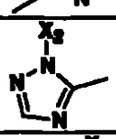
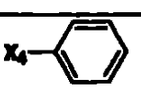
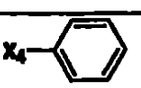
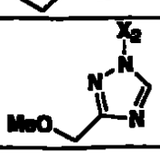
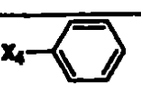
178 (Example 221)	F	H		H		A
179 (Example 222)	F	H		H		A
180 (Example 223)	OMe	H		H		A
181 (Example 224)	OMe	H		H		A
182 (Example 225)	OMe	H		H		A
183 (Example 226)	OMe	H		H		A
185 (Example 240)	OMe	H		H		A
186 (Example 247)	OMe	H		H		A
187 (Example 248)	OMe	H		H		A
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189 (Example 250)	OMe	H		H		A

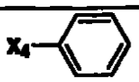
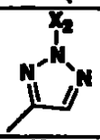
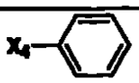
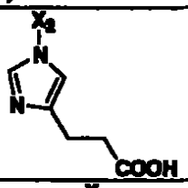
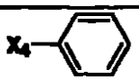
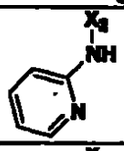
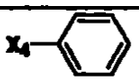
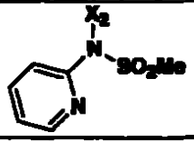
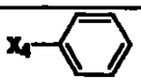
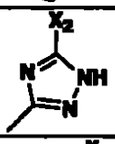
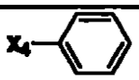
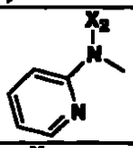
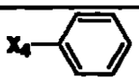
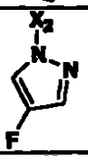
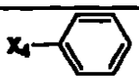
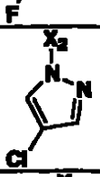
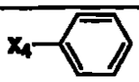
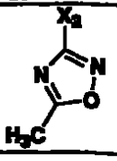
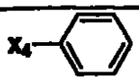
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191 (Example 252)	OMe	H		H		A
192 (Example 264)	OMe	H		H		A
193 (Example 273)	OMe	H		H		A
194 (Example 274)	OMe	H		H		A
195 (Example 275)	OMe	H		H		A
196 (Example 276)	OMe	H		H		A
197 (Example 277)	OMe	H		H		A
198 (Example 278)	OMe	H		H		A

199 (Example 279)	OMe	H		H		A
200 (Example 280)	OMe	H		H		A
201 (Example 281)	OMe	H		H		A
202 (Example 282)	OMe	H		H		A
203 (Example 283)	OMe	H		H		A
204 (Example 284)	OMe	H		H		A
205 (Example 285)	OMe	H		H		A
206 (Example 286)	OMe	H		H		A
207 (Example 287)	OMe	H		H		A

208 (Example 288)	OMe	H		H		A
209 (Example 289)	OMe	H		H		A
210 (Example 290)	OMe	H		H		A
211 (Example 291)	OMe	H		H		A
212 (Example 292)	OMe	H		H		A
213 (Example 293)	OMe	H		H		A
214 (Example 294)	OMe	H		H		A
215 (Example 295)	OMe	H		H		A

216 (Example 296)	OMe	H		H		A
217 (Example 297)	OMe	H		(R)-Me		A
218 (Example 298)	F	H		H		A
219 (Example 299)	F	H		H		A
220 (Example 300)	F	H		H		A
221 (Example 301)	F	H		H		A
222 (Example 303)	F	H		H		A
223 (Example 304)	F	H		H		A
223 (Example 305)	F	H		H		A
224 (Example 306)	F	H		H		A

225 (Example 307)	F	H		H		A
226(Example 308)	F	H		H		A
227 (Example 309)	F	H		H		A
228 (Example 310)	F	H		H		A
229 (Example 311)	F	H		H		A
230 (Example 312)	F	H		H		A
231 (Example 313)	F	H		H		A
232 (Example 316)	MeO	H		H		A
233 (Example 318)	MeO	H		H		A
234 (Example 319)	MeO	H		H		A
234 (Example 321)	MeO	H		H		A
235 (Example 323)	MeO	H		H		A

236 (Example 325)	MeO	H		H		A
237 (Example 327)	MeO	H		H		A
238 (Example 329)	MeO	H		H		A
239 (Example 330)	MeO	H		H		A
240 (Example 331)	MeO	H		H		B
241 (Example 342)	MeO	H		H		A
242(Example 341)	MeO	H		H		C
243 (Example 343)	OMe	H		H		A
244 (Example 344)	OMe	H		H		A
245 (Example 346)	OMe	H		H		A

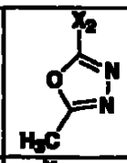
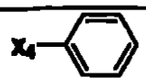
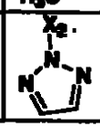
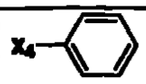
246 (Example 349)	OMe	H		H		A
247 (Example 351)	OMe	H		H		A

Table 2-1

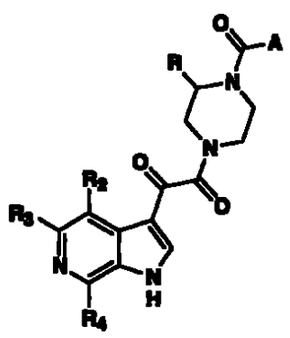
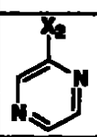
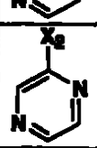
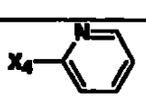
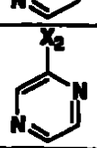
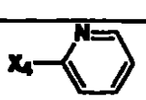
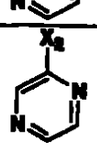
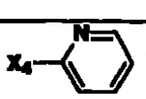
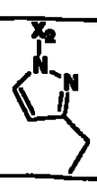
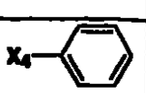
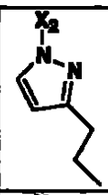
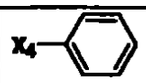
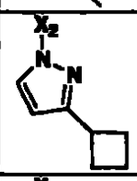
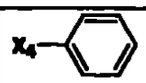
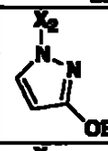
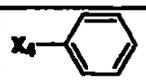
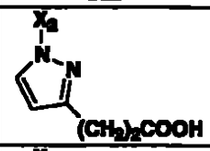
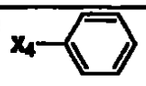
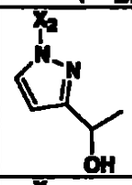
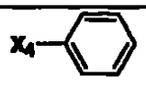
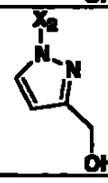
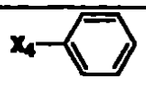
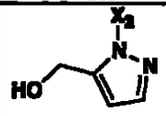
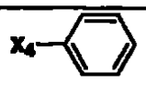
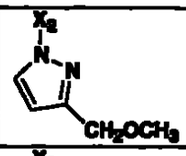
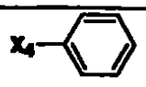
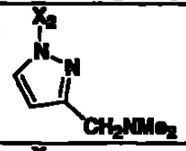
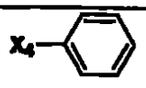
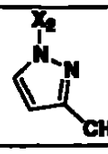
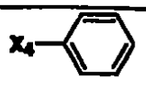
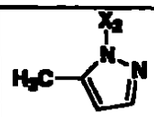
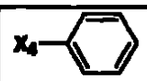
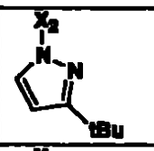
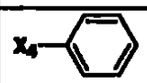
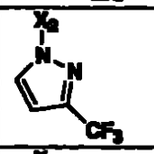
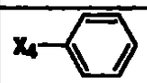
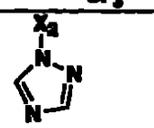
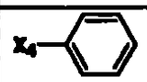
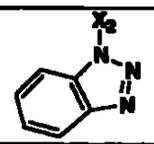
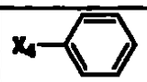
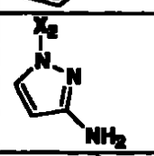
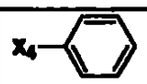
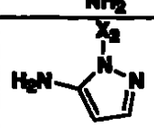
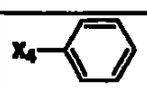
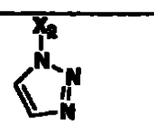
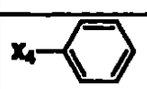
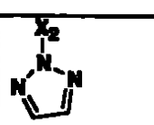
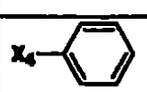
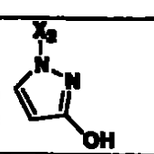
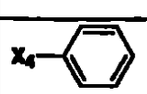
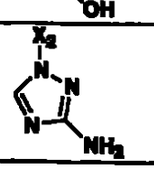
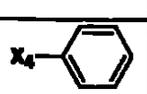
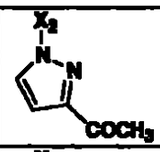
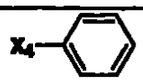
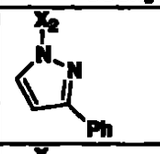
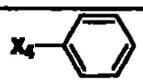
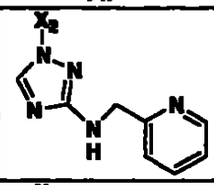
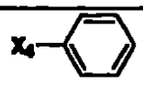
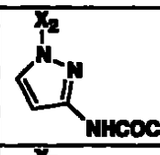
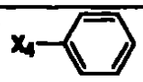
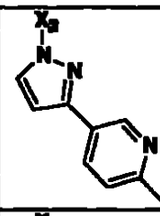
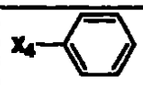
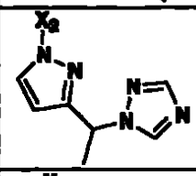
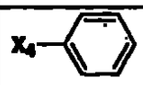
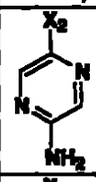
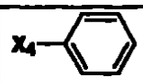
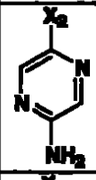
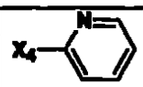
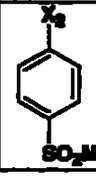
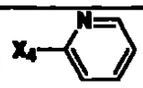


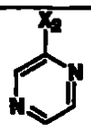
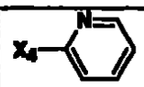
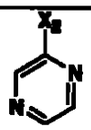
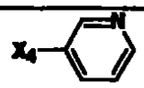
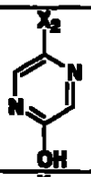
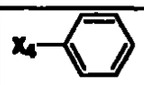
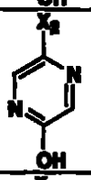
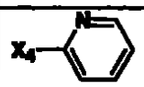
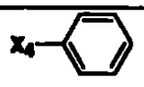
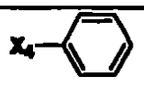
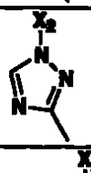
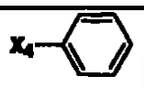
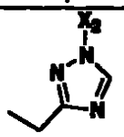
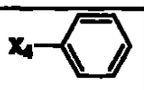
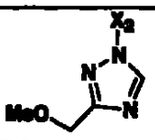
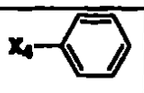
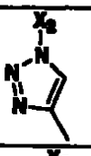
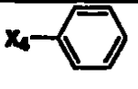
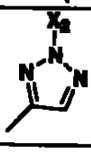
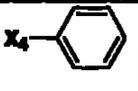
Table Entry (Example Number.)	R2	R3	R4	R	A	EC_{50} Group from Table 1
1 (Example 194)	OMe	H		Me		A
2 (Example 227)	OMe	H		(R)-Me		A
3(Example 228)	OMe	H		(S)-Me		A
4 (Example 229)	OMe	H		Et		A
5 (Example 230)	OMe	H		(R)-Me		A

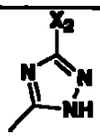
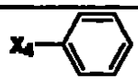
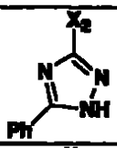
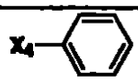
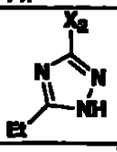
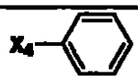
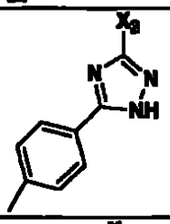
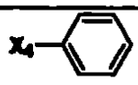
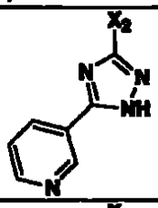
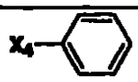
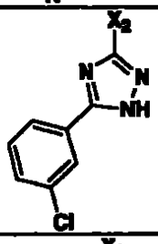
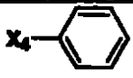
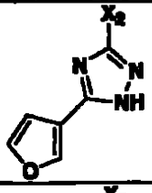
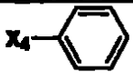
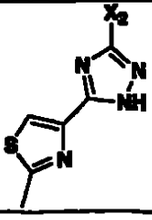
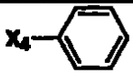
6 (Example 231)	OMe	H		(R)-Me		A
7 (Example 232)	OMe	H		(R)-Me		A
7 (Example 233)	OMe	H		(R)-Me		A
8 (Example 234)	OMe	H		(R)-Me		A
8 (Example 235)	OMe	H		(R)-Me		A
9 (Example 236)	OMe	H		(R)-Me		A
10 (Example 237)	OMe	H		(R)-Me		A
11 (Example 238)	OMe	H		(R)-Me		A
12 (Example 239)	OMe	H		(R)-Me		A
13 (Example 241)	OMe	H		(R)-Me		A

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14 (Example 242)	OMe	H		(R)-Me		A
15 (Example 243)	OMe	H		(R)-Me		A
16 (Example 244)	OMe	H		(R)-Me		A
17 (Example 245)	OMe	H		(R)-Me		A
18 (Example 246)	OMe	H		(R)-Me		A
19 (Example 253)	OMe	H		(R)-Me		A
20 (Example 254)	OMe	H		(R)-Me		A
21 (Example 255)	OMe	H		(R)-Me		A
22 (Example 256)	OMe	H		(R)-Me		A
23 (Example 257)	OMe	H		(R)-Me		A
24 (Example 258)	OMe	H		(R)-Me		A

25 (Example 259)	OMe	H		(R)-Me		A
26 (Example 260)	OMe	H		(R)-Me		A
27 (Example 261)	OMe	H		(R)-Me		A
28 (Example 262)	OMe	H		(R)-Me		A
29 (Example 263)	OMe	H		(R)-Me		A
30 (Example 265)	OMe	H		(R)-Me		A
31 (Example 266)	OMe	H		(R)-Me		A
32 (Example 267)	OMe	H		(R)-Me		A
33 (Example 268)	OMe	H		(R)-Me		A

34 (Example 269)	OMe	H		(R)-Me		A
35 (Example 270)	OMe	H		(R)-Me		A
36 (Example 271)	OMe	H		(R)-Me		A
37 (Example 272)	OMe	H		(R)-Me		A
38 (Example 314)	F	H		(R)-Me		A
39 (Example 315)	F	H		(R)-Me		A
40 (Example 317)	OMe	H		(R)-Me		A
41 (Example 322)	MeO	H		(R)-Me		A
42 (Example 324)	MeO	H		(R)-Me		A
43 (Example 326)	MeO	H		(R)-Me		A
44 (Example 328)	MeO	H		(R)-Me		A

45 (Example 334)	MeO	H		(R)-Me		A
46 (Example 335)	MeO	H		(R)-Me		A
47 (Example 336)	MeO	H		(R)-Me		A
48 (Example 337)	MeO	H		(R)-Me		A
49 (Example 338)	MeO	H		(R)-Me		A
50 (Example 339)	MeO	H		(R)-Me		A
51 (Example 340)	MeO	H		(R)-Me		A
52 (Example 341)	MeO	H		(R)-Me		A

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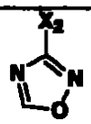
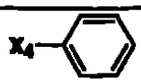
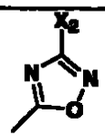
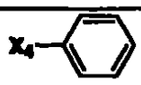
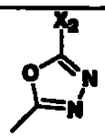
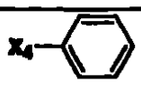
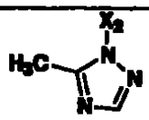
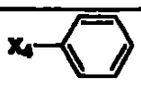
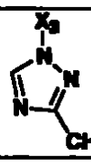
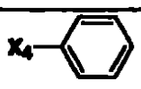
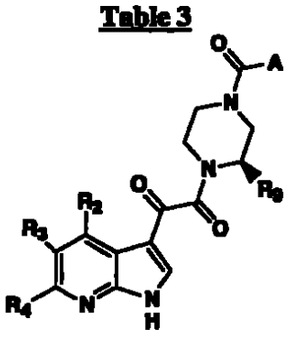
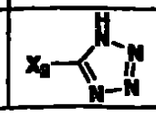
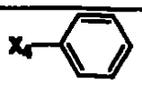
53 (Example 345)	MeO	H		(R)-Me		A
54 (Example 347)	MeO	H		(R)-Me		A
55 (Example 348)	MeO	H		(R)-Me		A
56 (Example 350)	MeO	H		(R)-Me		A
57 (Example 352)	MeO	H		(S)-Me		A

Table 3



Example 58

Table Entry (Example number)	R 2	R3	R4	R9	A	EC_{50} Group from Table 1
1 (Example 56)	H	H		CH_3		B

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Table 4

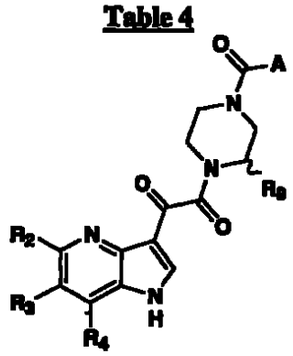
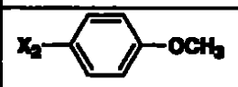
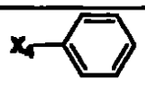
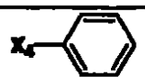
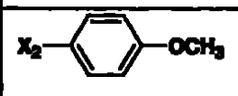
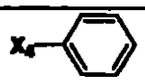
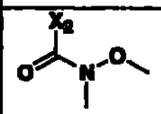
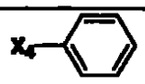
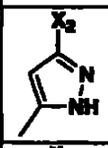
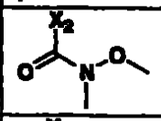
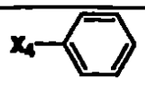
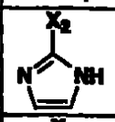
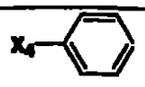
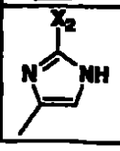
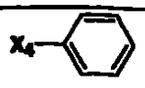
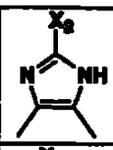
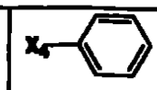
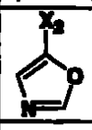
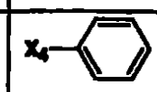
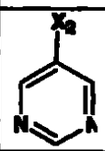
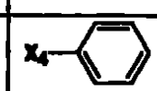
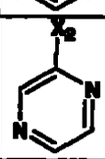
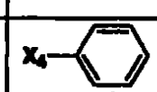
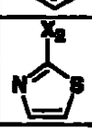
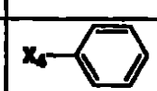
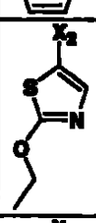
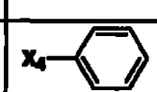
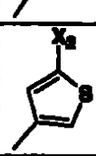
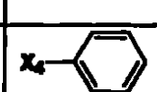
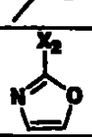
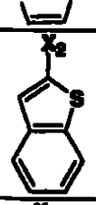
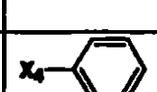
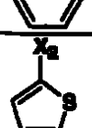
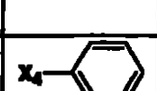
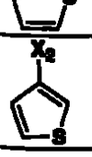
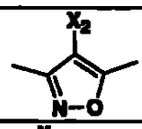
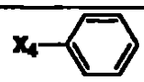
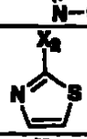
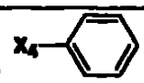
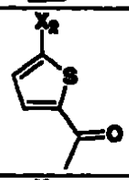
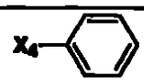
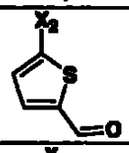
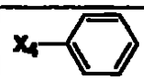
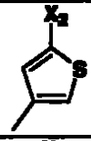
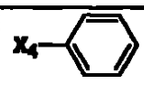
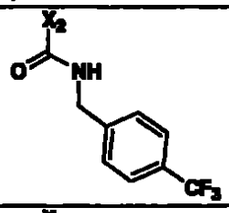
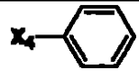
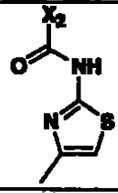
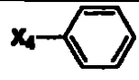
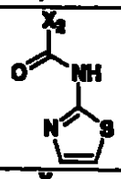
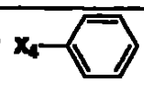
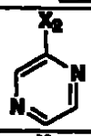
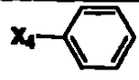
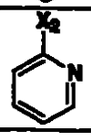
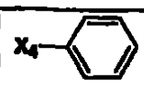


Table Entry (Example No.)	R2	R3	R4	R9	A	EC_{50} Group from Table1
1 (Example 65)	H	H		H		A
2 (Example 66)	H	H		(S)-CH_3		A
3 (Example 67)	H	H		(R)-Me		A
4 Example (57)	H	H		(R)-Me		A
6 (Example 64)	Cl	H		(R)-Me		A
7 (Example 58)	Cl	H		(R)-Me		A
8 (Example 60)	Cl	H		(R)-Me		A
9 (Example 61)	Cl	H		(R)-Me		A

10 (Example 62)	Cl	H		(R)-Me		A
11 (Example 63)	Cl	H		(R)-Me		A
12						
13 (Example 51)	H	H		(R)-Me		A
14 (Example 52)	H	H		(R)-Me		A
15 (Example 53)	H	H		(R)-Me		A
16 (Example 54)	H	H		(R)-Me		A
17 (Example 86)	H	H		(R)-Me		A
18 (Example 126)	H	H		(R)-Me		A
19 (Example 127)	H	H		(R)-Me		A
20 (Example 128)	H	H		(R)-Me		A
21 (Example 129)	H	H		(R)-Me		A

22 (Example 130)	H	H		(R)-Me		A
23 (Example 131)	H	H		H		A
24 (Example 132)	H	H		H		A
25 (Example 133)	H	H		H		A
26 (Example 134)	H	H		H		A
27 (Example 135)	H	H		(R)-Me		A
28 (Example 136)	H	H		(R)-Me		A
29 (Example 137)	H	H		(R)-Me		A
30 (Example 158)	H	H		H		A
31 (Example 159)	H	H		H		A

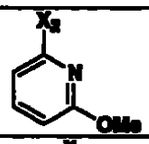
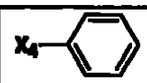
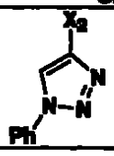
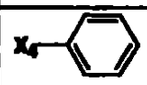
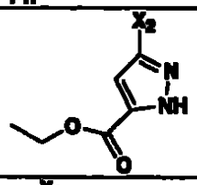
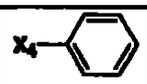
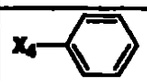
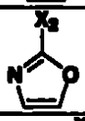
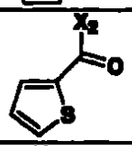
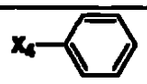
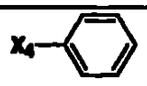
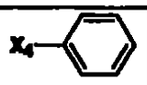
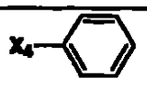
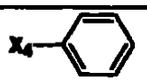
32 (Example 160)	H	H		H		A
33 (Example 161)	H	H		H		A
34 (Example 202)	H	H		H		A
35 (Example 203)	H	H		H		A
36 (Example 204)	H	H		H		A
37 (Example 168)	H	H		H		A
38 (Example 205)	H	H		H		A
39 (Example 206)	H	H		H		A
40 (Example 207)	H	H		H		A
41 (Example 208)	H	H		H		A

Table 4-1

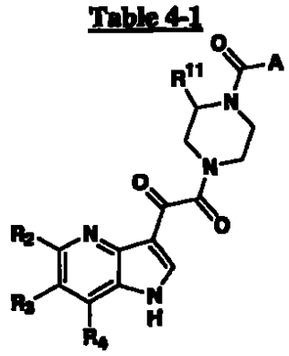
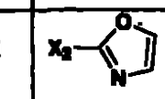
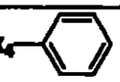
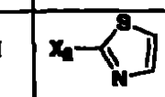
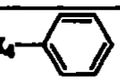
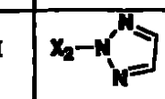
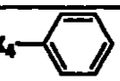
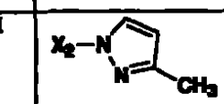
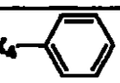
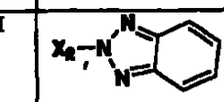
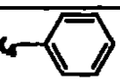
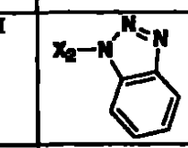
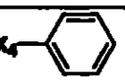
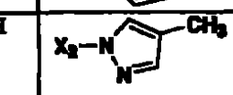
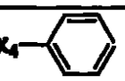
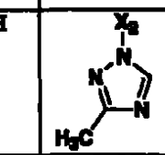
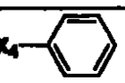
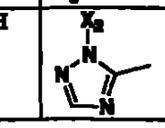
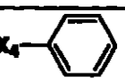


Table Entry (Example No.)	R2	R3	R4	R9	A	HC_m Group from Table1
1 (Example 353)	H	H		H		A
2 (Example 354)	H	H		(S)-CH_3		A
3 (Example 355	H	H		(R)-Me		A
4 Example (356)	H	H		(R)-Me		A
6 (Example 357)	Cl	H		(R)-Me		A
7 (Example 358)	Cl	H		(R)-Me		A
8 (Example 359)	Cl	H		(R)-Me		A
9 (Example 360)	Cl	H		(R)-Me		A
10 (Example 361)	Cl	H		(R)-Me		A

Method for extrapolating % inhibition at 10μM

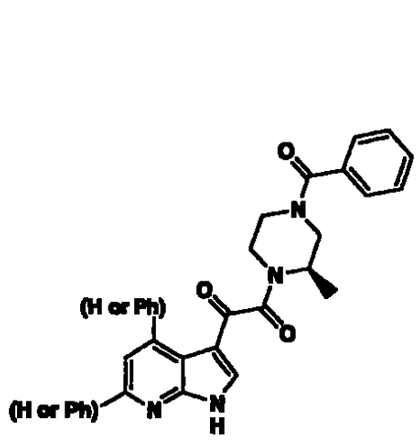
The compounds of Table 5 below were all found to be very potent in the assay described above using % inhibition as a criteria. In Table 5, X_2, X_4 etc. indicates the point of attachment. The vast majority of the compounds exhibited greater than 98% inhibition at a concentration of 10uM. The data at 10μM was calculated in the following manner:

Method for extrapolating % inhibition at 10μM

The data in Table 5 was obtained using the general procedures above and by the following methods. Data is not reported for all compounds since data for all the compounds is reported by the alternate method in the previous Tables 1-4. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100. For compounds tested at concentrations less than 10 μM, the percent inhibition at 10 μM was determined by extrapolation using the XLfit curve fitting feature of the Microsoft Excel spreadsheet software. Curves were obtained from 10 data points (% inhibition determined at 10 concentrations of compound) by using a four parameter logistic model (XLfit model 205: $y = A + ((B-A)/(1+((C/x)^D)))$, where, A = minimum y, B = maximum y, C = $\log EC_{50}$, D = slope factor, and x and y are known data values. Extrapolations were performed with the A and B parameters unlocked.

Thus the compounds of this invention are all potent antiviral inhibitors based on this assay.

Table 5



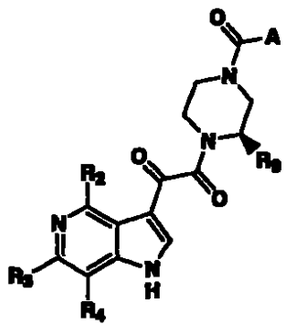
Precursor 8 Example 1

Compound #	Average % inhibition at 10 μM
Precursor 8	85%
Example 1	56%

Other Compounds of the Invention:

The 5-aza inhibitors shown in Table 6 should also be active antiviral agents. They are also part of the invention and could be prepared from precursors 1a or 2s or the corresponding 7-desbromo-7-chloro precursors which are prepared analogously and the methods herein or by using other methods described herein.

Table 6

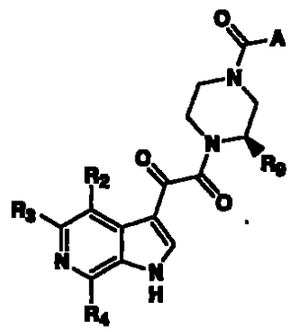


5-aza inhibitors

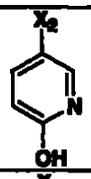
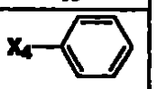
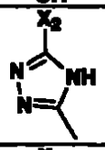
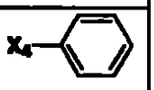
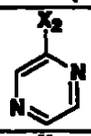
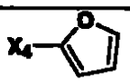
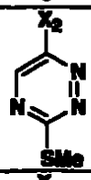
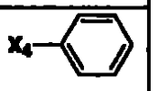
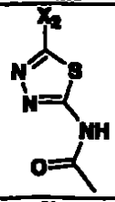
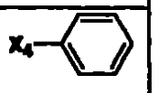
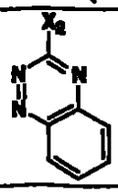
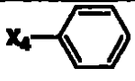
Table Entry (Example Number.)	R2	R3	R4	R9	A
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2	MeO	H		H	
3	MeO	H		H	
4	MeO	H		H	

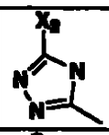
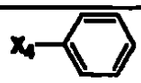
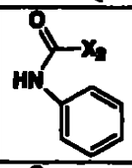
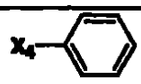
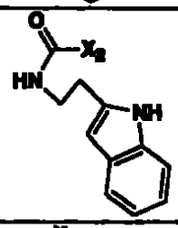
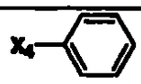
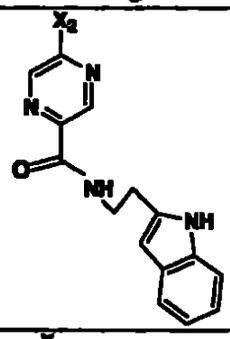
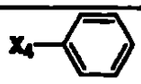
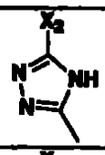
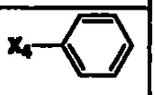
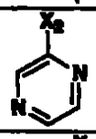
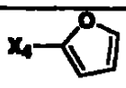
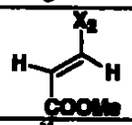
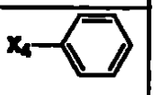
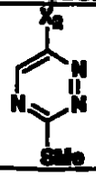
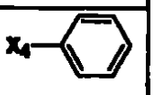
The compounds in the following Tables exemplify without restriction some of the many additional inhibitors which could be prepared by using methodology contained herein or exemplified in the preparation of the compounds of the invention.

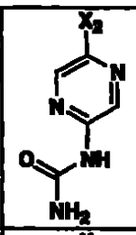
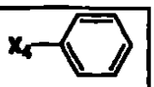
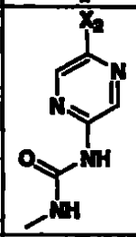
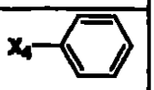
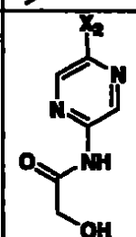
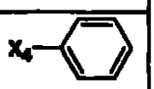
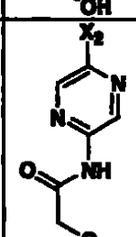
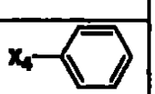
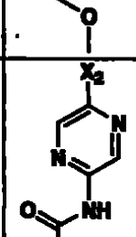
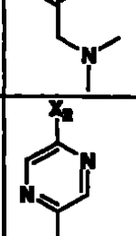
Table 2a



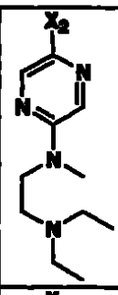
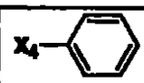
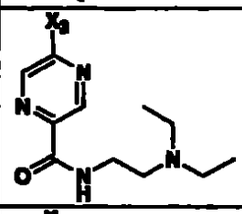
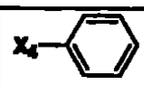
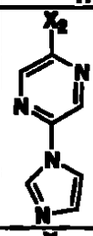
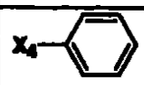
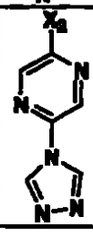
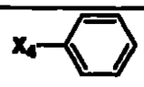
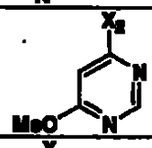
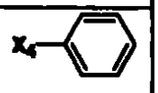
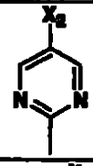
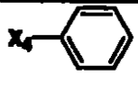
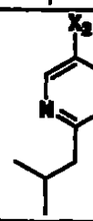
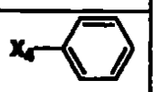
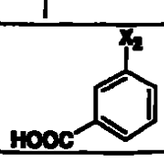
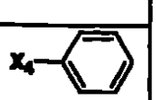
Additional Inhibitors

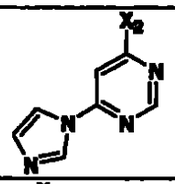
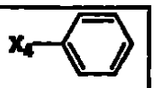
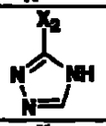
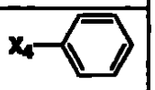
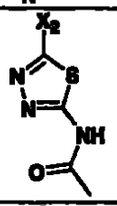
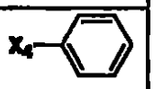
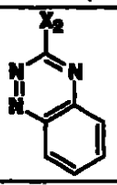
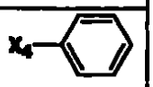
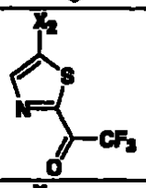
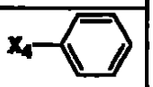
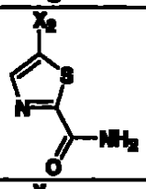
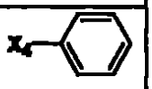
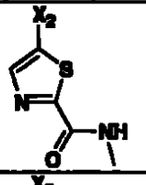
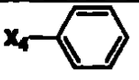
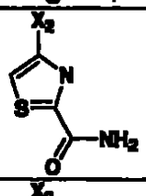
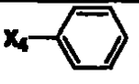
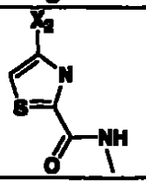
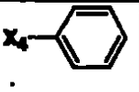
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	OMe	H		H	

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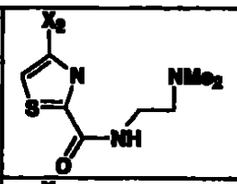
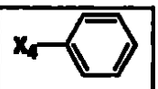
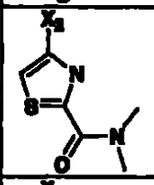
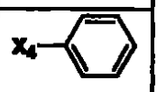
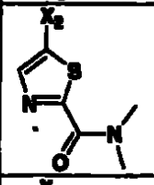
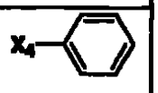
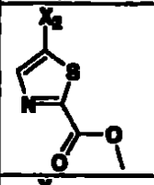
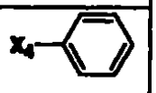
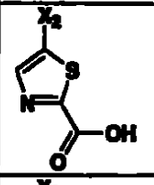
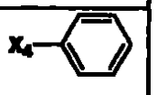
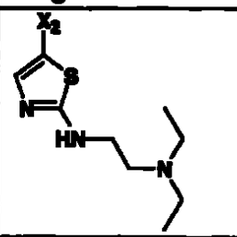
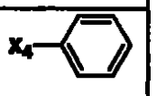
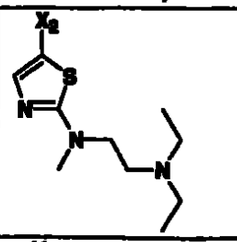
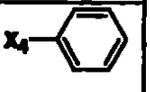
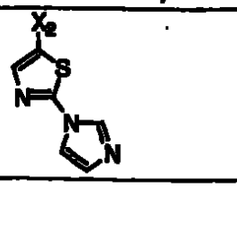
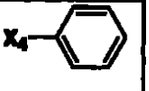
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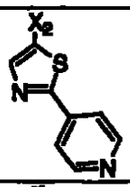
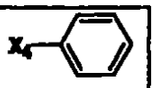
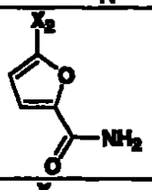
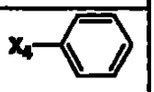
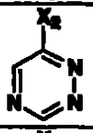
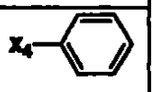
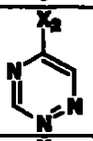
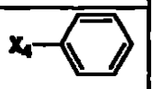
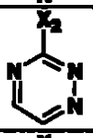
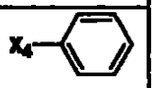
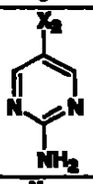
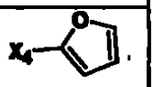
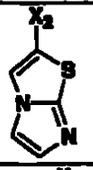
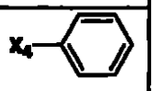
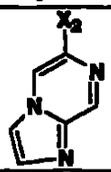
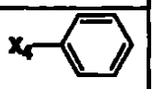
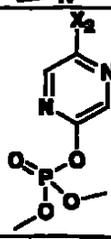
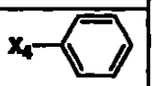
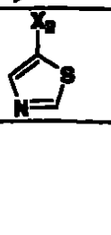
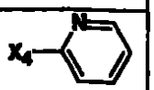
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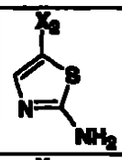
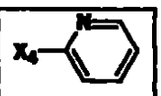
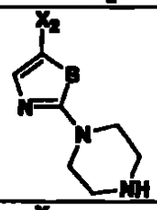
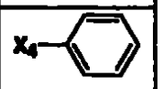
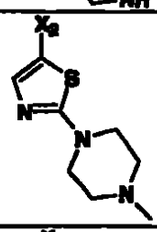
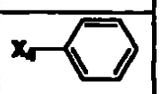
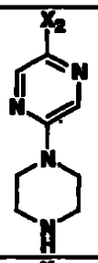
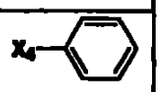
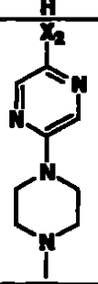
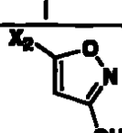
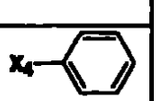
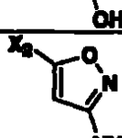
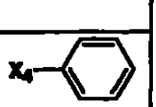
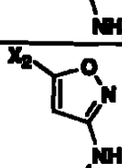
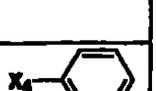
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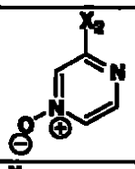
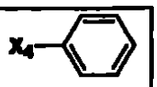
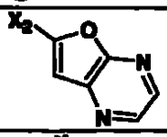
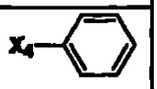
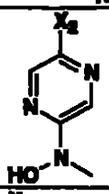
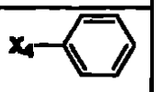
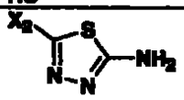
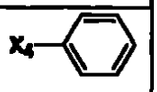
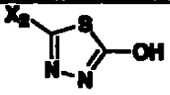
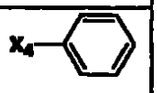
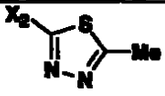
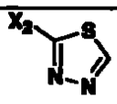
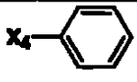
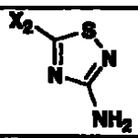
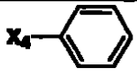
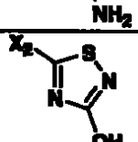
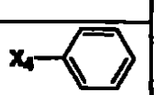
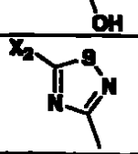
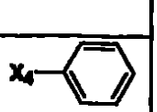
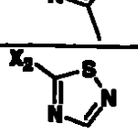
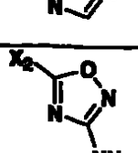
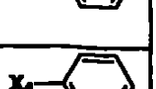
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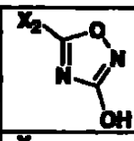
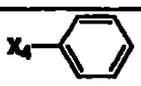
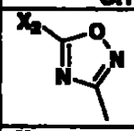
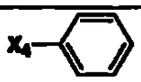
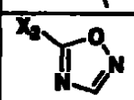
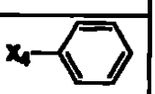
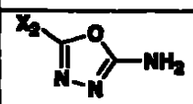
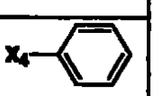
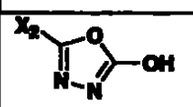
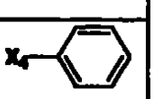
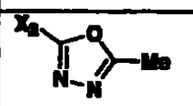
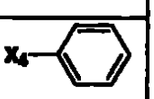
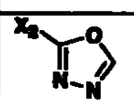
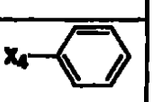
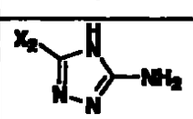
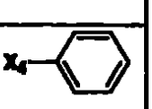
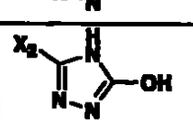
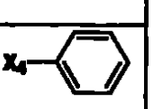
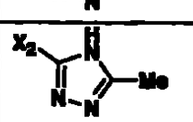
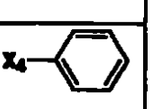
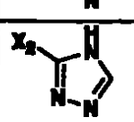
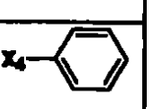
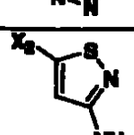
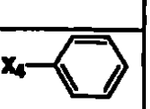
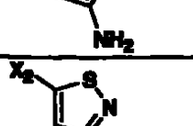
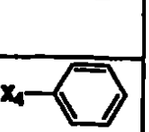
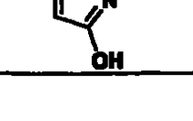
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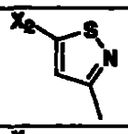
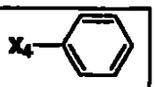
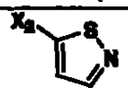
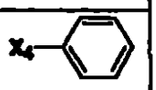
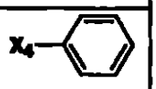
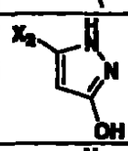
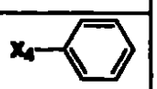
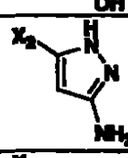
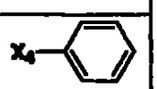
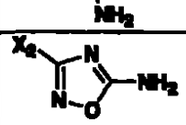
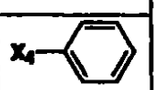
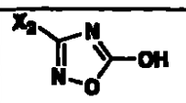
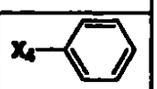
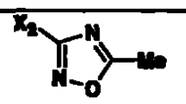
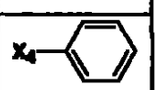
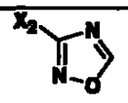
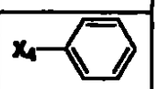
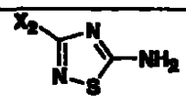
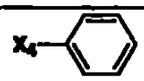
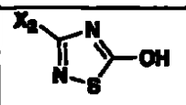
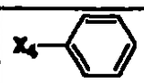
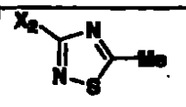
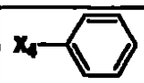
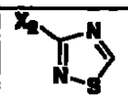
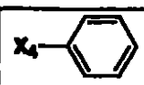
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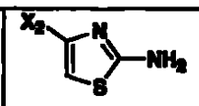
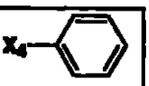
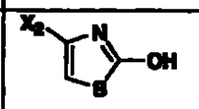
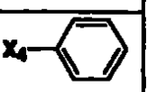
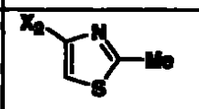
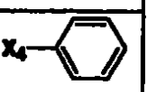
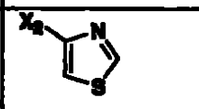
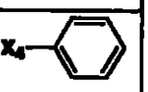
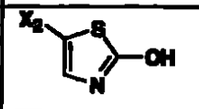
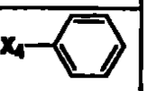
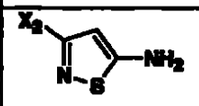
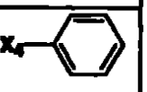
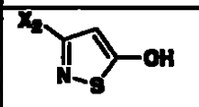
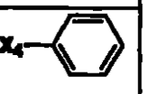
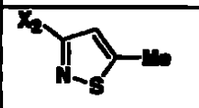
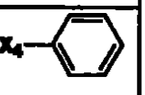
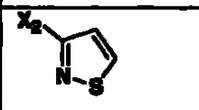
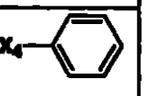
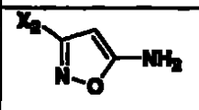
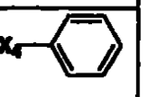
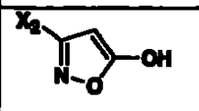
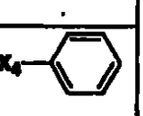
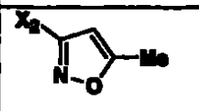
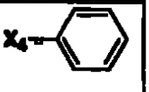
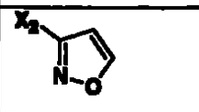
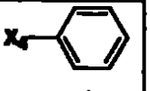
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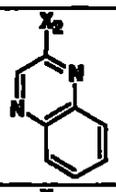
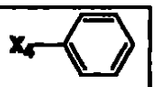
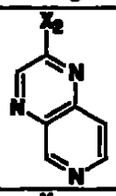
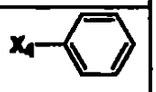
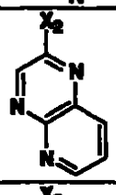
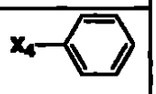
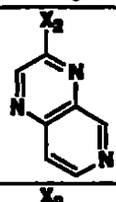
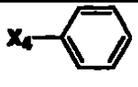
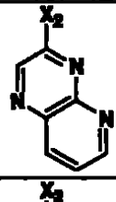
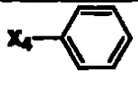
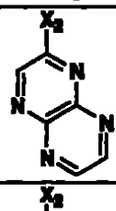
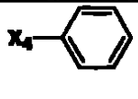
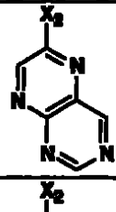
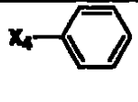
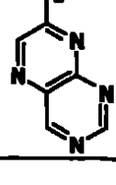
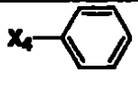
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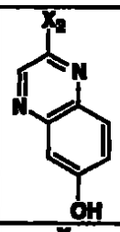
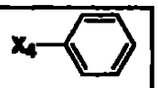
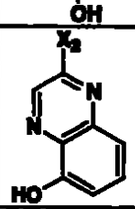
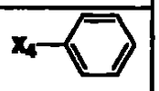
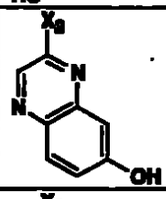
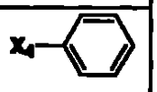
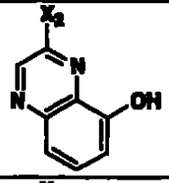
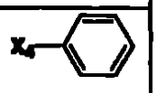
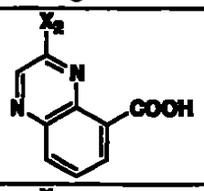
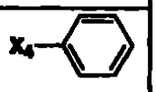
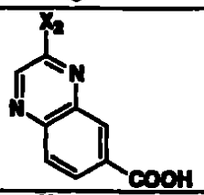
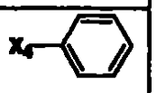
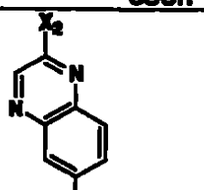
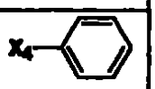
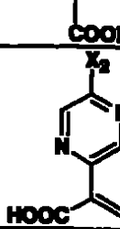
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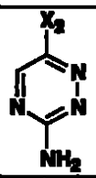
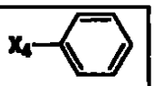
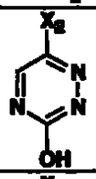
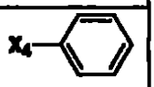
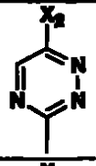
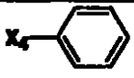
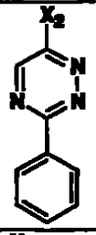
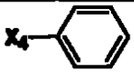
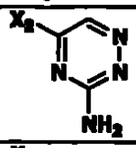
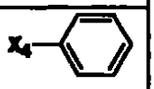
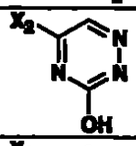
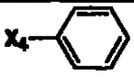
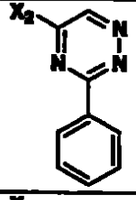
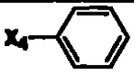
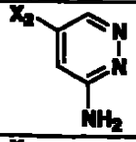
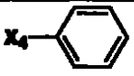
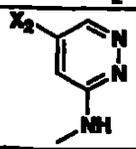
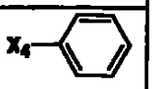
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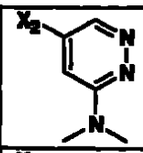
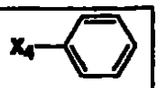
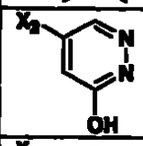
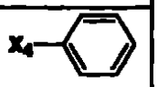
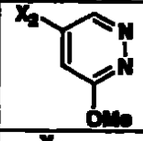
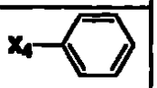
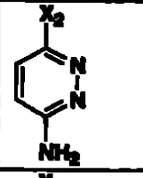
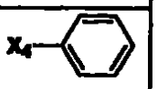
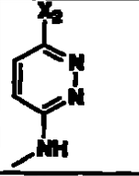
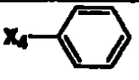
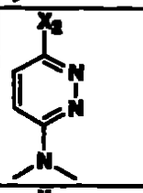
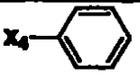
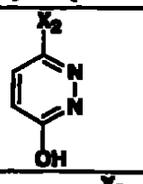
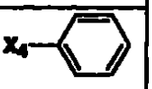
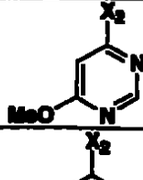
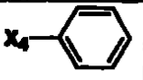
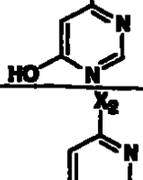
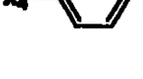
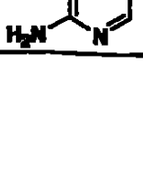
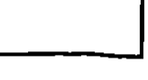
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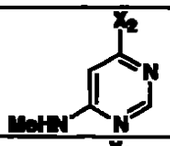
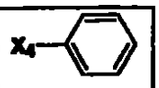
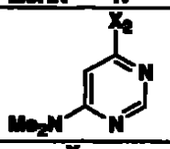
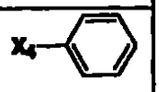
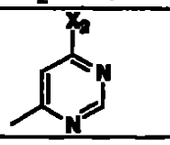
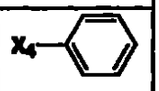
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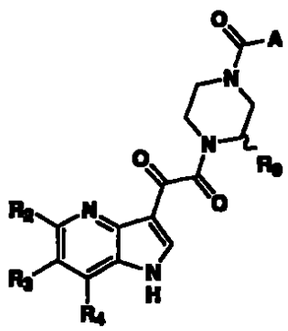
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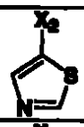
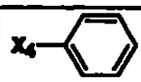
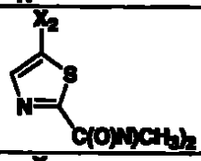
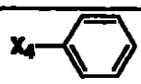
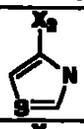
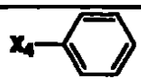
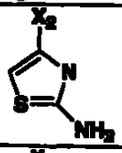
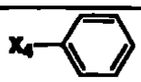
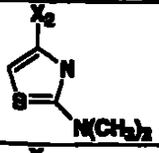
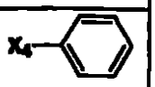
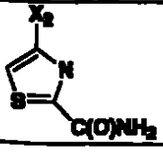
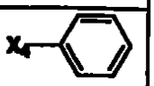
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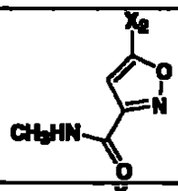
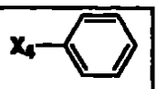
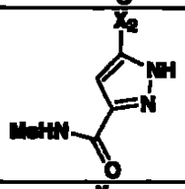
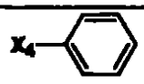
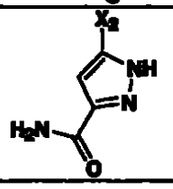
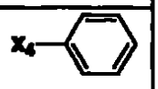
The inhibitors in Table 4a could be prepared using analogous procedures which were demonstrated to prepare the examples in Table 4.

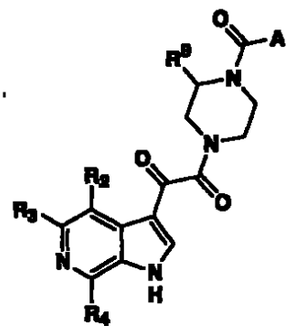
Table 4a

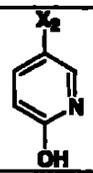
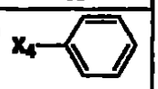
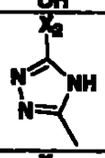
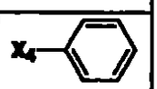
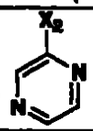
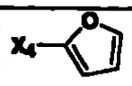
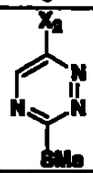


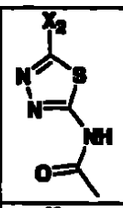
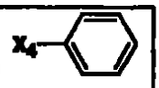
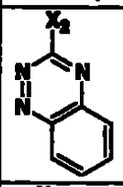
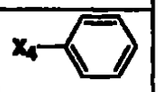
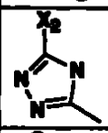
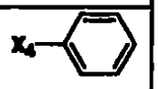
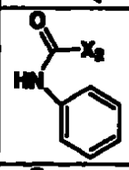
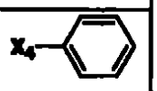
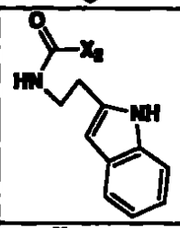
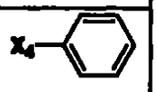
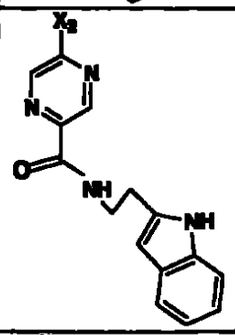
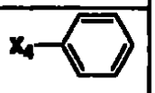
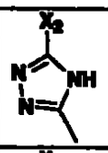
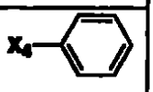
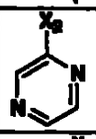
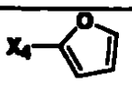
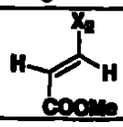
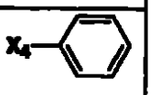
Other inhibitors

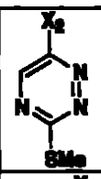
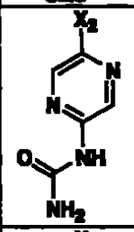
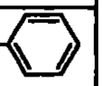
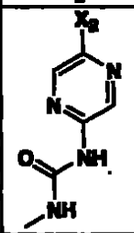
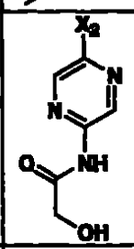
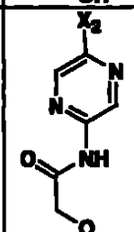
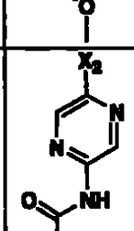
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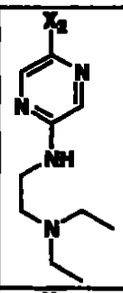
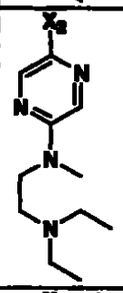
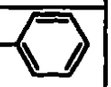
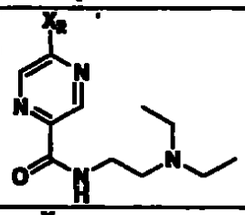
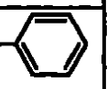
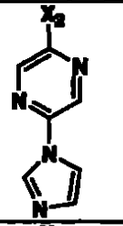
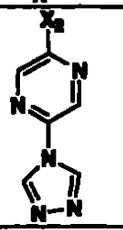
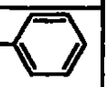
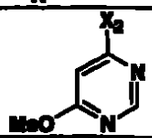
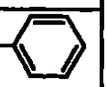
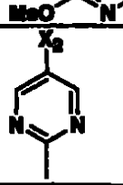
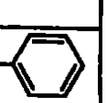
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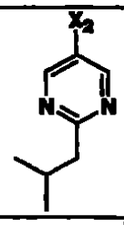
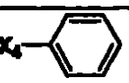
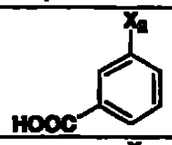
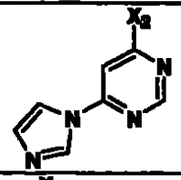
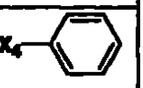
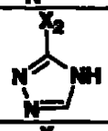
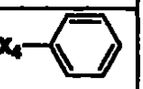
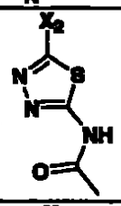
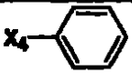
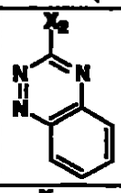
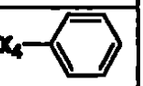
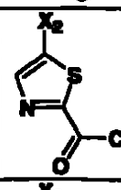
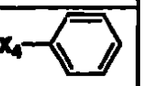
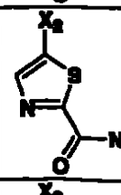
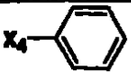
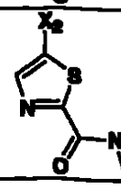
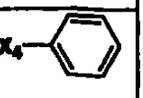


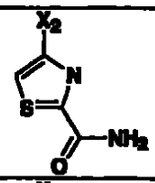
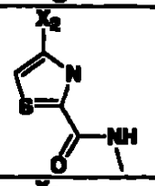
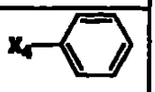
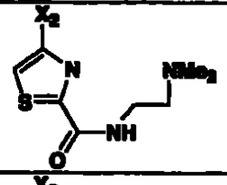
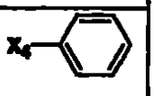
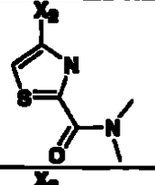
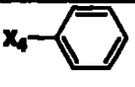
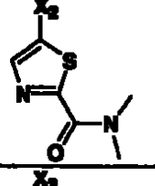
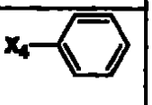
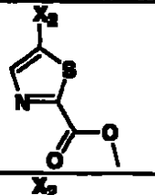
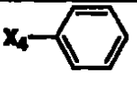
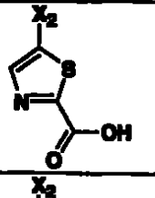
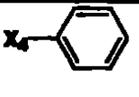
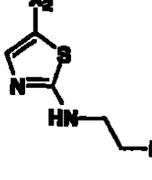
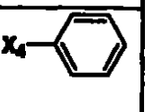
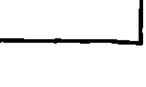
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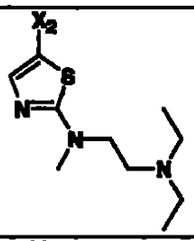
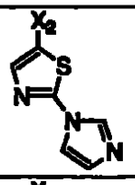
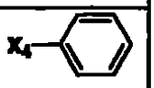
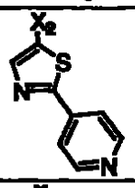
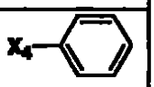
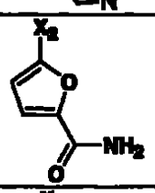
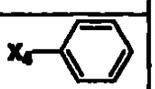
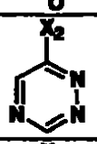
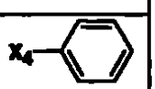
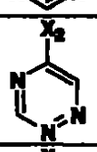
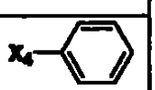
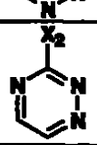
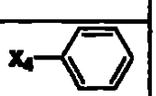
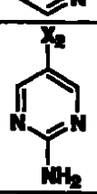
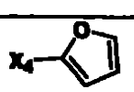
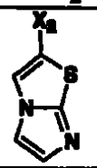
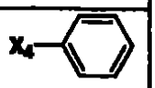
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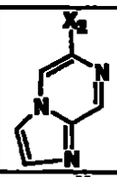
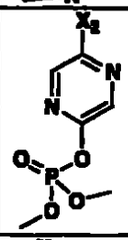
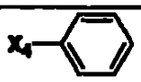
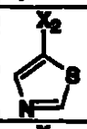
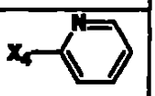
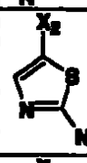
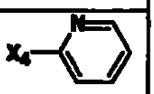
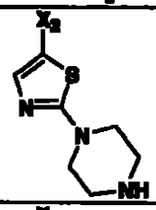
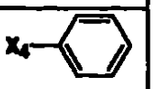
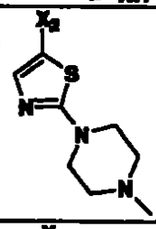
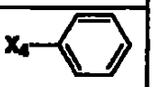
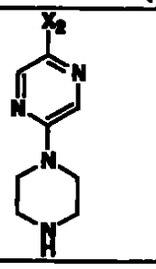
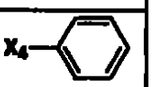
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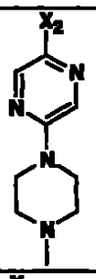
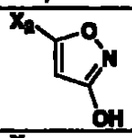
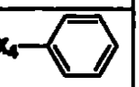
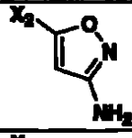
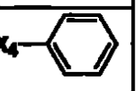
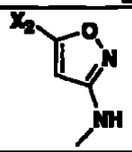
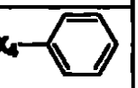
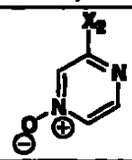
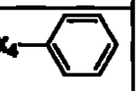
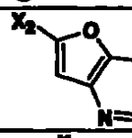
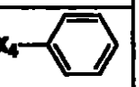
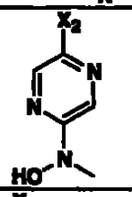
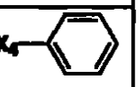
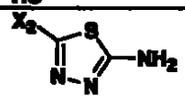
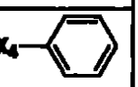
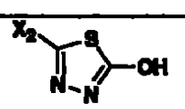
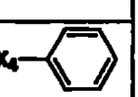
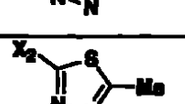
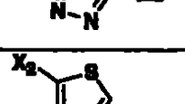
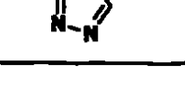
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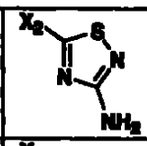
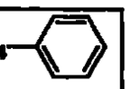
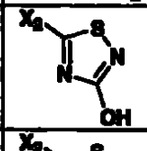
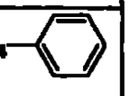
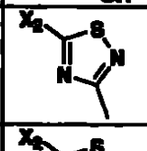
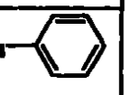
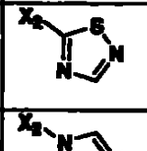
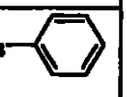
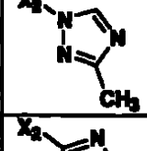
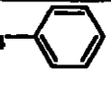
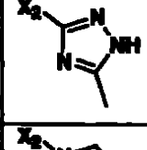
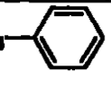
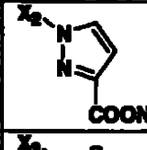
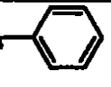
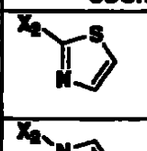
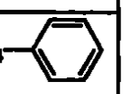
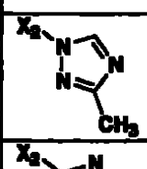
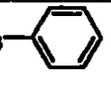
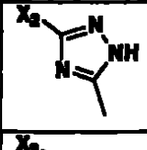
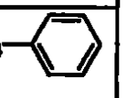
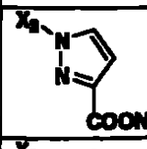
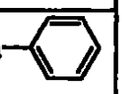
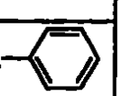
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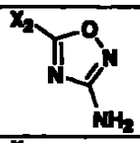
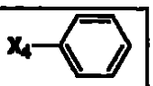
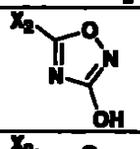
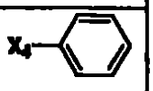
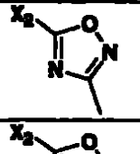
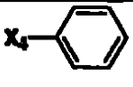
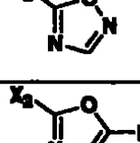
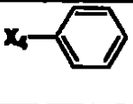
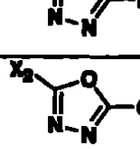
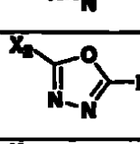
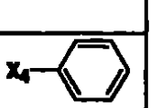
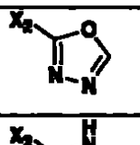
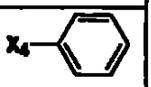
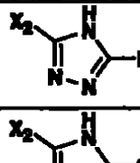
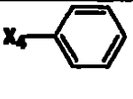
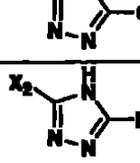
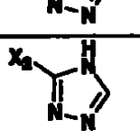
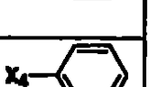
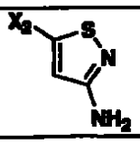
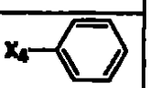
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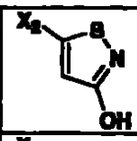
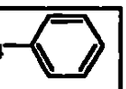
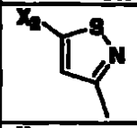
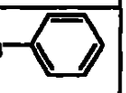
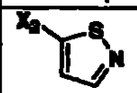
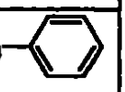
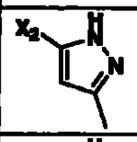
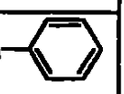
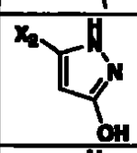
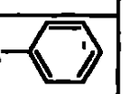
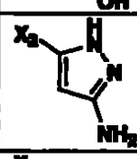
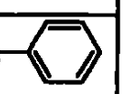
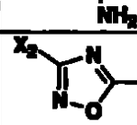
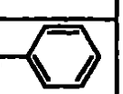
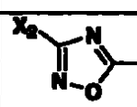
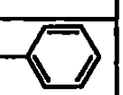
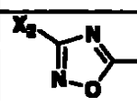
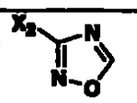
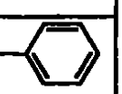
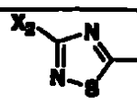
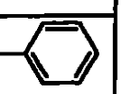
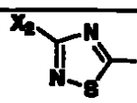
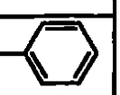
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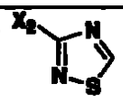
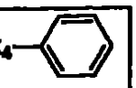
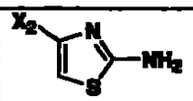
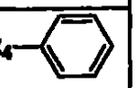
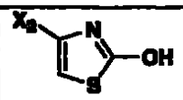
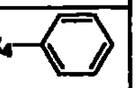
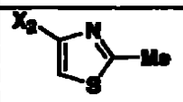
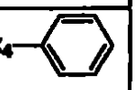
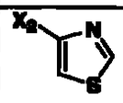
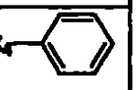
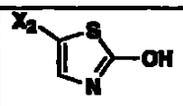
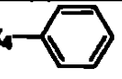
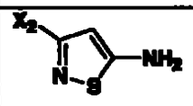
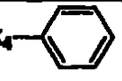
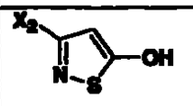
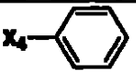
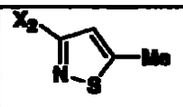
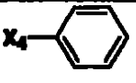
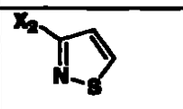
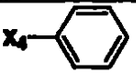
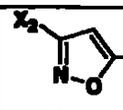
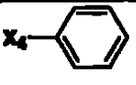
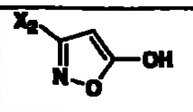
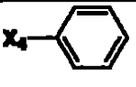
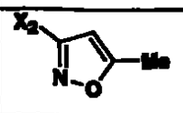
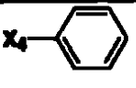
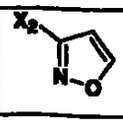
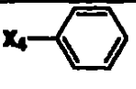
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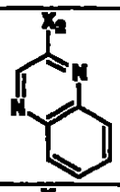
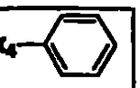
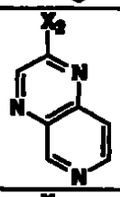
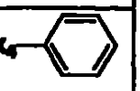
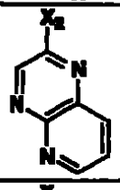
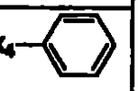
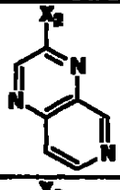
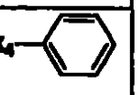
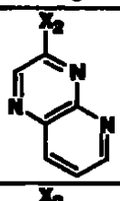
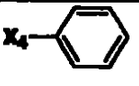
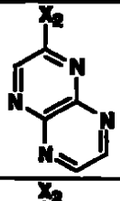
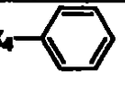
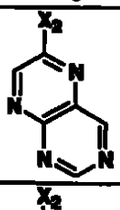
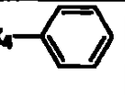
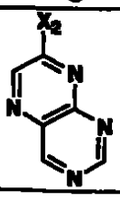
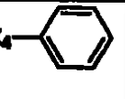
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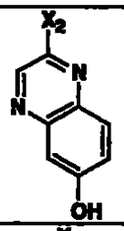
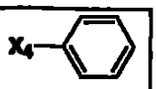
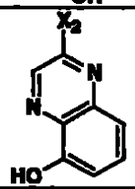
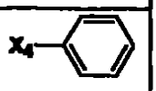
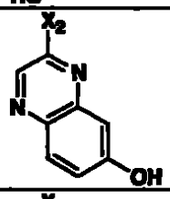
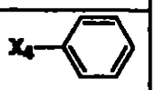
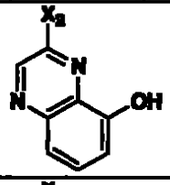
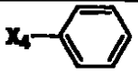
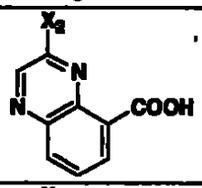
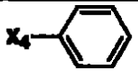
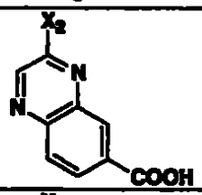
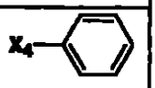
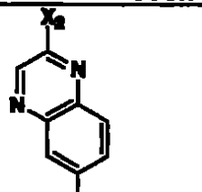
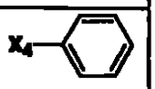
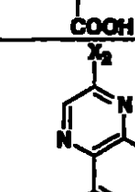
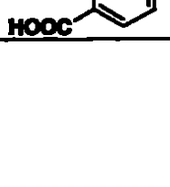
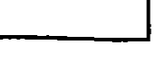
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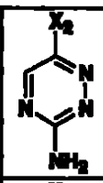
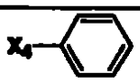
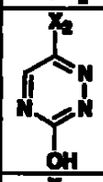
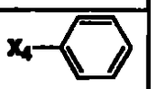
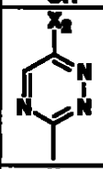
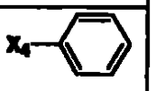
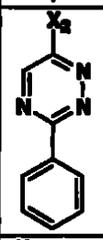
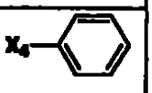
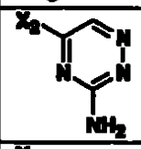
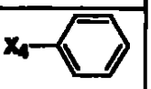
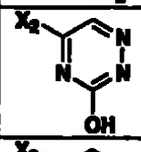
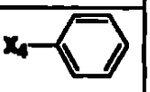
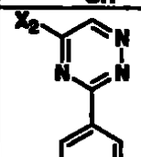
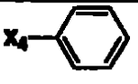
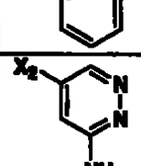
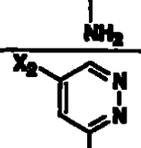
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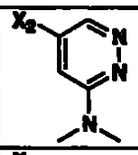
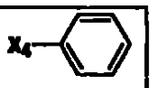
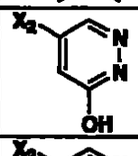
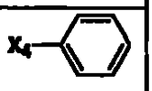
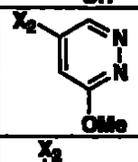
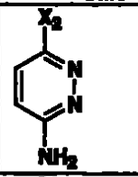
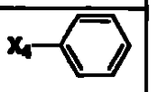
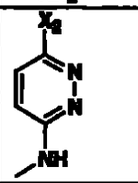
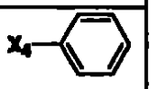
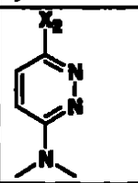
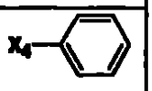
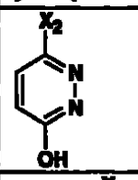
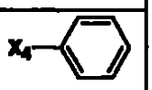
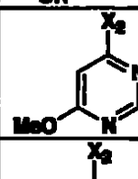
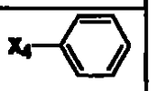
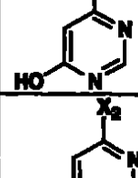
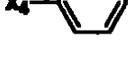
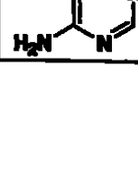
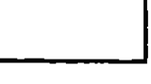
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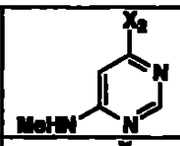
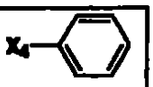
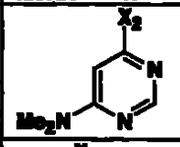
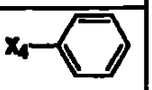
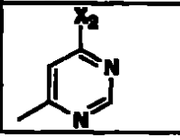
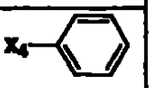
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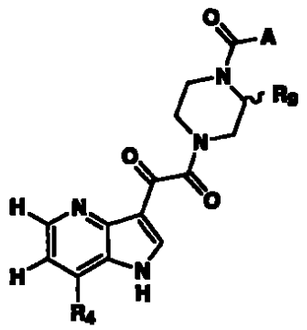
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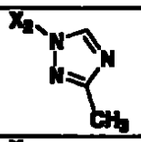
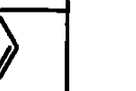
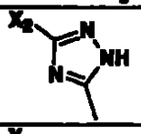
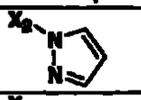
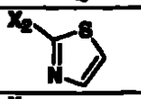
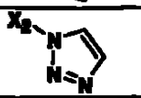
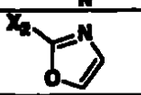
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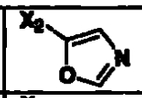
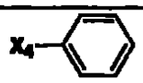
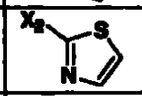
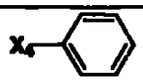
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Other inhibitors

	R4	R9	A
		(R) or (S) Me	
		(R) or (S) Me	
		(R) or (S) Me	
		(R) or (S) Me	
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Metabolic Stability Studies of compounds in Liver Microsomes. The metabolic stability of compounds were investigated in pooled liver microsomes from humans. The human liver microsomes were obtained from BD Gentest (Lot #16, Woburn, MA) with a protein concentration of 20 mg/ml and a total cytochrome P450 (CYP) concentration of 0.55 nmol/mg protein.

A stock solution of drug was prepared in acetonitrile at 1 mM. An aliquot of the stock solution was added to the incubation media to give a final concentration of 3 μM of drug, and the acetonitrile concentration not exceeding 1% in the incubation. The incubation media consisted of potassium phosphate buffer (0.1 M, pH 7.4), liver microsomes (final concentration 0.9 mg/ml), magnesium chloride (0.033 mM), and a NADPH-regenerating system. The cofactors of the NADPH-regenerating system consisted of NADPH (final concentration 0.425 mg/ml), glucose-6-phosphate (final concentration 0.512 mg/ml), and glucose-6-phosphate dehydrogenase (final concentration 0.6 unit/ml). The test compound was pre-incubated in the media for 2 min. The reaction was initiated by the addition of the cofactors. The incubation was carried out at 37°C for 10 min. The reaction was terminated by drawing an aliquot of 100 μL from the incubation and adding into 200 μL of acetonitrile containing a reference compound as an external analytical standard. Following vortex-mixing and centrifugation, an aliquot of 10 μL of the supernatant was analyzed by LC/MS.

GUIDELINES can be used to categorized test substances as low, intermediate or highly cleared compounds.

Rate (nmol/min/mg)	Clearance Estimate
0 - 0.100	Low
0.101 - 0.200	Intermediate

0.201 - 0.300 High

Rat Pharmacokinetic Studies:

For the IV and PO pharmacokinetic studies of compounds in rats, the compound was dissolved in PEG-400/ethanol (90/10) as a solution.

Rat. Male Sprague-Dawley rats (300–350 g, Hilltop Lab Animals, Inc., Scottdale, PA) with cannulas implanted in the jugular vein were used. The rats were fasted overnight in the PO pharmacokinetic studies. Blood samples of 0.3 ml were collected from the jugular vein in EDTA-containing microtainer tubes (Becton Dickinson, Franklin Lakes, NJ), and centrifuged to separate plasma.

In the IV study, the test compound was delivered at 1 mg/kg as a bolus over 0.5 min (n = 3). Serial blood samples were collected before dosing and 2, 10, 15, 30, 45, 60, 120, 240, 360, 480, and 1440 min after dosing.

In the PO study of the test compound, the rats (n = 3) received an oral dose of 5 mg/kg of BMS-585248. Serial blood samples were collected before dosing and 15, 30, 45, 60, 120, 240, 360, 480, and 1440 min after dosing.

Quantitation of Compounds in Plasma. Aliquots of plasma samples from rat, studies were prepared for analysis by precipitating plasma proteins with two volumes of acetonitrile containing an internal standard of a similar compound. The resulting supernates were separated from the precipitated proteins by centrifugation for 10 minutes and transferred to autosampler vials. Samples were either prepared manually, or with the use of the Tomtec automated liquid handler.. An aliquot of 5 µL was injected for analysis.

The HPLC system consisted of two Shimadzu LC10AD pumps (Columbia, MD), a Shimadzu SIL-HTC autosampler (Columbia, MD), and a Hewlett Packard Series 1100 column compartment (Palo Alto, CA). The column was a YMC Pro C18 (2.0 x 50 mm, 3 µm particles, Waters Co., Milford, MA), maintained at 60°C and a flow rate of 0.3 ml/min. The mobile phase consisted of 10 mM ammonium formate and 0.1% formic acid in water (A) and 100% 10 mM ammonium formate and 0.1%

formic acid in methanol (B). The initial mobile phase composition was 95% A. After sample injection, the mobile phase was changed to 15% A/85% B over 2 minutes and held at that composition for an additional 1 minute. The mobile phase was then returned to initial conditions and the column re-equilibrated for 1 minute. Total analysis time was 4 minutes.

The HPLC was interfaced to a Micromass Quattro LC. Ultra high purity nitrogen was used as the nebulizing and desolvation gas at flow rates of 100 L/hr for nebulization and 1100 L/hr for desolvation. The desolvation temperature was 300°C and the source temperature was 150°C. Data acquisition utilized selected reaction monitoring (SRM). Ions representing the $(M+H)^+$ species for the compound and the internal standard were selected in MS1 and collisionally dissociated with argon at a pressure of 2×10^{-3} torr to form specific product ions which were subsequently monitored by MS2.

The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

The pharmaceutical composition may be in the form of orally-administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate

as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

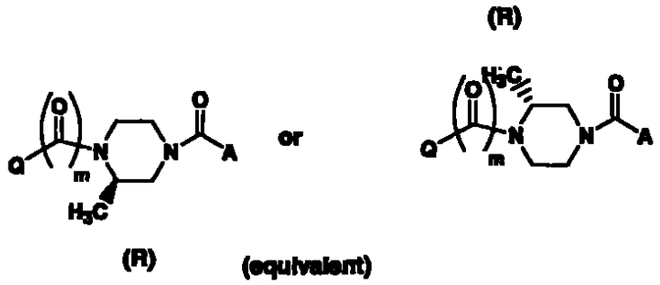
The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Scheme 41a depicts methodology for converting a carboxylic acid to an alkynyl ketone. The alkynyl ketone precursors can then be converted to pyrazoles or isoxazoles upon reaction with hydrazines or hydroxyl amines, respectively.

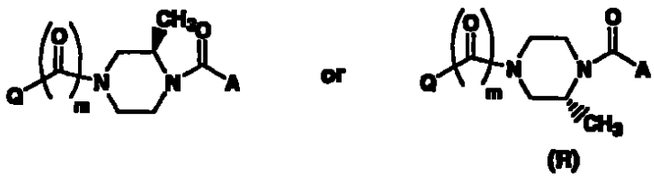
The invention is intended to cover isomers, diastereoisomers, stereoisomers, and enantiomers of the depicted formulas when one or more asymmetric carbons are present in the molecules. An asymmetric carbon is one in which the carbon is attached to four different substitutions. In particular, the invention is intended to

cover isomers or a single enantiomer especially when one enantiomer displays superior properties. Enantiomers differ from one another in that the spacial arrangement of the substituents around the chiral centers of the asymmetric carbons result in each molecule being a nonsuperimposable mirror image of the other. In this application, the configuration of the substituents around an asymmetric carbon are defined unambiguously as either (R) which is a standard representation which stands for Latin rectus, right or (S) which is the standard representation for Latin sinister, left in the Cahn-Ingold-Prelog nomenclature system which has been in use since the 1960s. Standard rules for defining the configuration of these centers are found in any basic organic chemistry textbook. In particular, for this application and based on initial examples, when W contains a single methyl group as depicted below, when the carbon bearing the methyl group is in the (R) configuration it may show a potency advantage over the (S) enantiomer. Occasionally the (R)-methyl piperazine may show a potency advantage over the unsubstituted piperazine. These observations are compound specific effect and are not always present. The unsubstituted piperazine and (S) enantiomers are still potent antiviral compounds despite occasionally being less potent than the (R) enantiomer.



When the configuration of a methyl piperazine shown as below is (R) the methyl group may improve the metabolic stability of the adjacent amide as compared to the (S) methyl piperazine or the unsubstituted piperazine. However, the metabolic stability of the amide bond is compound specific and a methyl substituent is not necessarily required for optimal properties.

(II)



(equivalent)

It has now also been surprisingly found that compounds of Formula Ia, in which specifically R_4 is an N-linked triazolyl group, attached at the 1-nitrogen position, are particularly effective for inhibiting HIV. This is discussed more fully below.

The effective treatment of HIV and other viruses requires compounds that are potent inhibitors of the virus, are selective for the virus, and have the properties which allow them to safely achieve and maintain plasma level concentrations which are a maximum number multiples above the concentration required to minimally inhibit the virus. Higher exposures suppress viral replication and reduced rates of replication mean that strains of virus with resistance to the drug treatment will develop at a slower rate. Potent drugs exhibit equivalent activity from a lower concentration or lower dose than that needed to achieve the same effect from a less potent drug. Drugs which intrinsically produce higher exposures from an equivalent dose in animal models or patients (as determined by pharmacokinetic measurements such as AUC (the sum of the concentration of drug over a particular time), Cmax, or Cmin will also provide greater benefit to the patient. Drugs which have higher stability in the presence of metabolizing pathways and enzymes will maintain their concentrations longer and thus require less frequent dosing or dosing of smaller quantities. In animals or people the rate of clearance is a frequently measured parameter to assess this property but mean retention time is also used. For accuracy, the determined measure of viral inhibition is an EC50; but the minimum plasma concentrations which should be maintained in a patient is generally believed to be at least four or five fold higher. Thus the antiviral or anti HIV drug candidates which will be most likely to provide maximum benefits in patients and those that preclinical research programs strive to identify will exhibit 1) maximum potency 2) no general

cytotoxicity vs the cell line used for the assay 3) low predicted rates of metabolism in human based on *in vitro* models 4) high exposure after oral dosing. Many other properties of potential drug candidates are evaluated in order to determine which compounds will have the best chance of showing optimal utility in human patients but the compounds of this invention were evaluated initially in part by determining:

1) Potency vs HIV as determined by an EC50 in an initial pseudotype assay as described in the biology section.

2) Lack of general cytotoxicity vs a Hela cell line. >100uM was used as an arbitrary cut off for safety.

3) Measurement of the rate of metabolism vs human liver microsomal preparations and from this data projecting human rate of clearance. Lower is better.

4) Estimating potential exposure in man by measuring parameters such as AUC and rate of clearance by oral and iv dosing in rats. High exposure and low clearance was desired.

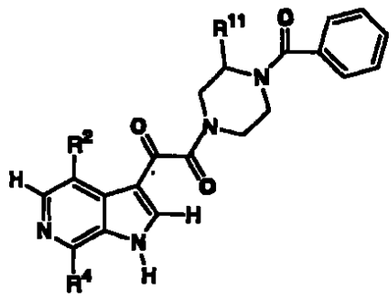
Aazaindole oxoacetic piperazine amides have been disclosed in two series of patent applications. The first series discloses azaindole derivatives which have promising potential as antiviral agents (hereinafter called, reference 94) Wang, Tao et al, U.S. patent 6476034 and WO 0162255 A1, filed January 19, 2001, published August 30, 2001. The second series (hereinafter called, reference 106) Wang, Tao, et al discloses HIV Antiviral Activity of Substituted Azaindoleoxoacetic Piperazine Derivatives in U.S. Patent Application Serial Number 10/214,982 filed August 7, 2002, which is a continuation-in-part application of U.S. Serial Number 10/038,306 filed January 2, 2002 (corresponding to PCT Int. Appl. (PCT/US02/00455), WO 02/062423 A1, filed January 2, 2002, published August 15, 2002. All of the references for these two series are incorporated by reference herein. Reference 106 describes in part C-7 heteroaryl, aryl or substituted 4,5,6,or 7-azaindoles as antiviral agents and is the most relevant prior art.

We have evaluated the properties of many compounds covered within the scope of references 94 and 106 and have found that the compounds having C-7, N-linked triazole groups are surprisingly and unexpectedly superior.

We initially evaluated compounds to determine which showed maximum potency or the lowest EC50 using the pseudotype assay described in the biology section of this application. In our case compounds with EC50s less than 0.20 nM were considered of most interest since this covered the most potent compounds and accounted for assay variability of our initial screen. The stability of compounds were also evaluated to determine metabolic stability when incubated in *in vitro* preparations of human liver microsomes (HLM). This is one commonly used predictive system for evaluating the potential for human metabolism and projecting clearance rates in man. Compounds with low clearance rates were most desireable. Intermediate and high clearance compounds would be more likely to have difficulty achieving feasible dosing regimen's in man vs low clearance compounds. Compounds for which accurate determinations could not be made were also not advanced.

Surprisingly, when the most promising compounds from the potency and metabolic stability criterias were evaluated in rats to measure their pharmacokinetic properties, one class of C-7 substituents, N linked triazoles of Formula Ia showed very low clearance and very high AUCs (exposure) when compared to the compounds of references 94 and 106.

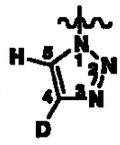
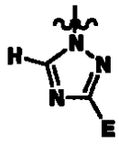
The compounds I having Formula Ia are described below:



Ia

wherein:

R^2 is methoxy, fluoro or chloro;

R^4 is  or  ;

D is hydrogen or C_1-C_3 alkyl;

E is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, $O(C_1$-$C_3)$alkyl or CH_2OCH_3.

R^{11} is either hydrogen or methyl in which the configuration to which the methyl is attached is (R) with the proviso that when R^4 is 1,2,3-triazole, then R^{11} is hydrogen.

The C-7 N-linked triazoles thus showed surprising properties as they were essentially equivalent in potency to the most potent compounds covered by references 94 and 106 that we have evaluated to date. They showed metabolic stability in human liver microsomes that was equivalent to the best compounds from the application. Unexpectedly, they showed clearance rates in rats that were much lower, usually 10 fold lower than the best compounds from those described in the applications of reference 94 and were the best of any compounds evaluated in reference 106. Even more surprisingly, they were the only class of compounds to show significantly increased exposure in rats as shown by their AUCs.

In summation, these N-linked triazoles exhibited a surprising combination of properties that would not be obvious to one skilled in the art relying on the disclosure of references 94 and 106. Only a single triazole is disclosed in WO 02/06423. This compound has an R^4 substituent which is a C-linked triazole, and not an N-linked triazole, and exhibited potency which was not comparable to the N-linked triazoles. No N-linked triazoles were described in the examples of the published PCT application from reference 106.

The following data tables summarize the potency, predicted human clearance based on human liver microsomes, and the AUC and clearance determined by

pharmacokinetic studies in rats for these N-linked triazoles of the invention herein compared with representative compounds and close analogs contained in PCT application WO 02/062423 A1, filed January 2, 2002, published August 15, 2002 and the published applications and patents contained in reference 94. As seen in the following tables the N linked triazoles herein identified as most preferred groups exhibit surprising superiority especially in terms of displaying maximum potency, metabolic stability equivalent to best in class and uniquely a high AUC (exposure) and low clearance in rats which is determined by oral and iv dosing at 5mg/kg and 1mg/kg respectively. The rat model is an initial model used to assess potential for exposure in man.

The utility of compounds in the triazole class is surprisingly very dependent on the substitution patterns as depicted. For example the 1,2,3 triazoles attached at the 2-position nitrogen atom have to date shown significantly reduced AUC (exposure) in rats compared to the compounds depicted. In addition, moving the E group when E is methyl, in the 1,2,4-N-linked triazole from position 3 to 5 provides compounds with significantly reduced potency. As can be seen in Table A2, the N-linked triazoles specified showed high potency in an initial antiviral assay.

As evidenced by Tables A3-A8 of Comparator compounds, the metabolic stability of the N-linked triazole compounds Ia of the invention is surprisingly equivalent to or better than any of the compounds covered in either series of published azaindole applications (i.e. references 94 and 106).

As dramatically shown in the tables, the low clearance and high exposure seen in rats for the compounds in table A2 was surprising and unexpected since the prior art taught compounds did not exhibit these properties as one would have expected.

In the tables that follow these terms have the following in meanings:

"NT" meant not tested.

"Difficulties" means results could not be interpreted (i.e. in HLM test).

Results

Table A1. Biological Data Key for EC_{50}s in Tables A2-A7

Compounds* with EC_{50} >1μM	Compounds with EC_{50} >0.2 nM but <1μM	Compounds with EC50 ≤ 0.20 nM
Group 3	Group 2	Group 1

Table A2 N linked Triazoles as R4 with Surprising Superior Properties

Example Number	EC50 category	CC50 >100uM	HLM predicted human clearance class	AUC 24h (ug.hr/mL)	CL, iv (mL/min/kg)	
216	1	Yes	Low	32 ± 12	1.6 ± 0.2	
188	1	Yes	Low	20 ± 4.6	2.4 ± 0.08	
187	1	Yes	Low	22.4 ± 7.2	2.4 ± 0.5	
215, 303	1	Yes	Low	83.7± 9.8	0.7 ± 0.12	
245	1	Yes	Low	12.1 ± 1.3	5.6 ± 1.8	
313	1	Yes	Low			
316	1	Yes	Low	52 ± 12	1.3 ± 0.19	
317	1	Yes	Low	43 ± 12	1.9 ± 0.26	
306	1	Yes	Low	160 ± 11	0.39 ± 0.07	
321	1	Yes	Low			
322	1	Yes	Low	82 ± 23	1.6 ± 0.4	
314	1	Yes	Low			
315	1	Yes	Low			
352	1	Yes	Low			
325	1	Yes	Low			
326	1	Yes	Low	9.6 ± 2.9		8.3
274	1	Yes	Low			
273	1	Yes	Low			
324	1	Yes	Low			
275	1	Yes	Low			

Table A3 Some Other Alternatively Substituted N linked Triazoles at R4 as Comparators

Example Number	EC50 category	CC50 >100uM	HLM predicted human clearance class	AUC 24h (ug.hr/mL)	CL, iv (mL/min/kg)
217	2	Yes	NT	NT	NT
307	2	Yes	NT	NT	NT
256	2	Yes	NT	NT	NT
350	2	Yes	Low	NT	NT
327	2	Yes	Low	NT	NT
328	1	Yes	Low	NT	NT
351	NT	NT	Low	1.5 ± 0.14	18.6 ± 1.4

Table A4 Some Other Relevant N linked Heteroaryls at R4 as Comparators

Example Number	EC50 category	CC50 >100uM	HLM predicted human clearance class	AUC 24h (ug.hr/mL)	CL, iv (mL/min/kg)
139	2	Yes	High		
219,305	1	Yes	High		
193	1	No	Low	14 ± 8	4.5 ± 0.4
189	2	Yes	Low		
222	2	Yes	Low		
221	2	Yes	Low		
220	2	Yes	NT		
218,304	2	Yes	Low		
190	1	Yes	Low	7.4 ± 3.4*	3.7 ± 1.0
191	2	Yes	NT		
309	1	Yes	Low	0.09 ± 0.05	34.3 ± 2.6
318	2	Yes	Low		
310	1	Yes	Low	2.1 ± 0.4*	16.5 ± 3.3
241	1	Yes	Low	6.4 ± 4.2*	11.2 ± 0.9
312	2	Yes	Low		
241	1	Yes	Low	0.0086 ± 0.005 **	131 ± 4.3
236	1	Yes	Low	0.56 ± 0.25	29 ± 6.7
251	1	Yes	Low		

230	1	Yes	Intermediate		
343	1	Yes	Low		
344	2	No	Low		
276	1	Yes	NT		
255	1	Yes	Intermediate		
258	1	Yes	Low		
314	1	Yes	Low		
315	1	Yes	Low		
352	1	Yes	Low		
328	1	Yes	Low	9.8 ± 2.9	8.3
274	1	Yes			
273	1	Yes			
275	1	Yes			

Table A5 Some Relevant C linked Heteroaryl Comparators

Example Number	EC50 category	CC50 >100uM	HLM predicted human clearance class	AUC 24h (ug.hr/mL)	CL, iv (mL/min/kg)
40	2	No	Low		
42	2	Yes	Low		
22	1	No	Intermediate		
35	1	Yes	Intermediate		
37	1	No	NT		
38	1	No	Low		
39	2	No	Intermediate		
28	3	No	NT		
29	2	No	High		
22	2	No	High		
74	2	No	Intermediate		
71	1	Yes	Intermediate		
73	1	Yes	Intermediate		
78	2	Yes	Intermediate		
94	1	Yes	NT		
102	2	Yes	Low	6.9 ± 1.3	12 ± 5.5
163	2	Yes	Difficulties		
95	1	Yes	Intermediate		

140	2	Yes	Intermediate		
146	2	Yes	Intermediate		
145	1	Yes	Difficulties	12 ± 3.8	1.4 ± 0.29
148	2	Yes	NT		
210	1	Yes	Intermediate		
211	1	No	Intermediate		
212	1	Yes	Low		
223	2	Yes	Low		
224	2	Yes	Low		
225	2	Yes	NT		
227	2	Yes	Low	3.8 ± 0.83	8.8 ± 3.7
228	1	Yes	Low	0.5 ± 0.13*	24.5 ± 3
299	1	No	Low		
300	2	Yes	Low		
266	1	Yes	Low	0.16 ± 0.04*	37.4 ± 3.2
345	2	Yes	Low		
301	2	Yes	NT		
346	2	Yes	NT		
347	2	Yes	Low		
334	2	Yes	NT		
348	2	Yes	Low		
349	2	Yes	NT		
342	1	Yes	Low		

Table A6 Some Relevant 4-azaindole Comparators and data

Example Number	EC50 category	CC50 >100uM	HLM predicted human clearance class	AUC 24h (ug.hr/mL)	CL, iv (mL/min/kg)
204	2	Yes	Low	12±1.4	10±1.3
161	1	Yes	High		
205	2	Yes	Low	9.6±1.2	5.4±0.4
207	2	Yes	Low		
206	2	Yes	NT		
208	2	Yes	NT		
353	2	Yes	Low	1363±307	5.6±1.1*

354	2	Yes	Low	1.26	11.2±0.8
355	2	Yes	Low	0.18* 3.3±0.77*	13.9±5.3
356	2	Yes	Low		
357	2	Yes	Intermediate		
358	2	Yes	High		
359	2	Yes	NT		
360	2	Yes	Low		
361	2	Yes	NT		

Table A7 Some Relevant Comparators and data from U.S. patent 6476034 (Reference 94)

Reference Compound Number	EC50 category	CC50 >100uM?	HLM predicted human clearance class	AUC 24h (ug.hr/mL)	CL, iv (mL/min/kg)
1	2	Yes	Low	0.5	32 ± 1.8
2	2	Yes	Intermediate		
3	2	Yes	Low	6.3 ± 2.7	13±4.0
4	2	Yes	Low		
5	1	Yes	Intermediate		
6	2	Yes	Low	1.7 ± 0.58	31 ± 5.9
7	1	Yes	Low	2.6±0.12*	19.3 ± 0.65
8	1	Yes	Low	1.03±0.07*	47.2 ± 11.5
9	2	Yes	Low	5.9 ± 2.2	5.9 ± 2.2
10	2	Yes	Low	2.9 ± 0.3	11.7 ± 1.0
11	1	Yes		1.4 ± 0.2*	24.8 ± 0.41
12	1	Yes	Low	4.7 ± 1.1	11.9 ± 1.8
13	2	Yes	NT		

Structures of Reference Compounds as a Key for Table A7

Reference Compound 1

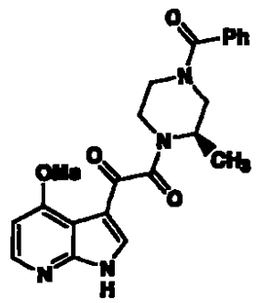
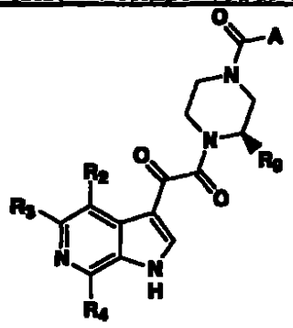


Table A8 (Reference compounds structures 2-9)



Reference Compound Number	R2	R3	R4	R9	A
2	OMe	H	X_2—OMe	(R)-Me	X_4
3	OMe	H	X_2—OMe	H	X_4
4	OMe	H	X_2—OH	H	X_4
5	Cl	H	X_2 (NH$_2$, O)	H	X_4
6	F	H	X_2 (NHMe, O)	H	X_4

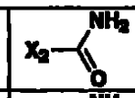
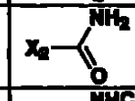
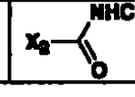
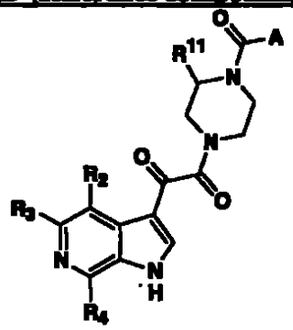
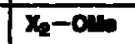
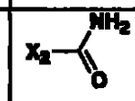
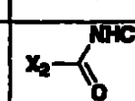
7	F	H		H	
8	MeO	H		H	
9	MeO	H		H	

Table A9 (Reference compounds 10-12)



Reference Compound Number	R2	R3	R4	R11	A
10	MeO	H		(R)-Me	
11	MeO	H		(R)-Me	
12	MeO	H		(R)-Me	

In Tables A8 and A9, X_2 and X_4 refer to point of attachment.

CLAIMS

What is claimed is:

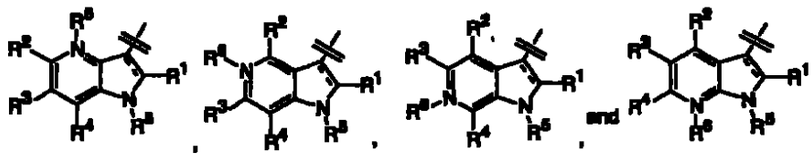
1. A compound of Formula I, including pharmaceutically acceptable salts thereof,



I

wherein:

Q is selected from the group consisting of:



R^1, R^2, R^3, and R^4, are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, $COOR^{56}$, XR^{57}, $C(O)R^7$, $C(O)NR^{55}R^{56}$, B, D, and E with the proviso that at least one of R^1-R^4 is selected from B or E;

wherein - - represents a carbon-carbon bond or does not exist;

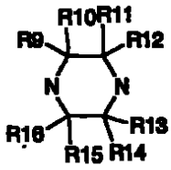
m is 1 or 2;

R^5 is hydrogen or $(CH_2)_nCH_3$, $-C(O)(CH_2)_nCH_3$, $-C(O)O(CH_2)_nCH_3$, $-C(O)(CH_2)_nN(CH_3)_2$ wherein n is 0-5;

R^6 is O or does not exist;

A is selected from the group consisting of C_{1-6}alkoxy, aryl and heteroaryl; in which said aryl is phenyl or napthyl; said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, benzoimidazolyl and benzothiazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different members selected from the group consisting of amino, nitro, cyano, hydroxy, C_{1-6}alkoxy, $-C(O)NH_2$, C_{1-6}alkyl, $-NHC(O)CH_3$, halogen and trifluoromethyl;

-W- is



;

B is selected from the group consisting of $-C(=NR^{46})(R^{47})$, $C(O)NR^{40}R^{41}$, aryl, heteroaryl, heteroalicyclic, $S(O)_2R^8$, $C(O)R^7$, XR^{8a}, (C_{1-6})alkyl$NR^{40}R^{41}$, (C_{1-6})alkyl$COOR^{8b}$; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group F; wherein aryl is napthyl or substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;

q is 0, 1, or 2;

D is selected from the group consisting of (C_{1-6})alkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of $C(O)NR^{55}R^{56}$, hydroxy, cyano and XR^{57};

E is selected from the group consisting of (C_{1-6})alkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, $-C(O)NR_{56}R_{57}$, $C(O)R_{57}$, $SO_2(C_{1-6})$alkyl and SO_2Ph; wherein heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, (C_{1-6})thioalkoxy, cyano, halogen, nitro, $-C(O)R^{57}$, benzyl, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}C(O)-(C_{3-6})$cycloalkyl, $-NR^{42}C(O)$-aryl, $-NR^{42}C(O)$-heteroaryl, $-NR^{42}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$alkyl, $-NR^{42}S(O)_2-(C_{3-6})$cycloalkyl, $-NR^{42}S(O)2$-aryl, $-NR^{42}S(O)_2$-heteroaryl, $-NR^{42}S(O)2$-heteroalicyclic, $S(O)_2(C_{1-6})$alkyl, $S(O)_2$aryl, $-S(O)2\ NR^{42}R^{43}$, $NR^{42}R^{43}$; (C_{1-6})alkyl$C(O)NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$, $NHC(O)NR^{42}R^{43}$, $OC(O)NR^{42}R^{43}$, $NHC(O)OR^{54}$, (C_{1-6})alkyl$NR^{42}R^{43}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, and aryloxy, are optionally substituted with one to nine same or different halogens or from one to five same or different substituents selected from the group G; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

G is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, cyano, halogen, nitro, $-C(O)R^{57}$, benzyl, $-NR^{48}C(O)-(C_{1-6})$alkyl, $-NR^{48}C(O)-(C_{3-6})$cycloalkyl, $-NR^{48}C(O)$-aryl, $-NR^{48}C(O)$-heteroaryl, $-NR^{48}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{48}S(O)_2-(C_{1-6})$alkyl, $-NR^{48}S(O)_2-(C_{3-6})$cycloalkyl, $-NR^{48}S(O)2$-aryl, $-NR^{48}S(O)_2$-heteroaryl, $-NR^{48}S(O)2$-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide, $NR^{49}R^{49}$, (C_{1-6})alkyl $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$, $NHC(O)NR^{48}R^{49}$, $OC(O)NR^{48}R^{49}$, $NHC(O)OR^{54'}$,

(C_{1-6})alkylNR^{48}R^{49}, COOR^{54}, and (C_{1-6})alkylCOOR^{54}; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^7 is selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or with from one to three same or different substituents selected from the group F;

wherein for R^7, R^8, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^8 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

R^{8a} is a member selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein each member is independently optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

R^{8b} is selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, are each independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; wherein said (C_{1-6})alkyl is optionally substituted with one to three same or different halogens;

X is selected from the group consisting of NH or NCH_3, O, and S;

R^{40} and R^{41} are independently selected from the group consisting of (a) hydrogen; (b) (C_{1-6})alkyl or (C_{3-7})cycloalkyl substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F; and (c) (C_{1-6})alkoxy, aryl, heteroaryl or heteroalicyclic; or R^{40} and R^{41} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F; wherein for R^{40} and R^{41} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine; provided when B is $C(O)NR^{40}R^{41}$, at least one of R^{40} and R^{41} is not selected from groups (a) or (b);

R^{42} and R^{43} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, allyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl and heteroalicyclic; or R^{42} and R^{43} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G; wherein for R^{42} and R^{43} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R_a and R_b are each independently H, (C_{1-6})alkyl or phenyl;

R^{46} is selected from the group consisting of H, OR^{57}, and $NR^{55}R^{56}$;

R^{47} is selected from the group consisting of H, amino, halogen, phenyl, and (C_{1-6})alkyl;

R^{48} and R^{49} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl;

R^{50} is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, and benzyl; wherein each of said (C_{1-6})alkyl, (C_{3-7})cycloalkyl and benzyl are optionally substituted with one to three same or different halogen, amino, OH, CN or NO_2;

R^{54} is selected from the group consisting of hydrogen and (C_{1-6})alkyl;

$R^{54'}$ is (C_{1-6})alkyl;

R^{55} and R^{56} are independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; and

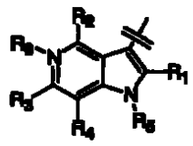
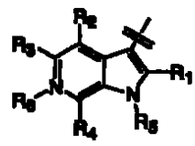
R^{57} is selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl.

2. A compound of claim 1, including pharmaceutically acceptable salts thereof

wherein:

R^1 is hydrogen;

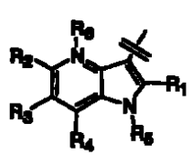
Q is either:

(a)  or  ;

wherein R^2 is selected from the group consisting of hydrogen, halogen, hydroxy, -O(C_{1-6})alkyl, cyano, nitro and XR^{57};

wherein R^3 is selected from the group consisting of hydrogen, halogen, hydroxy, -O(C_{1-6})alkyl, cyano, -$COOR^{56}$, nitro, XR^{57}; phenyl optionally substituted with one to three same or different halogens or one of methoxy, hydroxy or XR^{57}; furyl, oxazolyl, or pyrazolyl, independently optionally substituted with halogen, methoxy, (C_{1-3})alkyl or XR^{57}; or

(b) Q is:

 ;

wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, hydroxy, -O(C_{1-6})alkyl, cyano, nitro , -$COOR^{56}$, XR^{57}, -C(O) $NR^{55}R^{56}$; phenyl optionally substituted with one to three same or different halogens or one of methoxy, hydroxy or XR^{57}; furyl, oxalzolyl or pyrazolyl, independently optionally substituted with (C_{1-3})alkyl, halogen, methoxy or XR^{57};

and for both (a) and (b):

m is 2;

R^5 is hydrogen;

R^6 does not exist;

A is selected from the group consisting of C_{1-6}alkoxy, aryl and heteroaryl; wherein said aryl is phenyl; heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl and isoxazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different members selected from the group consisting of amino, cyano, hydroxy C_{1-6}alkoxy, C_{1-6}alkyl, $-NHC(O)CH_3$, halogen and trifluoromethyl;

- - represents a carbon-carbon bond;

X is NH or NCH_3;

R^{57} is H or (C_{1-3})alkyl; and

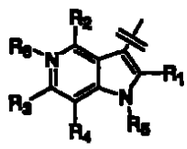
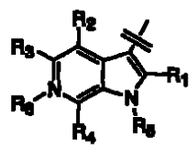
R^{55} and R^{56} are independently H or (C_{1-6})alkyl.

3. A compound of claim 2, including pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, hydroxy, or halogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} are each independently hydrogen or methyl with the proviso that only one is methyl;

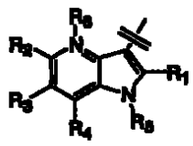
Q is either:

(a)  or  ;

and then R^2 is selected from the group consisting of hydrogen, halogen and methoxy; and

R_3 is hydrogen; or

(b) Q is:



;

and R^2 is halogen or hydrogen and R^3 is hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B;

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl, heteroaryl, oxazoline, pyrazinone and methylene dioxy or ethylene dioxy fused to a benzene or pyridine; wherein said heteroaryl or phenyl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

4. A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl and heteroaryl; wherein said phenyl is substituted and heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, (C_{1-6})thioalkoxy, cyano, halogen, $-C(O)R^{57}$, benzyl, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}C(O)-(C_{3-6})$cycloalkyl, $-NR^{42}C(O)$-aryl, $-NR^{42}C(O)$-heteroaryl, $-NR^{42}C(O)$-heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$alkyl, $-NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ and $COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic,

(C_{1-6})alkoxy, are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G;

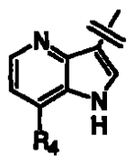
G is selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, halogen, $-NR^{48}C(O)-(C_{1-6})$alkyl, $-NR^{48}C(O)-(C_3)$cycloalkyl, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{48}S(O)_2-(C_{1-6})$alkyl, $NR^{48}R^{49}$, (C_{1-6})alkyl $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ and (C_{1-6})alkyl$NR^{48}R^{49}$;

R^{40} is hydrogen; and

R^{41} is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl and heteroaryl; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, or heteroaryl are substituted with one to three same or different halogens or one to two same or different substituents selected from the group consisting of methyl, (C_{1-3})alkoxy, heteroaryl and aryl; wherein said aryl or heteroaryl are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, $-NR^{42}C(O)-(C_{1-6})$alkyl, $NR^{42}R^{43}$ and $C(O)NR^{42}R^{43}$.

5. A compound of claim 4, including pharmaceutically acceptable salts thereof, wherein:

Q is



;

A is Phenyl, 2-pyridyl, or 3-pyridyl;

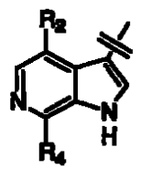
B is selected from the group consisting of -C(O)NR^{40}R^{41} or heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

6. A compound of claim 5, including pharmaceutically acceptable salts thereof, wherein:

B is heteroaryl, wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

7. A compound of claim 4, including pharmaceutically acceptable salts thereof, wherein:

Q is



;

R^2 is selected from the group consisting of hydrogen, halogen, and methoxy;

R^4 is B;

B is selected from the group consisting of -C(O)NR^{40}R^{41} or heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

8. A compound of claim 7, including pharmaceutically acceptable salts thereof, wherein:

A is phenyl, 2-pyridyl, or 3-pyridyl.

9. A compound of claim 8 including pharmaceutically acceptable salts thereof, wherein:

B is -C(O)$NR^{40}R^{41}$.

10. A compound of claim 8 including pharmaceutically acceptable salts thereof, wherein:

B is heteroaryl, wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

11. A compound of claim 4 wherein:

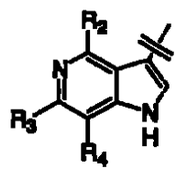
F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl (C_{1-6})alkoxy, hydroxy, heteroaryl, heteroalicyclic, methoxy, -S(C_{1-3})alkyl, halogen, -$C(O)R^{57}$, $C(O)NR^{42}R^{43}$, -$NR^{42}C(O)$-(C_{1-6})alkyl, -$NR^{42}C(O)$-(C_{3-6})cycloalkyl, -$NR^{42}C(O)$-aryl, -$NR^{42}C(O)$-heteroaryl, -$NR^{42}C(O)$-heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, -$NR^{42}S(O)_2$-(C_{1-6})alkyl, -$NR^{42}S(O)_2$-(C_{3-6})cycloalkyl, -$NR^{42}S(O)2$-aryl, -$NR^{42}S(O)_2$-heteroaryl, -$NR^{42}S(O)2$-heteroalicyclic, $NR^{42}R^{43}$, $NR^{55}(C_{1-3})$alkyl$NR^{55}R^{56}$ and $COOR^{54}$.

12. A compound of claim 11 wherein:

A is phenyl, 2-pyridyl, or 3-pyridyl.

13. A compound of claim 4, including pharmaceutically acceptable salts thereof, wherein:

Q is



;

R^2 is selected from the group consisting of hydrogen and methoxy;

R^3 is hydrogen; and

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$ and heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

14. A compound of claim 8 wherein R^2 is fluoro.

15. A compound of claim 8 wherein R^2 is methoxy.

16. A compound of claim 8 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

17. A compound of claim 5 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

18. A compound of claim 13 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

19. A compound of claim 7 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

20. A compound of claim 6 wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, -thiazole, pyrrole, piperazine, pyrrolidine and N-pyrrolidone.

21. A compound of claim 7 wherein:

B is –C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -methoxy, -$NHC(C_1$-C_6 alkyl) and -$N(C_1$-C_6 alkyl)$_2$.

22. A compound of claim 10 wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -NHS(O)$_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -NHC(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -heteroaryl and a 4, 5, or 6 membered cyclic N-lactam.

23. A compound of claim 9 wherein:

B is –C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -methoxy, -NHC(C_1-C_6 alkyl) and -N(C_1-C_6 alkyl)$_2$.

24. A compound of claim 16 wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -COOC_1-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -NHS(O)$_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, -thiazole, pyrrole, piperazine, pyrrolidine and N-pyrrolidone.

25. A compound of claim 13 wherein:

B is –C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -methoxy, -NHC(C_1-C_6 alkyl) and -N(C_1-C_6 alkyl)$_2$.

26. A compound of claim 5 wherein:

B is thienyl.

27. A compound of claim 24 wherein:

B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

28. A compound of claim 10 wherein:

B is thienyl.

29. A compound of claim 27 wherein:

B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, amino, -NHC(O)-(C_1-C_6 alkyl), -C(O)-NH_2, C(O)NHMe, $C(O)NMe_2$ and -$NR^{55}R^{56}$.

30. A compound of claim 10 wherein:

B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

31. A compound of claim 16 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

32. A compound of claim 17 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

33. A compound of claim 18 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3 thioalkoxy, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alkyl, -NHC(O)-(C_1-C_6 alkyl), -$NHS(O)_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-

(C_1-C_6 alkyl)-$NR^{55}R^{56}$, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

34. A compound of claim 3 which is depicted in Table 2.

35. A compound of claim 3 which is depicted in Table 2-1.

36. A compound of claim 3 which is depicted in Table 3.

37. A compound of claim 3 which is depicted in Table 4.

38. A compound of claim 3 which is depicted in Table 5.

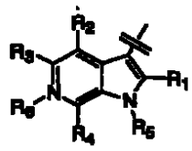
39. A compound of claim 1 wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; wherein said phenyl or heteroaryl is independently optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, or halogen;

- - represents a carbon-carbon bond;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} , and R^{16} are each independently hydrogen or methyl, with the proviso that only zero, one, or two is methyl;

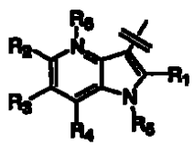
Q is either:

(a)  ;

R^2 is selected from the group consisting of hydrogen, halogen, and methoxy; and

R_3 is hydrogen; or

(b) Q is:



;

R^2 and R^3 are hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B;

B is heteroaryl selected from the group consisting of triazole, pyrazole, oxazole, pyrazine, pyrimidine and oxadiazole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

F is selected from the group consisting of (C_{1-6})alkyl, heteroaryl, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}R^{43}$ and $C(O)NR^{42}R^{43}$;

R^5 is hydrogen;

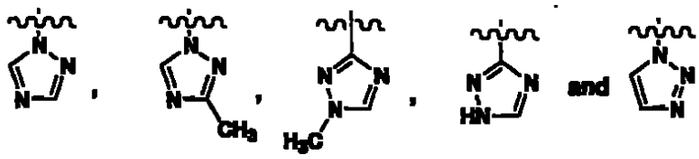
R^6 does not exist; and

R^{42} and R^{43} are independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; or R^{42} and R^{43} taken together with the nitrogen to which they are attached form a heteroalicyclic selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, tetrahydrofuran, tetrahydropyran, azepine and morpholine.

40. A compound of claim 39 wherein:

R^2 is H, Cl , F, or methoxy; and

R^4 is selected from the group consisting of



41. A compound of claim 40 wherein:

R^2 is methoxy or fluoro; and

one of R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, or R^{16} is methyl and the others are hydrogen.

42. A compound of claim 40 wherein:

R^2 is methoxy; and

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} are each hydrogen.

43. A compound of claim 41 wherein:

one of R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, or R^{16} is (R)-methyl and the others are hydrogen.

44. A compound of claim 41 wherein:

one of R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, or R^{16} is (S)-methyl and the others are hydrogen.

45. A compound of claim 39 wherein:

R^2 is methoxy, hydrogen, chloro, or fluoro; and

R^4 is oxadiazole.

46. A compound of claim 54 wherein:

R^2 is methoxy, hydrogen, chloro or fluoro; and

R^4 is oxadiazole substituted with a single fluoro, chloro, amino or methyl group.

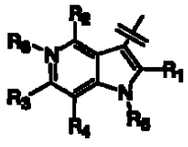
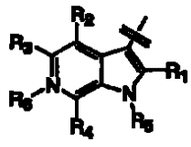
47. A compound of claim 2, including pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein said heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, hydroxy, or halogen;

R^9, R^{10}, R^{11}, R^{12}, R^{15}, and R^{16} are each hydrogen;

R^{13} and $R^{14}$are each independently hydrogen or methyl with the proviso that only one is methyl;

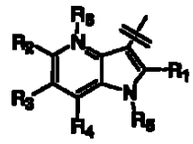
Q is either:

(a)  or  ;

R^2 is selected from the group consisting of hydrogen, halogen and methoxy; and

R_3 is hydrogen; or

(b) Q is:



and R^2 is halogen or hydrogen and R^3 is hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B; and

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl, heteroaryl, oxazoline, pyrazinone, methylene dioxy or ethylene dioxy fused to a benzene or pyridine; wherein said heteroaryl or phenyl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

48. A compound of claim 47, including pharmaceutically acceptable salts thereof, wherein:

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl and heteroaryl; wherein said phenyl is substituted and heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, (C_{1-6})thioalkoxy, cyano, halogen, $-C(O)R^{57}$, benzyl, $-NR^{42}C(O)-(C_{1-6})$alkyl, $-NR^{42}C(O)-(C_{3-6})$cycloalkyl, $-NR^{42}C(O)$-aryl, $-NR^{42}C(O)$-heteroaryl, $-NR^{42}C(O)$-heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$alkyl, $-NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ and $COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G;

G is selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, halogen, $-NR^{48}C(O)-(C_{1-6})$alkyl, $-NR^{48}C(O)-(C_3)$cycloalkyl, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{48}S(O)_2-(C_{1-6})$alkyl, $NR^{48}R^{49}$, (C_{1-6})alkyl $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ and (C_{1-6})alkyl$NR^{48}R^{49}$;

R^{40} is hydrogen;

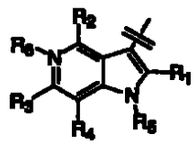
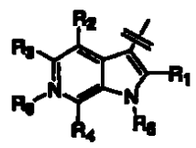
R^{41} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, or heteroaryl; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, or heteroaryl are substituted with one to three same or different halogens or one to two same or different methyl, (C_{1-3})alkoxy, heteroaryl or aryl; wherein said aryl or heteroaryl are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group consisting of (C_{1-6})alkyl, hydroxy, (C_{1-6})alkoxy, $-NR^{42}C(O)-(C_{1-6})$alkyl, $NR^{42}R^{43}$ and $C(O)NR^{42}R^{43}$.

49. A compound of claim 2, including pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C_{1-6}alkyl, hydroxy, or halogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} ,and R^{16} are each independently hydrogen or methyl with the proviso that only one is methyl;

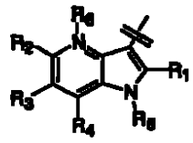
Q is either:

(a)  or  ;

wherein R^2 is selected from the group consisting of hydrogen, halogen and methoxy; and

R_3 is hydrogen; or

(b) Q is:



wherein R^2 is halogen or hydrogen; and R^3 is hydrogen;

and for both (a) and (b):

R^4 is selected from the group consisting of B;

B is selected from the group consisting of $-C(O)NR^{40}R^{41}$, substituted phenyl, heteroaryl, oxazoline, pyrazinone, methylene dioxy or ethylene dioxy fused to a benzene or pyridine; wherein said heteroaryl or phenyl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

50. A compound of claim 49, including pharmaceutically acceptable salts thereof, wherein:

B is selected from the group consisting of pyrazinone and methylene dioxy or ethylene dioxy fused to a benzene ring; wherein said group is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -NHS(O)$_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -NHC(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -heteroaryl and a 4, 5, or 6 membered cyclic N-lactam.

51. A compound of claim 49, including pharmaceutically acceptable salts thereof, wherein:

B is selected from the group consisting of oxadiazole, triazole, pyrazole, pyrazine and pyrimidine; wherein said group is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of (C_1-C_6 alkyl), amino, -NHC(O)-(C_1-C_6 alkyl), -NHS(O)$_2$-(C_1-C_6 alkyl), methoxy, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluoromethyl, -NHC(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -heteroaryl, a 4, 5, or 6 membered cyclic N-lactam and (C_{1-6})alkylNR^{48}R^{49}.

52. A compound of claim 49, including pharmaceutically acceptable salts thereof, wherein:

heteroaryl in B is selected from the group consisting of pyrazine and pyrimidine..

53. A compound of claim 50, including pharmaceutically acceptable salts thereof, wherein:

heteroaryl in B is selected from the group consisting of pyrazine and pyrimidine.

54. A compound of claim 1 wherein R^9, R^{10}, R^{15} and R^{16} are each hydrogen; and

R^{11}, R^{12}, R^{13}, and R^{14} are each independently hydrogen or methyl with the proviso that up to one can be methyl.

55. A compound of claim 54, including pharmaceutically acceptable salts thereof, wherein one of R^{11}, R^{12}, R^{13}, and R^{14} is methyl.

56. A compound of claim 55, wherein the carbon atom of the piperazine ring to which the methyl group of R^{11}, R^{12}, R^{13}, and R^{14} is attached has an (R) configuration.

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57. A compound of claim 1 wherein R^{11}, R^{12}, R^{13}, and R^{14} are each hydrogen; and R^9, R^{10}, R^{15} and R^{16} are each independently hydrogen or methyl with the proviso that up to one can be methyl.

58. A compound of claim 57, wherein one of R^9, R^{10}, R^{15} and R^{16} is methyl.

59. A compound of claim 58, wherein the carbon atom of the piperazine ring to which the methyl group of R^9, R^{10}, R^{15} and R^{16} is attached has an (R) configuration.

60. A compound of claim 1, including pharmaceutically acceptable salts thereof

wherein:

R^1 is hydrogen;

m is 2;

R^5 is hydrogen;

R^6 does not exist;

A is selected from the group consisting of C_{1-6}alkoxy, aryl and heteroaryl; wherein aryl is phenyl; heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl and isoxazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different amino, cyano, hydroxy C_{1-6}alkoxy, C_{1-6}alkyl, $-NHC(O)CH_3$, halogen and trifluoromethyl; and

- - represents a carbon-carbon bond.

61. A pharmaceutical formulation which comprises an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier.

62. The pharmaceutical formulation of claim 61, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

(a) an AIDS antiviral agent;

(b) an anti-infective agent;

(c) an immunomodulator; and

(d) HIV entry inhibitors.

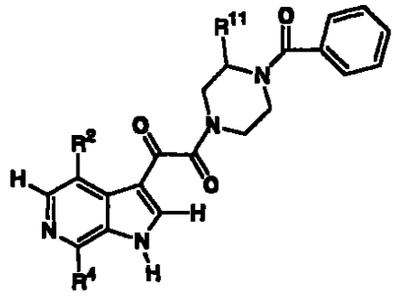
63. A method for treating mammals infected with a virus, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, as claimed in claim 1.

64. The method of claim 63, comprising administering to said mammal an antiviral effective amount of a compound of Formula I in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: an AIDS antiviral agent; an anti-infective agent; an immunomodulator; and HIV entry inhibitors.

65. The method of claim 63 wherein the virus is HIV.

66. The method of claim 64 wherein the virus is HIV.

67. A compound of claim 1 having the Formula Ia, including pharmaceutically acceptable salts thereof,

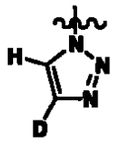


Ia

wherein:

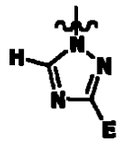
R^2 is methoxy, fluoro or chloro;

R^4 is selected from the group consisting of a 1,2,3-triazolyl group having the formula



, or

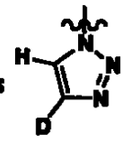
a 1,2,4-triazolyl group having the formula



;

D is hydrogen or C_1-C_3 alkyl;

E is selected from the group consisting of hydrogen, (C_1-C_3)alkyl, O(C_1-C_3)alkyl and CH_2OCH_3; and

R^{11} is either hydrogen or methyl in which the configuration to which the methyl is attached is (R); with the proviso that when R^4 is  , then R^{11} is hydrogen.

68. A compound of claim 67, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is methoxy or fluorine;
D is hydrogen or methyl; and
E is hydrogen, methyl or ethyl.

69. A compound of claim 68, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is methoxy;
D is hydrogen or methyl; and
E is hydrogen, methyl or ethyl.

70. A compound of claim 69, including pharmaceutically acceptable salts thereof,

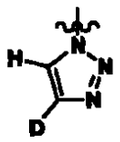
wherein:

R^{11} is hydrogen.

71. A compound of claim 70, including pharmaceutically acceptable salts thereof,

wherein:

R^4 is


; and

R^{11} is hydrogen.

72. A compound of claim 71, including pharmaceutically acceptable salts thereof,

wherein:

D is hydrogen.

73. A compound of claim 71, including pharmaceutically acceptable salts thereof,

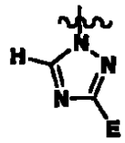
wherein:

D is methyl.

74. A compound of claim 70, including pharmaceutically acceptable salts thereof,

wherein:

R^4 is



75. A compound of claim 74, including pharmaceutically acceptable salts thereof,

wherein:

E is hydrogen.

76. A compound of claim 74, including pharmaceutically acceptable salts thereof,

wherein:

E is methyl.

77. A compound of claim 74, including pharmaceutically acceptable salts thereof,

wherein:

E is ethyl.

78. A compound of claim 68, including pharmaceutically acceptable salts thereof,

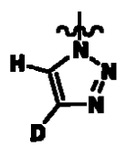
wherein:

R^2 is fluoro;
D is hydrogen or methyl; and
E is hydrogen or methyl.

79. A compound of claim 78, including pharmaceutically acceptable salts thereof,

wherein:

R^4 is



; and

R^{11} is hydrogen.

80. A compound of claim 79, including pharmaceutically acceptable salts thereof,

wherein:

D is hydrogen.

81. A compound of claim 79, including pharmaceutically acceptable salts thereof,

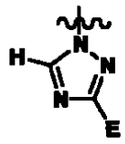
wherein:

D is methyl.

82. A compound of claim 78, including pharmaceutically acceptable salts thereof,

wherein:

R^4 is



83. A compound of claim 82, including pharmaceutically acceptable salts thereof,

wherein:

E is hydrogen.

84. A compound of claim 82, including pharmaceutically acceptable salts thereof,

wherein:

E is methyl.

85. A compound of claim 68, including pharmaceutically acceptable salts thereof,

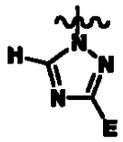
wherein:

R^2 is methoxy;
D is hydrogen or methyl;
E is hydrogen, methyl or ethyl; and
R^{11} is (R)-methyl.

86. A compound of claim 85, including pharmaceutically acceptable salts thereof,

wherein:

R^4 is



87. A compound of claim 86, including pharmaceutically acceptable salts thereof,

wherein:

E is hydrogen.

88. A compound of claim 86, including pharmaceutically acceptable salts thereof,

wherein:

E is methyl.

89. A compound of claim 86, including pharmaceutically acceptable salts thereof,
wherein:

E is ethyl.

90. A pharmaceutical formulation which comprises an antiviral effective amount of a compound of Formula Ia, including pharmaceutically acceptable salts thereof, as claimed in claim 67, and a pharmaceutically acceptable carrier.

91. The pharmaceutical formulation of claim 90, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

(a) an AIDS antiviral agent;

(b) an anti-infective agent;

(c) an immunomodulator; and

(d) HIV entry inhibitors.

92. A method for treating mammals infected with the HIV virus, comprising administering to said mammal an antiviral effective amount of a compound of Formula Ia, including pharmaceutically acceptable salts thereof, as claimed in claim 67.

93. The method of claim 92, comprising administering to said mammal an antiviral effective amount of a compound of Formula Ia in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: an AIDS antiviral agent; an anti-infective agent; an immunomodulator; and HIV entry inhibitors.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/496, 31/497, 31/506; C07D 487/04.
US CL : 514/252.11, 252.18, 253.04; 544/295, 357, 362.
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/252.11, 252.18, 253.04; 544/295, 357, 362.

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/0061892 A1 (WANG et al.) 23 May 2002 (23.05.2002), see entire document especially pages 4-7 and page 34, left column.	1-9,11-15,47-49,54-66

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2003 (19.10.2003)	05 NOV 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Felicia D. Roberts for Kelly Bernhardt Telephone No. (703) 308-1235

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Para códigos de dos letras y otras abreviaciones, refiérase a la "Notas Guías en Códigos y Abreviaciones" que aparece al inicio de cada publicación regular de la Gaceta PCT"

(54) Título: COMPOSICIÓN Y ACTIVIDAD ANTIVIRAL DE DERIVADOS DE PIPERAZINA AZAINDOLOXOACÉTICO SUBSTITUIDOS

(57) Resumen: Esta invención proporciona compuestos que tienen propiedades bioafectadoras y de fármacos; sus composiciones farmacéuticas y método de uso. En particular, la invención se refiere a derivados de azaindoloxoacetil piperazina. Estos compuestos poseen actividad antiviral única, ya sea al usarse solos o en combinación con otros antivirales, anti-infecciosos, inmunomoduladores o inhibidores de la entrada del VIH. Más particularmente, la presente invención se refiere al tratamiento del VIH y SIDA.

COMPOSICIÓN Y ACTIVIDAD ANTIVIRAL DE DERIVADOS DE PIPERAZINA AZAINDOLOXOACÉTICO SUBSTITUIDOS

CAMPO DE LA INVENCIÓN

Esta invención proporciona compuestos que tienen propiedades de fármacos y bioafectadoras, sus composiciones farmacéuticas y métodos de uso. En particular, la invención se refiere a nuevos derivados de diazaindol que poseen una actividad antiviral única. Más particularmente, la presente invención se refiere a compuestos útiles para el tratamiento del VIH y SIDA.

ANTECEDENTES DE LA INVENCIÓN

La infección por VIH-1 (virus de inmunodeficiencia humana-1) queda como un problema médico mayor, con un estimado de 42 millones de personas infectadas en todo el mundo al final del 2002. El número de casos de VIH y SIDA (síndrome de inmunodeficiencia adquirida) se ha elevado rápidamente. En 2002, alrededor de 5.0 millones de nuevos infectados se reportaron, y 3.1 millones de personas murieron de SIDA. Los fármacos actualmente disponibles para el tratamiento del VIH incluyen diez inhibidores de la transcriptasa inversa de nucleósido (RT) o combinaciones aprobadas de píldora sencilla (zidovudina o AZT (o Retrovir®), didanosina (o Videx®), estavudina (o Zerit®),

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lamivudina (o 3TC o Epivir®), zalcitabina (o DDC o Hivid®), succinato de abacavir (o Ziagen®), sal de disoproxil fumarato de Tenofovir (o Viread®), Combivir® (contiene -3TC más AZT), Trizivir® (contiene abacavir, lamivudina, y zidovudina); tres inhibidores de transcriptasa inversa no nucleósidos: nevirapina (o Viramune®), delavirdina (o Rescriptor®) y efavirenz (o Sustiva®), y ocho inhibidores de la proteasa péptido miméticos o formulaciones aprobados: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra® (lopinavir y Ritonavir), y Atazanavir (Reyataz®). Cada uno de estos fármacos únicamente pueden detener transitoriamente la replicación si se usan solos. Sin embargo, cuando se usan en combinación, estos fármacos tienen un efecto profundo en la viremia y el progreso de la enfermedad. De hecho, las reducciones importantes en las tasas de mortalidad entre los pacientes con SIDA se han documentado recientemente como una consecuencia de una aplicación ampliada de terapia de combinación. Sin embargo, a pesar de estos resultados impresionantes, del 30 hasta el 50% de los pacientes fallan de último momento a las terapias de fármaco de combinación. La potencia del fármaco insuficiente, el no cumplimiento o apego, la penetración de tejidos restringida y limitaciones específicas del fármaco dentro de ciertos tipos de células (por ejemplo, la mayoría de los análogos de nucleósido no se pueden fosforilar en las células

en reposo), pueden significar la supresión incompleta de los virus sensibles. Adicionalmente, la alta tasa de replicación y la rápida conversión del VIH-1 en combinación con la incorporación frecuente de mutaciones, lleva a la aparición de variantes resistentes al fármaco y fallas en el tratamiento cuando se presentan concentraciones de fármacos sub-óptimas (Larder y Kemp; Gulick; Kuritzkes; Morris-Jones et al; Schinazi et al; Vacca y Condra; Flexner; Berkhout y Ren et al; (Ref. 6-14)): Por lo tanto, se necesitan agentes anti-VIH novedosos que exhiban patrones de resistencia distintos, y farmacocinéticos favorables así como perfiles de seguridad para proporcionar más opciones de tratamiento.

Los fármacos de VIH-1 actualmente comercializados están dominados por los inhibidores de la transcriptasa inversa de nucleósido o inhibidores de la proteasa péptido miméticos. Los inhibidores de la transcriptasa inversa no de nucleósido (NNRTIs) actualmente han ganado un papel incrementadamente importante en la terapia de infecciones por VIH (Pedersen & Pedersen, Ref 15). Al menos 30 diferentes casos de NNRTI se han descrito en la literatura (De Clercq, Ref. 16) y varios NNRTI se han evaluado en ensayos clínicos. La dipiridodiazepinona (nevirapina), benzoxazinona (efavirenz) y derivados de bis(heteroaril) piperazina (delavirdina) se han aprobado para su uso clínico. Sin embargo, la mayor desventaja para el desarrollo y aplicación de los NNRTI es la

tendencia para una emergencia rápida de cepas resistentes al fármaco, tanto en el cultivo celular de tejido y en individuos en tratamiento, particularmente aquellos sometidos a una monoterapia. Como consecuencia, hay considerable interés en la identificación de NNRTI menos propensos al desarrollo de resistencia (Pedersen & Pedersen, Ref 15).

Varios derivados de indol, que incluyen indol 3 sulfonas, piperazino indoles, pirazino indoles, y derivados de 5H-indolo[3,2-b][1,5]benzotiazepina se han reportado como inhibidores de la transcriptasa inversa del VIH-1 (Greenlee et al, Ref. 1; Williams et al, Ref. 2; Romero et al, Ref. 3; Font et al, Ref. 17; Romero et al, Ref 18; Young et al, Ref. 19; Genin et al, Ref 20; Silvestri et al, Ref. 21). Las indol-2-carboxamidas también se han descrito como inhibidores de la adhesión celular e infección por VIH (Boschelli et al, US 5,424,329, Ref. 4). Finalmente, los productos naturales de indol-3-substituidos (semicocliodinol A y B, didemetilasterriquinona e isococliodinol) se han descrito como inhibidores de la proteasa del VIH-1 (Fredenhagen et al, Ref. 22). Otros derivados de indol exhiben actividad antiviral útil para tratar el HIV se describe en la PCT WO 00/76521 (Ref. 93). También, los derivados de indol se describen en la PCT WO 00/71535 (Ref. 94).

Los derivados de amida azaindol estructuralmente relacionados se han descrito previamente (Kato et al, Ref.

23; Levacher et al, Ref. 24; Dompe Spa, WO-09504742, Ref. 5(a); SmithKline Beecham PLC, WO-09611929, Ref. 5(b); Schering Corp., US-05023265, Ref. 5(c)). Sin embargo, estas estructuras difieren de aquellas reivindicadas en la presente, en que estas son monoazaindol monoamida en vez de derivados de oxoacetamida, y no se hace mención del uso de estos compuestos para tratar infecciones virales, particularmente VIH. Los otros azaindoles también son descritos en Wang et al, Ref. 95. El indol y azaindol de piperazina contienen derivados que se describen en 4 diferentes PCT y se emiten en la solicitud de patente E.U.A. (Referencia 93-95, 106). Ninguna de esta referencia pueden describir o sugerir los compuestos novedoso de esta invención y su usó para inhibir la infección de VIH.

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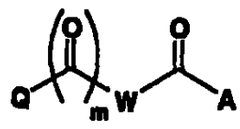
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BREVE DESCRIPCIÓN DE LA INVENCIÓN

La presente invención comprende compuestos de la fórmula I, o sales farmacéuticamente aceptables del mismo, los cuales son agentes antivirales efectivos, particularmente como inhibidores del VIH.

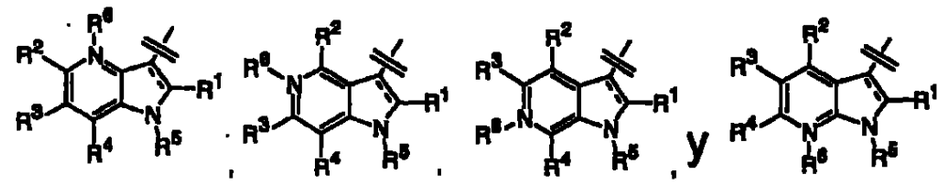
Una primera modalidad de un primer aspecto de la invención son compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables del mismo,



I

En donde:

Q se selecciona del grupo que consiste de:



R^1, R^2, R^3, y R^4, son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, ciano, nitro, $COOR^{56}$, XR^{57}, $C(O)R^7$, $C(O)NR^{55}R^{56}$, B, D, y E con la condición de que al menos uno de R^1-R^4 se selecciona de B o E;

En donde - representa un enlace carbono-carbono o no existe;

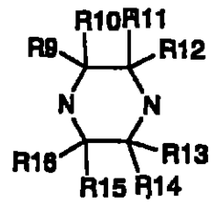
m es 1 ó 2;

R^5 es hidrógeno o $(CH_2)_nCH_3$, $-C(O)(CH_2)_nCH_3$, $-C(O)O(CH_2)_nCH_3$, $-C(O)(CH_2)_nN(CH_3)_2$ en donde n es 0-5;

R^6 es O o no existe;

A se selecciona del grupo que consiste de C_{1-6}alcoxi, arilo y heteroarilo; en los cuales arilo es fenilo o naftilo; el heteroarilo se selecciona del grupo que consiste de piridinilo, pirimidinilo, pirazinilo, triazinilo, furanilo, tienilo, pirrolilo, imidazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, quinolinilo, isoquinolinilo, benzofuranilo, benzotienilo, benzoimidazolilo y benzotiazolilo; y el arilo o heteroarilo es opcionalmente substituido con uno o dos de los mismos o diferentes miembros seleccionados del grupo que consiste de amino, nitro, ciano, hidroxi, C_{1-6}alcoxi, $-C(O)NH_2$, C_{1-6}alquilo, $-NHC(O)CH_3$, halógeno y trifluorometilo;

-W- es



;

B se selecciona del grupo que consiste de $-C(=NR^{46})(R^{47})$, $C(O)NR^{40}R^{41}$, arilo, heteroarilo, heteroalicíclico, $S(O)_2R^8$, $C(O)R^7$, XR^{8a}, (C_{1-6})alquilo$NR^{40}R^{41}$, (C_{1-6})alquil$COOR^{8b}$; en donde el arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o

diferentes o de uno hasta tres iguales o diferentes substituyentes seleccionados del grupo F; en donde arilo es naftilo o fenilo substituido; en donde heteroarilo es un sistema mono o bicíclico el cual contiene desde 3 hasta 7 átomos en el anillo por un sistema mono cíclico y hasta 12 átomos en un sistema bicíclico fusionado, incluyendo desde 1 hasta 4 heteroátomos; en donde heteroalicíclico es un anillo mono cíclico de 3 hasta 7 miembros los cuales pueden contener desde 1 hasta 2 heteroátomos en la estructura del anillo y el cual puede ser fusionado a un anillo de benceno o piridina;

q es 0, 1, ó 2;

D se selecciona del grupo que consiste de (C_{1-6})alquilo y (C_{2-6})alquenilo; en donde el (C_{1-6})alquilo y (C_{2-6})alquenilo son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o de uno hasta tres iguales o diferentes substituyentes seleccionados del grupo que consiste de $C(O)NR^{55}R^{56}$, hidroxi, ciano y XR^{57};

E se selecciona del grupo que consiste de (C_{1-6})alquilo y (C_{2-6})alquenilo; en donde el (C_{1-6})alquilo y (C_{2-6})alquenilo son independientemente opcionalmente substituidos con un miembro seleccionado del grupo que consiste de fenilo, heteroarilo, SMe, SPh, $-C(O)NR_{56}R_{57}$, $C(O)R^{57}$, $SO_2(C_{1-6})$alquilo y SO_2Ph; en donde heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 7 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos;

F se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-7})cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, (C_{1-6})alcoxi, ariloxi, (C_{1-6})tioalcoxi, ciano, halógeno, nitro, $-C(O)R^{57}$, bencilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR_{42}C(O)$-heteroalicíclico, un anillo cíclico de N-lactama de 4, 5, ó 6 miembros, $-NR^{42}SC(O)_2-(C_{1-6})$alquilo,, $-NR^{42}SC(O)_2-(C_{3-6})$cicloalquilo, $-NR^{42}S(O)2$-arilo, $-NR^{42}S(O)_2$-heteroarilo, $-NR^{42}S(O)2$-heteroalicíclico, $S(O)_2(C_{1-6})$alquilo, $S(O)_2$arilo, $-S(O)_2NR^{42}R^{43}$, $NR^{42}R^{43}$, (C_{1-6})alquiloC(O)$NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$, $NHC(O)NR^{42}R^{43}$, $OC(O)NR^{42}R^{43}$, $NHC(O)OR^{54}$, (C_{1-6})alquil$NR^{42}R^{43}$, $COOR^{54}$ y (C_{1-6})alquil$COOR^{54}$; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, arilo, heteroarilo, heteroalicíclico, (C_{1-6})alcoxi, y ariloxi, son opcionalmente substituidos con uno hasta nueve halógenos iguales o diferentes o desde uno hasta cinco substituyentes iguales o diferentes seleccionados del grupo que consiste de G; en donde arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 7 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina;

G se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-7})cicloalquilo, arilo, heteroarilo, heteroalicíclico,

hidroxi, (C_{1-6})alcoxi, ariloxi, ciano, halógeno, nitro, $-C(O)R^{57}$, bencilo, $-NR^{48}C(O)-(C_{1-6})$alquilo, $-NR^{48}C(O)-(C_{3-6})$cicloalquilo, $-NR^{48}C(O)$-arilo, $-NR^{48}C(O)$-heteroarilo, $-NR^{48}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{48}SC(O)_2-(C_{1-6})$alquilo, $-NR^{48}S(O)_2-(C_{3-6})$cicloalquilo, $-NR^{48}S(O)_2$-arilo, $-NR^{48}S(O)_2$-heteroarilo, $-NR^{48}S(O)_2$-heteroalicíclico, sulfinilo, sulfonilo, sulfonamida, $NR^{48}R^{49}$, (C_{1-6})alquil $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$, $NHC(O)NR^{48}R^{49}$, $OC(O)NR^{48}R^{49}$, $NHC(O)OR^{54}$, (C_{1-6})alquil$NR^{48}R^{49}$, $COOR^{54}$, y (C_{1-6})alquil$COOR^{54}$; en donde arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 7 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina;

R^7 se selecciona del grupo que consiste de arilo, heteroarilo, y heteroalicíclico; en donde el arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o con desde uno hasta tres substituyentes iguales o diferentes seleccionados del grupo F;

en donde R^7, R^8, R^{8a}, R^{8b} arilo es fenilo; heteroarilo es un sistema mono o bicíclico el cual contiene desde 3 hasta 7 átomos en el anillo por el sistema mono cíclico y hasta 10 átomos en un sistema bicíclico, incluyendo desde 1 hasta 4

heteroátomos; en donde heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina;

R^8 se selecciona del grupo que consiste de hidrógeno, (C_{1-6})alquilo, (C_{3-7})cicloalquilo, (C_{2-6})alquenilo, (C_{3-7})cicloalquenilo, (C_{2-6})alquinilo, arilo, heteroarilo, y heteroalicíclico; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, (C_{2-6})alquenilo, (C_{3-7})cicloalquenilo, (C_{2-6})alquinilo, arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta seis halógenos iguales o diferentes o desde uno hasta cicno substituyentes iguales o diferentes seleccionados del grupo F;

R^{8a} es un miembro seleccionado del grupo que consiste de arilo, heteroarilo, y heteroalicíclico; en donde cada uno de los miembros es independientemente opcionalmente substituido con uno hasta seis halógenos iguales o diferentes o desde uno hasta cinco substituyentes iguales o diferentes seleccionados del grupo F;

R^{8b} se selecciona del grupo que consiste de hidrógeno, (C_{1-6})alquilo y fenilo;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16},

son cada uno independientemente seleccionado del grupo que consiste de hidrógeno y (C_{1-6})alquilo; en donde el (C_{1-6})alquilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes;

X se selecciona del grupo que consiste de NH o NCH_3, O, y S;

R^{40} y R^{41} son independientemente seleccionados del grupo que consiste de (a) hidrógeno; (b) (C_{1-6})alquilo o (C_{3-7})cicloalquilo substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes seleccionados del grupo F; y (c) (C_{1-6})alcoxi, arilo, heteroarilo o heteroalicíclico; o R^{40} y R^{41} se toman junto con el nitrógeno al cual se enlazan para formar un miembro seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, 4-NMe piperazina, piperidina, azepina, y morfolina; y en donde el arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres substituyentes iguales o diferentes seleccionados del grupo E; en donde R^{40} y R^{41} arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 6 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina; con la condición que cuando B es $C(O)NR^{40}R^{41}$, al menos uno de R^{40} y R^{41} no se seleccionan de grupos (a) o (b);

R^{42} y R^{43} son independientemente seleccionados del grupo que consiste de hidrógeno, (C_{1-6})alquilo, alilo, $(C_{1-}$

$_{6}$)alcoxi, (C_{3-7})cicloalquilo, arilo, heteroarilo y heteroalicíclico; o R^{42} y R^{43} se toman juntos con el nitrógeno al cual se enlazan para formar uno miembro seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, 4-NMe piperazina, piperidina, azepina, y morfolina; y en donde el (C_{1-6})alquilo, (C_{1-6})alcoxi, (C_{3-7})cicloalquilo, arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes seleccionados del grupo G; en donde R^{42} y R^{43} arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 6 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico es un miembro seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina;

R_a y R_b son cada uno independientemente H, (C_{1-6})alquilo o fenilo;

R^{46} se selecciona del grupo que consiste de H, OR^{57}, y $NR^{55}R^{56}$;

R^{47} se selecciona del grupo que consiste de H, amino, halógeno, fenilo, y (C_{1-6})alquilo;

R^{48} y R^{49} son independientemente seleccionados del grupo que consiste de hidrógeno, (C_{1-6})alquilo y fenilo;

R^{50} se selecciona del grupo que consiste de H, (C_{1-6})alquilo, (C_{3-6})cicloalquilo, y bencilo; en donde cada uno de los (C_{1-6})alquilo, (C_{3-7})cicloalquilo y bencilo son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes, amino, OH, CN o NO_2;

R^{54} se selecciona del grupo que consiste de hidrógeno y (C_{1-6})alquilo;

$R^{54'}$ es (C_{1-6})alquilo;

R^{55} y R^{56} son independientemente seleccionados del grupo que consiste de hidrógeno y (C_{1-6})alquilo; y

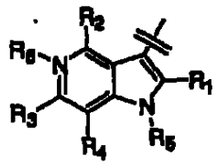
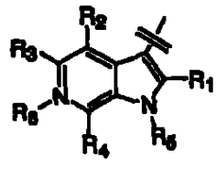
R^{57} se selecciona del grupo que consiste de hidrógeno, (C_{1-6})alquilo y fenilo.

Una modalidad preferida son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptable de los mismos,

en donde:

R^1 es hidrógeno;

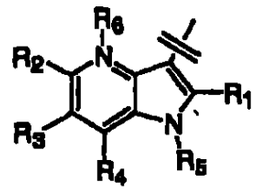
Q es ya sea:

(a)  o  ;

en donde R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, hidroxi, $-O(C_{1-6})$alquil, ciano, nitro y XR^{57};

en donde R^3 se selecciona del grupo que consiste de hidrógeno, halógeno, hidroxi, -O(C_{1-6})alquilo, ciano, -$COOR^{56}$, nitro, XR^{57}; fenilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o uno de metoxi, hidroxi o XR^{57}; furilo, oxazolilo, o pirazolilo, independientemente opcionalmente substituido con halógeno, metoxi, (C_{1-3})alquilo o XR^{57}; o

(b) Q es:



;

en donde R^2 y R^3 son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, hidroxi, -O(C_{1-6})alquilo, ciano, nitro, -$COOR^{56}$, XR^{57}, -C(O)$NR^{55}R^{56}$; fenilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o uno de metoxi, hidroxi o XR^{57}; furilo, oxalzolilo o pirazolilo, independientemente opcionalmente substituido con (C_{1-3})alquilo, halógeno, metoxi o XR^{57};

y ambos son (a) y (b):

m es 2;

R^5 es hidrógeno;

R^6 no existe;

A se selecciona del grupo que consiste de C_{1-6}alcoxi, arilo y heteroarilo; en donde el arilo es fenilo;

heteroarilo se selecciona del grupo que consiste de piridinilo, pirimidinilo, pirazinilo, triazinilo, furanilo, tienilo, pirrolilo, imidazolilo, tiazolilo, oxazolilo y isoxazolilo; y el arilo o heteroarilo es opcionalmente substituido con uno ó dos de los mismos o diferentes seleccionados del grupo que consiste de amino, ciano, hidroxi, C_{1-6}alcoxi, C_{1-6}alquilo, $-NHC(O)CH_3$, halógeno y trifluorometilo;

--- representa un enlace carbono-carbono;

X es NH o NCH_3;

R^{57} es H o (C_{1-3})alquilo; y

R^{55} y R^{56} son independientemente H o (C_{1-6})alquilo.

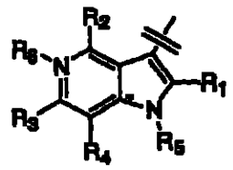
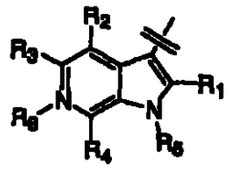
Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables del mismo,

en donde:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; y el fenilo o el heteroarilo son opcionalmente substituidos con uno hasta dos amino iguales o diferentes, C_{1-6}alquilo, hidroxi, o halógeno;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} son cada uno independientemente hidrógeno o metilo con la condición de que al menos uno es metilo;

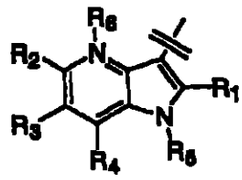
Q es ya sea:

(a)  o 

y luego R^2 se selecciona del grupo que consiste de hidrógeno, halógeno y metoxi; y

R^3 es hidrógeno; o

(b) Q es:



y R^2 es halógeno o hidrógeno y R^3 es hidrógeno;

y ambos son (a) y (b):

R4 se selecciona del grupo que consiste de B;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido, heteroarilo, oxazolina, pirazinona y metilen dioxi o etilen dioxi fusionado a benceno o piridina; en donde el heteroarilo o fenilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido y heteroarilo; en donde el fenilo es substitudo y heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F;

F se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, (C_{1-6})alcoxi, (C_{1-6})tioalcoxi, ciano, halógeno, $-C(O)R^{57}$, bencilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR^{42}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{42}S(O)_2-(C_{1-6})$alquilo, $-NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ y $COOR^{54}$; en donde el (C_{1-6})alquilo, (C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, (C_{1-6})alcoxi, son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo G;

G se selecciona del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, halógeno, $-NR^{48}C(O)-(C_{1-6})$alquilo, $-NR^{48}C(O)-(C_3)$cicloalquilo, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{48}S(O)_2-(C_{1-6})$alquilo, $NR^{48}R^{49}$, (C_{1-6})alquiloC(O)$NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ y (C_{1-6})alquilo$NR^{48}R^{49}$;

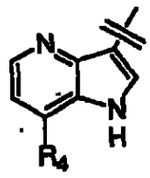
R^{40} es hidrógeno; y

R^{41} se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo y heteroarilo; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo, o heteroarilo son substituidos con uno hasta tres halógenos iguales o diferentes o uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de metilo, (C_{1-3})alcoxi, heteroarilo y arilo; en donde el arilo o heteroarilo son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, $-NR^{42}C(O)-(C_{1-6})$alquilo, $NR^{42}R^{43}$ y $C(O)NR^{42}R^{43}$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

Q es



;

A es fenilo, 2-piridilo, o 3-piridilo;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$ o heteroarilo; en donde el heteroarilo es opcionalmente

substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

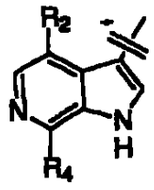
en donde:

B es heteroarilo, en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

Q es



;

R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, y metoxi;

R^4 es B;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$ o heteroarilo; en donde el heteroarilo es opcionalmente

substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

A es fenilo, 2-piridilo, o 3-piridilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es $-C(O)NR^{40}R^{41}$.

Otra modalidad preferida de la invención son compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo, en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables,

en donde:

F se selecciona del grupo que consiste de (C_{1-6})alquilo,

(C_{3-6})cicloalquilo, (C_{1-6})alcoxi, hidroxi, heteroarilo, heteroalicíclico, metoxi, $-S(C_{1-3})$alquilo, halógeno, $-C(O)R^{57}$, $C(O)NR^{42}R^{43}$, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR^{42}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{42}S(O)_2-(C_{1-6})$alquilo, $-NR^{42}S(O)_2-(C_{3-6})$cicloalquilo, $-NR^{42}S(O)_2$-arilo, $-NR^{42}S(O)_2$-heteroarilo, $-NR^{42}S(O)_2$-heteroalicíclico, $NR^{42}R^{43}$, $NR^{55}(C_{1-3})$alquil$NR^{55}R^{56}$ y $COOR^{54}$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

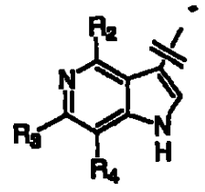
en donde:

A es fenilo, 2-piridilo, o 3-piridilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde;

Q es



;

R^2 se selecciona del grupo que consiste de hidrógeno y metoxi;

R^3 es hidrógeno; y

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$ y heteroarilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^2 es fluoro.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^2 es metoxi.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es

opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes

iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes seleccionados del grupo F.

En otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -COOC_1-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), -C(O)-NH_2, C(O)NHMe, C(O)NMe_2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, -tiazol, pirrol, piperazina, pirrolidina y N-

pirrolidona.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es -C(O)NH-heteroarilo en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -metoxi, -NHC(C_1-C_6 alquilo) y -N(C_1-C_6 alquilo)$_2$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -NHC(C_1-C_6 alquilo), -N(C_1-C_6 alquilo)$_2$, -heteroarilo y una N-lactama cíclica de 4, 5, ó 6 miembros.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

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en donde:

B es -C(O)NH-heteroarilo en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -metoxi, -NHC(C_1-C_6 alquilo) y -N(C_1-C_6 alquilo)$_2$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -COOC_1-C_6 alquilo, -NHC(O)-(C_1-C_6alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), -metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, -tiazol, pirrolo, piperazina, pirrolidina y N-pirrolidona.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es -C(O)NH-heteroarilo en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del

grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -metoxi, -NHC(C_1-C_6 alquilo) y -N(C_1-C_6 alquilo)$_2$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es tienilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es tienilo opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -COOC_1-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es tienilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es tienilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, amino, -NHC(O)-(C_1-C_6 alquilo), -C(O)-NH_2, C(O)NHMe, C(O)NMe_2 y -$NR^{55}R^{56}$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es tienilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol y piridilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquil), -$NHS(O)_2$-(C_1-C_6 alquil), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol y piridilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de hidroxi, C_1-C_6

alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol y piridilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquil)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales

farmacéuticamente aceptables del mismo,

en donde:

Un compuesto de la reivindicación 3 se detalla en la tabla 2.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

Un compuesto de la reivindicación 3 se detalla en la tabla 2-1.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

Un compuesto de la reivindicación 3 se detalla en la tabla 3.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

Un compuesto de la reivindicación 3 se detalla en la tabla 4.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

Un compuesto de la reivindicación 3 se detalla en la tabla 5.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

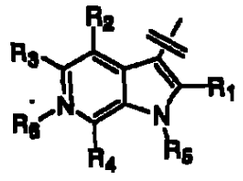
en donde:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; en donde el fenilo o heteroarilo es independientemente opcionalmente substituido con uno hasta dos de los mismo o diferentes amino, C_{1-6}alquilo, o halógeno;

- - representa un enlace carbono-carbono;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, y R^{16} son cada uno independientemente hidrógeno o metilo, con la condición de que solamente cero, uno, o dos es metilo;

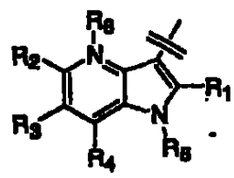
Q es ya sea:

(a)  ;

R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, y metoxi; y

R^3 es hidrógeno; o

(b) Q es:



;

R^2 y R^3 son hidrógeno;

y ambos son (a) y (b):

R^4 se selecciona del grupo que consiste de B;

B es heteroarilo seleccionado del grupo que consiste de triazol, pirazol, oxazol, pirazina, pirimidina y oxadiazol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o de uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F;

F se selecciona del grupo que consiste de (C_{1-6})alquilo, heteroarilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}R^{43}$ y $C(O)NR^{42}R^{43}$;

R^5 es hidrógeno;

R^6 no existe; y

R^{42} y R^{43} son independientemente seleccionados del grupo que consiste de hidrógeno y (C_{1-6})alquilo; o R^{42} y R^{43} se toman juntos con el nitrógeno al cual se enlazan para formar un heteroalicíclico seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, tetrahidrofurano, tetrahidropirano, azepina y morfolina.

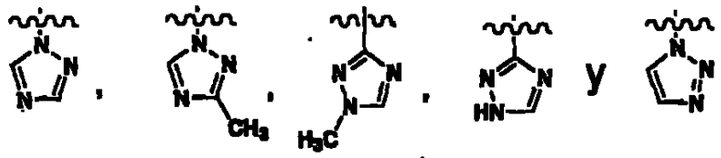
Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales

farmacéuticamente aceptables de los mismos,

en donde:

R^2 es H, Cl, F, o metoxi; y

R^4 se selecciona del grupo que consiste de



Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^2 es metoxi o fluoro; y

Uno de R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, ó R^{16} es metilo y los otros son hidrógeno.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^2 es metoxi; y

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, y R^{16} cada uno son hidrógeno.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

uno de R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, ó R^{16} es (R)-metilo y los otros son hidrógeno.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

uno de R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, ó R^{16} es (S)-metilo y los otros son hidrógeno.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^2 es metoxi, hidrógeno, cloro, o fluoro; y

R^4 es oxadiazol.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^2 es metoxi, hidrógeno, cloro o fluoro; y

R^4 es oxadiazol substituido con un grupo simple fluoro, cloro, amino o metilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

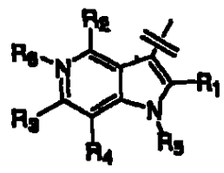
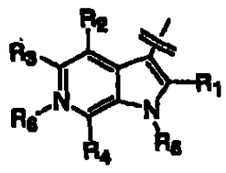
en donde:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde el heteroarilo es piridinilo, furanilo o tienilo; y el fenilo o el heteroarilo es opcionalmente substituido con uno hasta dos de los mismos o diferentes amino, C_{1-6}alquilo, hidroxi, o halógeno;

R^9, R^{10}, R^{11}, R^{12}, R^{15}, y R^{16} son cada uno hidrógeno;

R^{13} y R^{14} son cada uno independientemente hidrógeno o metilo con la condición de que solamente uno es metilo;

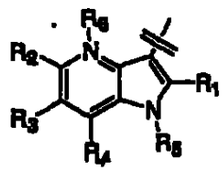
Q es ya sea:

(a)  o  ;

R^2 se selecciona del grupo que consiste de hidrógeno, halógeno y metoxi; y

R^3 es hidrógeno; o

(b) Q es:

 ;

y R^2 es halógeno o hidrógeno y R^3 es hidrógeno;

y ambos son (a) y (b):

R^4 se selecciona del grupo que consiste de B; y

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido, heteroarilo, oxazolina, pirazinona, metilen dioxi o etilen dioxi se fusionan a un benceno o piridina; en donde el heteroarilo o fenilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido y heteroarilo; en donde el fenilo es substituido y heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F;

F se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, (C_{1-6})alcoxi, (C_{1-6})tioalcoxi, ciano, halógeno, $-C(O)R^{57}$, bencilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR^{42}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{42}S(O)_2-(C_{1-6})$alquilo, $-NR^{42}R^{43}$,

$C(O)NR^{42}R^{43}$ y $COOR^{54}$; en donde el (C_{1-6})alquilo, (C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, (C_{1-6})alcoxi, son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo G;

G se selecciona del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, halógeno, $-NR^{48}C(O)-(C_{1-6})$alquilo, $-NR^{48}C(O)-(C_3)$cicloalquilo, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{48}S(O)_2-(C_{1-6})$alquilo, $NR^{48}R^{49}$, (C_{1-6})alquilo $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ y (C_{1-6})alquilo$NR^{48}R^{49}$;

R^{40} es hidrógeno;

R^{41} es (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo, o heteroarilo; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo, o heteroarilo son substituidos con uno hasta tres halógenos iguales o diferentes o uno hasta dos metilo, (C_{1-3})alcoxi, heteroarilo o arilo iguales o diferentes; en donde el arilo o heteroarilo son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, $-NR^{42}C(O)-(C_{1-6})$alquilo, $NR^{42}R^{43}$ y $C(O)NR^{42}R^{43}$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales

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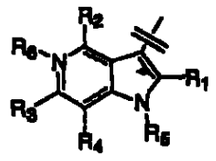
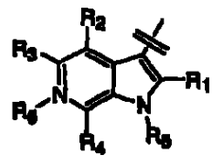
farmacéuticamente aceptables de los mismos,

en donde:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; y el fenilo o el heteroarilo es opcionalmente substituido con uno hasta dos de los mismos o diferentes amino, C_{1-6} alquilo, hidroxi, o halógeno;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, y R^{16} son cada uno independientemente hidrógeno o metilo con la condición de que solo uno es metilo;

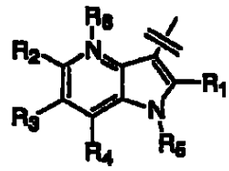
Q es ya sea:

(a)  o  ;

en donde R^2 se selecciona del grupo que consiste de hidrógeno, halógeno y metoxi; y

R_3 es hidrógeno; o

(b) Q es:

 ;

en donde R^2 es halógeno o hidrógeno; y R^3 es hidrógeno;

y ambos son (a) y (b):

R^4 se selecciona del grupo que consiste de B;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido, heteroarilo, oxazolina, pirazinona, metilen dioxi o etilen dioxi se fusiono a un benceno o piridina; en donde el heteroarilo o fenilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

B se selecciona del grupo que consiste de pirazinona y metilen dioxi o etilen dioxi fusionado a un anillo de benceno; en donde el grupo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -NHC(C_1-C_6 alquilo), -N(C_1-C_6 alquilo)$_2$, -heteroarilo y una N-lactama cíclica de 4, 5, ó 6 miembros.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales

farmacéuticamente aceptables de los mismos,

en donde:

B se selecciona del grupo que consiste de oxadiazol, triazol, pirazol, pirazina y pirimidina; en donde el grupo es opcionalmente substituido con uno hasta tres iguales o diferentes halógenos o un substituyente seleccionado del grupo F que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -NHC(C_1-C_6 alquilo), -N(C_1-C_6 alquilo)$_2$, -heteroarilo, una N-lactama cíclica de 4, 5, ó 6 miembros y (C_{1-6})alquil$NR^{48}R^{49}$.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

heteroarilo en B se selecciona del grupo que consiste de pirazina y pirimidina.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

heteroarilo en B se selecciona del grupo que consiste de pirazina y pirimidina.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales

farmacéuticamente aceptables de los mismos,

en donde:

en donde R^9, R^{10}, R^{15} y R^{16} son cada uno hidrógeno; y R^{11}, R^{12}, R^{13}, y R^{14} son cada uno independientemente hidrógeno o metil con la condición de que hasta uno puede ser metilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

uno de R^{11}, R^{12}, R^{13}, y R^{14} es metilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

el átomo de carbono del anillo de piperazina al cual el grupo metilo de R^{11}, R^{12}, R^{13}, y R^{14} se enlazan teniendo una configuración (R).

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^{11}, R^{12}, R^{13}, y R^{14} son cada uno hidrógeno; y R^9, R^{10}, R^{15} y R^{16} son cada uno independientemente hidrógeno o metilo con la condición de que uno puede ser metilo.

Otra modalidad preferida de la invención son los

compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

uno de R^9, R^{10}, R^{15} y R^{16} es metilo.

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

el átomo de carbono del anillo de piperazina al cual el grupo metilo de R^9, R^{10}, R^{15} y R^{16} se enlazan teniendo una configuración (R).

Otra modalidad preferida de la invención son los compuestos de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos,

en donde:

R^1 es hidrógeno;

m es 2;

R^5 es hidrógeno;

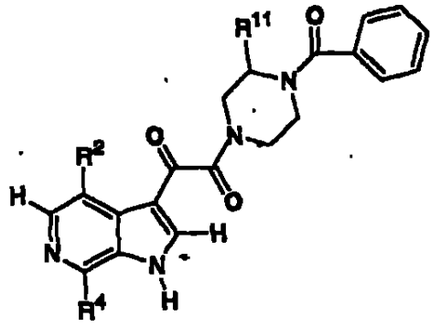
R^6 no existe;

A se selecciona del grupo que consiste de C_{1-6}alcoxi, arilo y heteroarilo; en donde arilo es fenilo; heteroarilo se selecciona del grupo que consiste de piridinilo, pirimidinilo, pirazinilo, triazinilo, furanilo, tienilo, pirrolilo, imidazolilo, tiazolilo, oxazolilo y isoxazolilo; y el arilo o heteroarilo es opcionalmente substituido con uno o

dos de los mismos o diferentes amino, ciano, hidroxi C_{1-6}alcoxi, C_{1-6}alquilo, $-NHC(O)CH_3$, halógeno y trifluorometilo; y

- - representa un enlace carbono-carbono.

Una modalidad más preferida es un compuesto de la fórmula Ia, incluyendo sales farmacéuticamente aceptables de los mismos,

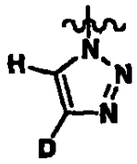


Ia

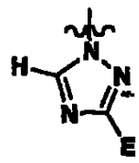
en donde:

R^2 es metoxi, fluoro o cloro.

R^4 se selecciona del grupo que consiste de ya sea:



El cual es un 1,2,3 triazol enlazado directamente por medio de un átomo de nitrógeno de la posición 1 del triazol en donde el 1,2,3 triazol es substituido con D en la posición 4 o R^4 es:



el cual es un 1,2,4 triazol enlazado por medio de un átomo de nitrógeno de la posición 1 del triazol en donde el 1,2,4 triazol es substituido con E en la posición 3.

D se selecciona de hidrógeno o C_1-C_3 alquilo.

E se selecciona del grupo que consiste de hidrógeno, (C_1-C_3)alquilo, O(C_1-C_3)alquilo o CH_2OCH_3.

R^{11} es ya sea hidrógeno o metilo en el cual la configuración a la cual el metilo se enlazó es (R) con la condición de que cuando R^4 es 1,2,3 triazol, luego R^{11} es hidrógeno.

Otra modalidad de la invención es una formulación farmacéutica que comprende una cantidad antiviral efectiva de un compuesto de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos y un portador farmacéuticamente aceptable. Cuando se usa para el tratamiento de infección de VIH, la formulación puede opcionalmente adicionalmente contener una cantidad antiviral efectiva de un agente de tratamiento del SIDA seleccionado del grupo que consiste de: un agente antiviral del SIDA, un agente antiinfeccioso; un immunodulador, e inhibidores de la entrada del VIH.

Una tercera modalidad de la invención es un método para el tratamiento de mamíferos infectados con un virus, tal como VIH, que comprende administrar a el mamífero una cantidad antiviral efectiva de un compuesto de la Fórmula I, incluyendo sales farmacéuticamente aceptable de los mismos, un portador farmacéuticamente aceptable, opcionalmente en combinación con una cantidad antiviral efectiva de un agente de tratamiento del SIDA seleccionado del grupo que consiste de: (a) un agente antiviral del SIDA; (b) un agente anti-infeccioso; (c) un immunomodulador; y (d) inhibidores de la entrada de VIH.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Ya que los compuestos de la presente invención pueden presentar centros asimétricos, y por lo tanto pueden presentarse como mezclas de diastereómeros y enantiómeros, la presente invención incluye los diastereoisómericos individuales y formas enantiomericas de los compuestos de la fórmula I en adición a las mezclas de los mismos.

DEFINICIONES

El término "alquilo C_{1-6}" como se usa en la presente y en las reivindicaciones (salvo que se especifique de otra manera) significa grupos alquilo de cadena recta o ramificada tales como metilo, etilo, propilo, isopropilo, butilo,

isobutilo, t-butilo, amilo, hexilo y similares.

"Halógeno" se refiere a cloro, bromo, yodo o flúor.

Un grupo "arilo" se refiere a todos los grupos policíclicos de anillo fusionado o monocíclico de carbono (esto es, anillos que portan pares adyacentes de átomos de carbono) que tienen un sistema de electrones "pi" completamente conjugado. Los ejemplos, sin limitación, de grupos arilo son fenilo, naftalenilo y antracenilo. El grupo arilo puede estar substituido o no substituido. Cuando se substituyen, los grupos substituyentes son preferiblemente uno o más seleccionados de alquilo, cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tiohidroxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halógeno, nitro, carbonilo, O-carbamilo, N-carbamilo, C-amido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometilo, ureido, amino y $-NR^xR^y$, en donde R^x y R^y se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo, cicloalquilo, arilo, carbonilo, C-carboxi, sulfonilo, trihalometilo, y, combinados, un anillo heteroalicíclico de cinco o seis miembros.

Como se usa en la presente, un grupo "heteroarilo" se refiere a un grupo anillo monocíclico o fusionado (esto es, anillos que portan un par de átomos adyacentes) que tienen en los anillos uno o más átomos seleccionados del grupo que

consiste de nitrógeno, oxígeno y azufre y, además, tienen un sistema de electrón "pi" completamente conjugado. Se notará que el término heteroarilo se pretende que abarque un N-óxido del heteroarilo precursor si tal N-óxido es químicamente posible como se conoce en el arte. Los ejemplos, sin limitación, de grupos heteroarilo son furilo, tienilo, benzotienilo, tiazolilo, imidazolilo, oxazolilo, oxadiazolilo, tiadiazolilo, benzotiazolilo, triazolilo, tetrazolilo, isoxazolilo, isotiazolilo, pirrolilo, piranilo, tetrahidropiranilo, pirazolilo, piridilo, pirimidinilo, quinolinilo, isoquinolinilo, purinilo, carbazolilo, benzoxazolilo, benzimidazolilo, indolilo, isoindolilo, pirazinilo, diazínilo, pirazina, triaziniltriazina, tetrazinilo, y tetrazolilo. Cuando se substituyen, los grupos substituidos son preferiblemente uno o más seleccionado de alquilo, cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tioalcoxi, tiohidroxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halógeno, nitro, carbonilo, O-carbamilo, N-carbamilo, C-amido, N-amido, C-carboxi, O carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometilo, ureido, amino, y $-NR^XR^Y$, en donde R^X y R^Y son como se define arriba.

Como se usa en la presente, un grupo "heteroalicíclico" se refiere a un grupo de anillo monocíclico o fusionado que

tiene en los anillos uno o más átomos seleccionados del grupo que consiste de nitrógeno, oxígeno y azufre. Los anillos también pueden tener uno o más enlaces dobles. Sin embargo, los anillos no tienen un sistema de electrón "pi" completamente conjugado. Los ejemplos, sin limitación, de grupos heteroalicíclico son azetidinilo, piperidilo, piperazinilo, imidazolinilo, tiazolidinilo, 3-pirrolidin-1-ilo, morfolinilo, tiomorfolinilo y tetrahidropiranilo. Cuando se substituyen, los grupos substituidos preferiblemente es uno o más seleccionado de alquilo, cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroaliciclóxi, tiohidroxi, tioalcoxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halógeno, nitro, carbonilo, tiocarbonilo, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo, sililo, guanilo, guanidino, ureido, fosfonilo, amino y $-NR^XR^Y$, en donde R^X y R^Y son como se define arriba.

Un grupo "alquilo" se refiere a un hidrocarburo alifático saturado que incluye grupos de cadena recta o ramificada. Preferiblemente, el grupo alquilo tiene 1 hasta 20 átomos de carbono (cada vez que un rango numérico; por ejemplo, "1-20", se establece en la

presente, significa que el grupo, en este caso el grupo alquilo puede contener 1 átomo de carbono, 2 átomos de carbono, 3 átomos de carbono, etc. hasta e incluyendo 20 átomos de carbono). Más preferiblemente, es un alquilo de tamaño medio que tiene 1 a 10 átomos de carbono. Más preferiblemente, es un alquilo inferior que tiene 1 a 4 átomos de carbono. El grupo alquilo puede estar substituido o no substituido. Cuando se substituye, los grupos substituyentes son preferiblemente uno o más individualmente seleccionados de trihaloalquilo, cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tiohidroxi, tioalcoxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halo, nitro, carbonilo, tiocarbonilo, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo, y combinados, un anillo heteroalicíclico de cinco o seis miembros.

Un grupo "cicloalquilo" se refiere a todos los grupos de anillo monocíclico o fusionado de carbono (esto es, anillos que portan un par adyacente de átomos de carbono) en donde uno o más anillos no tienen un sistema de electrón pi completamente conjugado. Los

ejemplos, sin limitación, de grupos cicloalquilo son ciclopropano, ciclobutano, ciclopentano, ciclopenteno, ciclohexano, ciclohexadieno, cicloheptano, cicloheptatrieno y adamantano. Un grupo cicloalquilo puede estar substituido o no substituido. Cuando se substituye, los grupos substituyentes preferiblemente son uno o más individualmente seleccionados de alquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tiohidroxi, tioalcoxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halo, nitro, carbonilo, tiocarbonilo, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo, sililo, guanilo, guanidino, ureido, fosfonilo, amino y $-NR^xR^y$ con R^x y R^y como se define arriba.

Un grupo "alquenilo" se refiere a un grupo alquilo, como se define en la presente, que consiste de al menos dos átomos de carbono y al menos un enlace doble carbono-carbono.

Un grupo "alquinilo" se refiere a un grupo alquilo, como se define en la presente, que consiste de al menos dos átomos de carbono y al menos un enlace triple carbono-carbono.

Un grupo "hidroxi" se refiere a un grupo -OH.

Un grupo "alcoxi" se refiere a tanto un grupo -O-alquilo y -O-cicloalquilo como se define en la presente.

Un grupo "ariloxi" se refiere a tanto un grupo -O-arilo y -O-heteroarilo, como se define en la presente.

Un grupo "heteroariloxi" se refiere a un grupo heteroaril-O- con heteroarilo como se define en la presente.

Un grupo "heteroalicicloxi" se refiere a un grupo heteroalicíclico-O- con heteroalicíclico como se define en la presente.

Un grupo "tiohidroxi" se refiere a un grupo -SH.

Un grupo "tioalcoxi" se refiere a un grupo S-alquilo y -S-cicloalquilo, como se define en la presente.

Un grupo "tioariloxi" se refiere a un grupo -S-arilo y -S-heteroarilo, como se define en la presente.

Un grupo "tioheteroariloxi" se refiere a un grupo heteroaril-S- con heteroarilo como se define en la presente.

Un grupo "tioheteroalicicloxi" se refiere a un grupo heteroalicíclico-S- con heteroalicíclico como se define en la presente.

Un grupo "carbonilo" se refiere a un grupo -C(=O)-R", donde R" se selecciona del grupo que consiste de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo (enlazado a través de un anillo de carbono) y heteroalicíclico (enlazado a través de un anillo de carbono), como cada uno se define en la presente.

Un grupo "aldehído" se refiere a un grupo carbonilo

donde R" es hidrógeno.

Un grupo "tiocarbonilo" se refiere a un grupo -C(=S)-R", con R" como se define en la presente.

Un grupo "ceto" se refiere a un grupo -CC(=O)C-, en donde el carbono en cualesquiera o ambos lados del C=O puede ser alquilo, cicloalquilo, arilo o un carbono de un grupo heteroarilo o heteroaliacíclico.

Un grupo "trihalometancarbonilo" se refiere a un grupo $Z_3CC(=O)$- con el Z siendo un halógeno.

Un grupo "C-carboxi" se refiere a grupos -C(=O)O-R", con R" como se define en la presente.

Un grupo "O-carboxi" se refiere a un grupo R"C(-O)O-, con R" como se define en la presente.

Un grupo "ácido carboxílico" se refiere a un grupo C-carboxi en el cual R" es hidrógeno.

Un grupo "trihalometilo" se refiere a un grupo $-CZ_3$, en donde Z es un grupo halógeno como se define en la presente.

Un grupo "trihalometansulfonilo" se refiere a grupos $Z_3CS(=O)_2$- con Z como se define arriba.

Un grupo "trihalometansulfonamido" se refiere a un grupo $Z_3CS(=O)_2NR^X$- con Z y R^X como se define en la presente.

Un grupo "sulfinilo" se refiere a un grupo -S(=O)-R", con R" como se define en la presente y, además, sólo como un enlace; esto es, -S(O)-.

Un grupo "sulfonilo" se refiere a un grupo $-S(=O)_2R"$ con R" como se define en la presente y, además sólo como un enlace; esto es, $-S(O)_2-$.

Un grupo "S-sulfonamido" se refiere a un $-S(=O)_2NR^XR^Y$, con R^X y R^Y como se define en la presente.

Un grupo "N-Sulfonamido" se refiere a un grupo $R"S(=O)_2NR_X-$ con R_X como se define en la presente.

Un grupo "O-carbamilo" se refiere a $-OC(=O)NR^XR^Y$ como se define en la presente.

Un grupo "N-carbamilo" se refiere a un grupo $R^XOC(=O)NR^Y$, con R^X y R^Y como se define en la presente.

Un grupo "O-tiocarbamilo" se refiere a un grupo $-OC(=S)NR^XR^Y$ con R^X y R^Y como se define en la presente.

Un grupo "N-tiocarbamilo" se refiere a un grupo $R^XOC(=S)NR^Y-$ con R^X y R^Y como se define en la presente.

Un grupo "amino" se refiere a un grupo $-NH_2$.

Un grupo "C-amido" se refiere a un grupo $-C(=O)NR^XR^Y$ con R^X y R^Y como se define en la presente.

Un grupo "C-tioamido" se refiere a un grupo $-C(=S)NR^XR^Y$, con R^X y R^Y como se define en la presente.

Un grupo "N-amido" se refiere a un grupo $R^XC(=O)NR^Y-$, con R^X y R^Y como se define en la presente.

Una N-lactama de anillo cíclico de 4, 5 ó 6 miembros se refiere a anillos de 4, 5 ó átomos que contiene un grupo amida simple cómo dos de los átomos en el anillo el

cual se enlaza para la molécula de origen al nitrógeno de amida.

Un grupo "ureido" se refiere a un grupo -$NR^xC(=O)NR^yR^{y2}$ con R^x y R^y como se define en la presente y R^{y2} define el mismo como R^x y R^y.

Un grupo "guanidino" se refiere a un grupo -$R^xNC(=N)NR^yR^{y2}$, con R^x, R^y y R^{y2} como se define en la presente.

Un grupo "guanilo" se refiere a un grupo $R^xR^yNC(=N)$-, con R^x y R^y como se define en la presente.

Un grupo "ciano" se refiere a un grupo -CN.

Un grupo "sililo" se refiere a $-Si(R'')_3$, con R'' como se define en la presente.

Un grupo "fosfonilo" se refiere a $P(=O)(OR^x)_2$ con R^x como se define en la presente.

Un grupo "hidrazino" se refiere a un grupo $-NR^xNR^yR^{y2}$ con R^x, R^y y R^{y2} como se define en la presente.

Cualesquiera de dos grupos R adyacentes pueden combinarse para formar un anillo arilo, cicloalquilo, heteroarilo o heterocíclico adicional fusionado al anillo que porta inicialmente aquellos grupos R.

Se conoce en el arte que los átomos de nitrógeno en los sistemas de heteroarilo pueden "participar en el enlace doble del anillo heteroarilo", y se refiere a la forma de enlaces dobles en las dos estructuras

tautoméricas que comprenden grupos heteroarilo de anillo de cinco miembros. Esto dictamina si los nitrógenos pueden substituirse como se entienden por los químicos en la técnica. La descripción y reivindicaciones de la presente invención se basan en el principio general conocido del enlace químico. Se entenderá que las reivindicaciones no abarcan estructuras conocidas por ser inestables o no capaces de existir con base en la literatura.

Las sales fisiológicamente aceptables y profármacos de los compuestos descritos en la presente, están dentro del alcance de esta invención. El término "sal farmacéuticamente aceptable" como se usa en la presente y en las reivindicaciones, se pretende que incluya sales de adición base no tóxicas. Las sales apropiadas incluyen aquellas derivadas de ácidos orgánicos e inorgánicos tales como, sin limitación, ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico, ácido metansulfónico, ácido acético, ácido tartárico, ácido láctico, ácido sulfínico, ácido cítrico, ácido maleico, ácido fumárico, ácido sórbico, ácido aconítico, ácido salicílico, ácido ftálico, y similares. El término "sal farmacéuticamente aceptable", como se usa en la presente, también se pretende que incluya sales de grupos ácidos, tal como

un carboxilato, con contraiones tales como amonio, sales de metal alcalino, particularmente sodio o potasio, sales de metal alcalinotérreo, particularmente calcio o magnesio, y sales con bases orgánicas apropiadas, tales como alquilaminas inferiores (metilamina, etilamina, ciclohexilamina, y similares) o con alquilaminas inferiores substituidas (por ejemplo, alquilamina substituidas con hidroxilo tales como dietanolamina, trietanolamina o tris(hidroximetil)-aminometano), o con bases tales como piperidina o morfolina.

En el método de la presente invención, el término "cantidad efectiva antiviral" significa la cantidad total de cada componente activo del método que es suficiente para mostrar un significativo beneficio del paciente, esto es, sanar las condiciones agudas caracterizadas por la inhibición de la infección del VIH. Cuando se aplica a un ingrediente activo individual, administrado solo, el término se refiere al ingrediente solamente. Cuando se aplica a una combinación, el término se refiere a cantidades combinadas de los ingredientes activos que resultan en un efecto terapéutico, si se administran en combinación, en serie o simultáneamente. Los términos "tratar, tratado, tratamientos" como se usa en la

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presente y en las reivindicaciones, significa prevenir o aliviar enfermedades asociadas con la infección del VIH.

La presente invención también se dirige a combinaciones de los compuestos con uno o más agentes útiles en el tratamiento del SIDA. Por ejemplo, los compuestos de esta invención pueden administrarse efectivamente, a periodos de pre-exposición y/o post-exposición, en combinación con cantidades efectivas de antivirales de SIDA, inmunomoduladores, antiinfecciones o vacunas, tales como aquellas en la siguiente tabla.

ANTIVIRALES

Nombre del Fármaco	Fabricante	Indicación
097	Hoechst/Bayer	infección por VIH, SIDA, ARC (inhibidor de la transcriptasa inversa (RT) no de nucleósido)
Amprenivir 141 W94 GW 141	Glaxo Wellcome	Infección por VIH SIDA, ARC (inhibidor de la proteasa)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	Infección por VIH, SIDA, ARC (inhibidor de RT)

Nombre del Fármaco	Fabricante	Indicación
Acemannan	Carrington Labs (Irving, TX)	ARC
Acylovir	Burroughs Wellcome	Infección por VIH, SIDA, ARC, en combinación con AZT
AD-439	Tanox Biosystems	Infección por VIH, SIDA, ARC
AD-519	Tanox Biosystems	Infección por VIH, SIDA, ARC
Adefovir dipivoxil	Gilead Sciences	Infección por VIH,
Al-721	Ethigen (Los Angeles, CA)	ARC, PGL, VIH positivo, SIDA
Alfa interferón	Glaxo Wellcome	Sarcoma de Kaposi, VIH en combinación c/Retrovir
Ansamicin LM 427	Adria Laboratories (Dublín, OH) Erbamont (Stamford, CT)	ARC
Anticuerpo que neutraliza el pH Alfa interferón inestable aberrante	Advance Biotherapy Concepts (Rockville, MD)	SIDA, ARC

Nombre del Fármaco	Fabricante	Indicación
AR177	Aronex Pharm	Infección por VIH, SIDA, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	Enfermedades asociadas con el SIDA
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/Novartis	Infección por VIH, SIDA, ARC (inhibidor de la proteasa)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/Novartis	Infección por VIH, SIDA, ARC (inhibidor de la proteasa)
CI-1012	Warner-Lambert	Infección por VIH-1
Cidofovir	Gilead Science	CMV retinitis, herpes, papilomavirus
Sulfato de curdlan	AJI Pharma USA	Infección por VIH
Citomegalovirus inmuno globina	MedImmune	Retinitis CMV
Cytovene	Syntex	Amenaza a la visión CMV
Ganciclovir		Retinitis CMV periférica

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Nombre del Fármaco	Fabricante	Indicación
Delaviridina	Pharmacia-Upjohn	Infección por VIH, SIDA, ARC (inhibidor RT)
Sulfato de dextrano	Ueno Fine Chem. Ind. Ltd (Osaka, Japón)	SIDA, ARC, VIH asintomático positivo
ddC Didesoxicitidina	Hoffman-La Roche	Infección por VIH, SIDA, ARC
ddI Didesoxiinosina	Bristol-Myers Squibb	Infección por VIH, SIDA, ARC; combinación con AZT/d4T
DMP-450	AVID (Camden, NJ)	Infección por VIH, SIDA, ARC (inhibidor de la proteasa)
Efavirenz (DMP 266) (-)6-cloro-4-(S)-ciclopropiletinil-4(S)-trifluoro-metil-1,4,-dihidro-2H-3,1-benzoxazin-2-ona, STOCRINE	DuPont Merck	Infección por VIH, SIDA, ARC (inhibidor RT no de nucleósido)

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Nombre del Fármaco	Fabricante	Indicación
EL10	Elan Corp, PLC (Gainesville, GA)	Infección por VIH
Famciclovir	Smith Kline	Herpes zoster, Herpes simplex
FTC	Emory University	Infección por VIH, SIDA, ARC (inhibidor de la transcriptasa inversa)
GS 840	Gilead	Infección por VIH, SIDA, ARC (inhibidor de la transcriptasa inversa)
HBY097	Hoechst Marion Roussel	Infección por VIH, SIDA, ARC (inhibidor de la transcriptasa inversa no de nucleósido)
Hypericin	VIMRx Pharm.	Infección por VIH, SIDA, ARC

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Nombre del Fármaco	Fabricante	Indicación
Beta Interferón Humano Recombinante	Triton Biosciences (Almeda, CA)	SIDA, sarcoma de Kaposi, ARC
Interferón alfa-n3	Interferon Sciences	ARC, SIDA
Indinavir	Merck	Infección por VIH, SIDA, ARC, VIH positivo asintomático, también en combinación con AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	Retinitis CMV
KNI-272	Natl Cancer Institute	Enfermedades asociadas con VIH
Lamivudina, 3TC	Glaxo Wellcome	Infección por VIH, SIDA, ARC (inhibidor de la transcriptasa inversa); también con AZT
Lobucavir	Bristol-Myers Squibb	Infección CMV

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Nombre del Fármaco	Fabricante	Indicación
Nelfinavir	Agouron Pharmaceuticals	Infección por VIH, SIDA, ARC (inhibidor de la proteasa)
Nevirapina	Boeheringer Ingleheim	Infección VIH, SIDA, ARC (inhibidor RT)
Novapren	Novaferon Labs, Inc. (Akron, OH)	Inhibidor del VIH
Secuencia del octapéptido del péptido T	Peninsula Labs (Belmont, CA)	SIDA
Fosfonoformiato de trisodio	Astra Pharm. Products, Inc.	Retinitis CMV, infección por VIH, otras infecciones de CMV
PNU-140690	Pharmacia-Upjohn	Infección por VIH, SIDA, ARC (inhibidor de la proteasa)
Probucol	Vyrex	Infección por VIH, SIDA
RBC-CD4	Sheffield Med Tech (Houston, TX)	Infección por VIH, SIDA, ARC

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Nombre del Fármaco	Fabricante	Indicación
Ritonavir	Abbott	Infección por VIH, SIDA, ARC (inhibidor de la proteasa)
Saquinavir	Hoffman-La Roche	Infección por VIH, SIDA, ARC (inhibidor de la proteasa)
Estavudina, d4T dideshidrodesoxi timidina	Bristol-Myers Squibb	Infección por VIH, SIDA, ARC
Valaciclovir	Glaxo Wellcome	Infecciones HSV y CMV genital
Virazol Ribavirin	Viratek/ICN (Costa Mesa, CA)	VIH positivo asintomático, LAS, ARC
VX-478	Vertex	Infección por VIH, SIDA, ARC
Zalcitabina	Hoffman-La Roche	Infección por VIH, SIDA, ARC, con AZT

Nombre del Fármaco	Fabricante	Indicación
Zidovudina; AZT	Glaxo Wellcome	Infección por VIH, SIDA, ARC, sarcoma de Kaposi, en combinación con otras terapias
Sal de fumarato Tenofovir disoproxil (Viread®)	Gilead	Infección por VIH, SIDA, (inhibidor transcriptasa reversa)
Combivir®	GSK	Infección por VIH, SIDA, (inhibidor transcriptasa reversa)
Succinato abacavir (o Ziagen®)	GSK	Infección por VIH, SIDA, (inhibidor transcriptasa reversa)
Reyataz® (o atazanavir)	Bristol-Myers Squibb	Infección por VIH, SIDA, (inhibidor transcriptasa reversa)
Fuzeon® (o T-20)	Roche/Trimeris	Infección por VIH, SIDA, (inhibidor transcriptasa reversa)

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INMUNOMODULADORES

Nombre del Fármaco	Fabricante	Indicación
AS-101	Wyeth-Ayerst	SIDA
Bropirimina	Pharmacia-Upjohn	SIDA avanzado,
Acemannan	Carrington Labs, Inc. (Irving, TX)	SIDA, ARC
CL246,738	American Cyanamid Lederle Labs	SIDA, sarcoma de Kaposi
EL10	Elan Corp, PLC (Gainesville, GA)	Infección por VIH
FP-21399	Fuki ImmunoPharm	Bloqueo de fusión del VIH con células CD4+
Gamma Interferón	Genentech	ARC, en combinación con w/TNF (factor de necrosis de tumor)
Granulocito Factor estimulante de la colonia de macrófagos	Genetics Institute Sandoz	SIDA

Nombre del Fármaco	Fabricante	Indicación
Granulocito Factor estimulante de la colonia de macrófagos	Hoechst-Roussel Immunex	SIDA
Granulocito Factor estimulante de la colonia de macrófago	Schering-Plough	SIDA, combinación con w/AZT
Inmunoestimulante de la partícula de núcleo de VIH	Rorer	VIH seropositivo
IL-2 Interleucina-2	Cetus	SIDA, en combinación con AZT
IL-2 Interleucina-2	Hoffman-La Roche Immunex	SIDA, ARC, VIH, en combinación con AZT
IL-2 Interleucina-2 (aldeslucina)	Chiron	SIDA, incremento en cuentas de células CD4
Inmuno globulina intravenosa (humana)	Cutter Biological (Berkeley, CA)	SIDA pediátrico, en combinación con AZT
IMREG-1	Imreg (New Orleans, LA)	SIDA, sarcoma de Kaposi, ARC. PGL

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Nombre del Fármaco	Fabricante	Indicación
IMREG-2	Imreg (New Orleans, LA)	SIDA, sarcoma de Kaposi, ARC. PGL
Inmutiol dietil ditio carbamato	Merieux Institute	SIDA, ARC
Alfa-2 Interferon	Schering Plough	Sarcoma de Kaposi con AZT, SIDA
Metionina-encefalina	TNI Pharmaceutical (Chicago, IL)	SIDA, ARC
MTP-PE	Ciba-Geigy Corp.	Sarcoma de Kaposi
Muramil-tripéptido	Amgen	SIDA, en combinación con AZT
Factor estimulante de la colonia de granulocitos		
Remune	Immune Response Corp.	Inmunoterapéutico
rCD4	Genentech	SIDA, ARC
CD4 humano soluble recombinante		
Híbridos rCD4-IgG		SIDA, ARC
CD4 humano soluble recombinante	Biogen	SIDA, ARC
Interferón alfa 2a	Hoffman-La Roche	Sarcoma de Kaposi, SIDA, ARC, en combinación con AZT

Nombre del Fármaco	Fabricante	Indicación
SK&F106528 T4 soluble	Smith Kline	Infección por VIH
Timopentina	Immunobiology Research Institute (Annandale, NJ)	Infección por VIH
Factor de Necrosis de Tumor; TNF	Genentech	ARC, en combinación con gamma interferón

ANTI-INFECCIOSOS

Nombre del Fármaco	Fabricante	Indicación
Clindamicina con Primaquina	Pharmacia-Upjohn	PCP
Fluconazol	Pfizer	Meningitis criptococal, candidiasis
Pastille, Nystatin Pastille	Squibb Corp.	Prevención de candidiasis oral
Ornidil eflornitina	Merrell Dow	PCP

Nombre del Fármaco	Fabricante	Indicación
Pentamidina Isetionato (IM y IV)	LyphoMed (Rosemont, IL)	Tratamiento del PCP
Trimetoprim		Antibacterial
Trimetoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	Tratamiento del PCP
Pentamidina Isetionato para Inhalación	Fisons Corporation	Profilaxis de PCP
Espiramicina	Rhone-Poulenc diarrea	Criptosporidial
Intraconazol-R5I211	Janssen-Pharm.	Histoplasmosis; meningitis criptococal
Trimetrexato	Warner-Lambert	PCP
Daunorrubicina	NeXstar, Sequus	Sarcoma de Kaposi
Eritropoyetina humana recombinante	Ortho Pharm. Corp.	Anemia severa asociada con terapia de AZT
Hormona de crecimiento humana recombinante	Serono	Desgaste relacionado con el SIDA, caquexia

Nombre del Fármaco	Fabricante	Indicación
Acetato de Megestrol	Bristol-Myers Squibb	Tratamiento de anorexia asociada con SIDA
Testosterona	Alza, Smith Kline	Desgaste relacionado con el SIDA
Nutrición Enteral Total	Norwich Eaton Pharmaceuticals	Diarrea y mala absorción relacionada con SIDA

Adicionalmente, los compuestos de la invención en la presente pueden usarse en combinación con otra clase de agentes para el tratamiento del SIDA, que se llaman inhibidores de la entrada del VIH. Los Ejemplos de tales inhibidores de la entrada del VIH se discuten en DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, Oct. 29, 1999; y DRUG DISCOVERY TODAY, Vol. 5, No. 5, Mayo 2000, pp. 183-194.

Se entenderá que el alcance de las combinaciones de los compuestos de esta invención con antivirales del SIDA, inmunomoduladores, anti-infecciosos, inhibidores de la entrada del VIH o vacunas, no se limita a la lista en la Tabla anterior, pero incluye en principio cualquier combinación con cualesquiera de las composiciones

farmacéuticas útiles para el tratamiento del SIDA.

Las combinaciones preferidas son tratamientos simultáneos o alternativos de los cuales el compuesto de la presente invención y un inhibidor de la proteasa del VIH y/o un inhibidor no de nucleósido de la transcriptasa inversa del VIH. Un cuarto componente opcional en la combinación es un inhibidor de nucleósido de la transcriptasa inversa del VIH, tal como AZT, 3TC, ddC o ddI. Un inhibidor preferido de la proteasa del VIH es indinavir, que es la sal de sulfato de N-(2(R)-hidroxi-1-(S)-indanil)-2(R)-fenilometil-4-(S)-hidroxi-5-(1-(4-(3-piridil-metil)-2(S)-N'-(t-butilcarboxamido)-piperazinil))-pentanamida etanolato, y se sintetiza de conformidad con la E.U.A. 5,413,999. El indinavir generalmente se administra a una dosis de 800 mg tres veces al día. Otros inhibidores de proteasa preferidos son nelfinavir y ritonavir. Otro inhibidor preferido de la proteasa del VIH es saquinavir que se administra en una dosis de 600 o 1200 mg tid. Los inhibidores no de nucleósido preferidos de la transcriptasa inversa del VIH incluyen efavirenz. La preparación de ddC, ddI y AZT también se describe en EPO 0,484,071. Estas combinaciones pueden tener efectos inesperados en la limitación del espectro y grado de infección del VIH. Las combinaciones preferidas incluyen aquellas con las siguientes (1) indinavir con efavirenz, y opcionalmente, AZT y/o 3TC y/o ddI y/o ddC; (2) indinavir, y cualesquiera de AZT y/o ddI y/o ddC y/o 3TC, en particular, indinavir y AZT y 3TC; (3) estavudina y 3TC y/o zidovudina; (4) zidovudina y lamivudina y

141W94 y 1592U89; (5) zidovudina y lamivudina.

En tales combinaciones, los compuestos de la presente invención y otros agentes activos pueden administrarse separadamente o en conjunto. Además, la administración de un elemento puede ser antes de, junto con, o posterior a la administración de otros agentes.

Los procedimiento preparativos y actividad anti-VIH-1 de los análogos de diamina de piperazina de azaindol novedosos de la fórmula I son resumidos a continuación en los esquemas de reacción 1-64.

Abreviaturas

Las siguientes abreviaturas, la mayoría de las cuales son abreviaturas convencionales bien conocidas por aquellos expertos en la técnica, se usan a través de la descripción de la invención y los ejemplos. Algunas de estas abreviaturas usadas son como siguen:

h	=	hora(s)
ta	=	temperatura ambiente
mol	=	mol(es)
mmol	=	milimol(es)
g	=	gramo(s)
mg	=	miligramo(s)
mL	=	mililitro(s)
TFA	=	ácido trifluoroacético

DCE = 1,2-Dicloroetano

CH_2Cl_2= Diclorometano.

TPAP = tetrapropilamonio perrutenato

THF = Tetrahidrofurano

DEPBT= 3-(Dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona

DMAP = 4-dimetilaminopiridina

P-EDC= polímero soportado en 1-(3-dimetilaminopropil)-3-etilcarbodiimida

EDC = 1-(3-dimetilaminopropil)-3-etilcarbodiimida

DMF = N,N-dimetilformamida

Base Hunig= N,N-Diisopropiletilamina

mCPBA = ácido meta-cloroperbenzoico

azaindol = 1H-Pirrolo-piridina

4-azaindol= 1H-pirrolo[3,2-b]piridina

5-azaindol= 1H-Pirrolo[3,2-c]piridina

6-azaindol= 1H-pirrolo[2,3-c]piridina

7-azaindol= 1H-Pirrolo[2,3-b]piridina

PMB = 4-Metoxibencilo

DDQ = 2,3-Dicloro-5,6-diciano-1,4-benzoquinona

OTf = Trifluorometansulfonoxi

NMM = 4-Metilmorfolina

PIP-COPh= 1'-Benzoilpiperazina

NaHMDS= hexametildisilazida de sodio

EDAC = 1-(3-Dimetilaminopropil)-3-etilcarbodiimida

TMS = Trimetilsililo

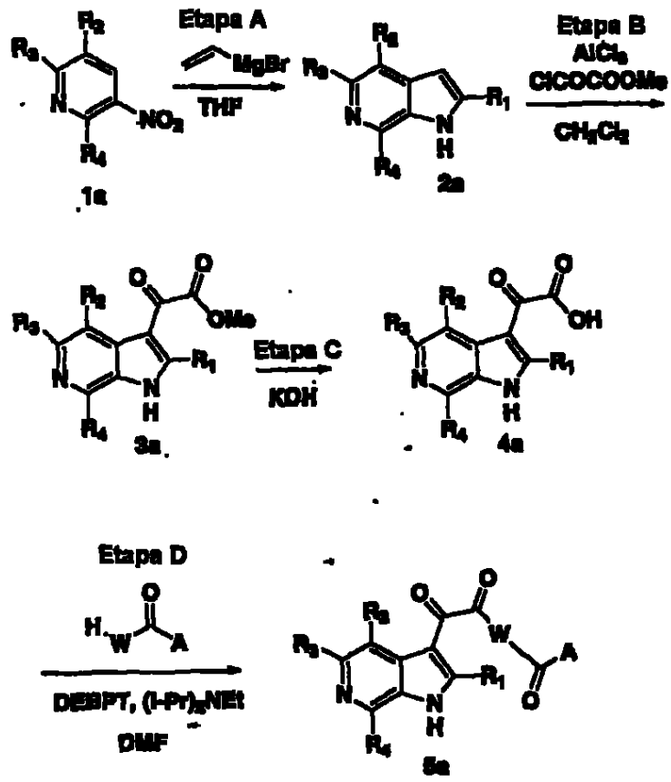
DCM	=	Diclorometano
DCE	=	Dicloroetano
MeOH	=	Metanol
THF	=	Tetrahidrofurano
EtOAc	=	Acetato de etilo
LDA	=	Diisopropilamida de litio
TMP-Li	=	2,2,6,6-tetrametilpiperidinil litio
DME	=	Dimetoxietano
DIBALH	=	hidruro de diisobutilaluminio
HOBT	=	1-hidroxibenzotriazol
CBZ	=	Benciloxicarbonilo
PCC	=	clorocromato de piridinio
Me	=	Metilo
Ph	=	Fenilo

Química

La presente invención comprende compuestos de la Fórmula I, sus fórmulaciones farmacéuticas, y su uso en pacientes que padecen de, o son susceptibles a, una infección por VIH. Los compuestos de la Fórmula I incluyen sales farmacéuticamente aceptables de los mismos.

Los procedimiento generales para construir diaminas substituidas de azaindol piperazina de la fórmula I e intermediarios útiles para su síntesis se describen en los siguientes esquemas de reacción, 1-81.

Esquema de reacción 1



La etapa A en el Esquema de reacción 1 describe la síntesis de un intermediario de aza indol, 2a, por medio de la reacción de Bartoli bien conocida en la cual el bromuro de vinil magnesio se hace reaccionar con un grupo nitro arilo o heteroarilo, tal como en 1, para formar un anillo que contiene nitrógeno de cinco miembros como se muestra. Algunas de las referencias para la transformación anterior incluyen: Bartoli et al. a) Tetrahedron Lett. 1989, 30, 2129. b) J. Chem. Soc. Perkin Trans. 1 1991,2757. c) J. Chem. Soc. Perkin Trans. II 1991, 657. d) SynLett (1999), 1594. En el

procedimiento preferido, una solución de bromuro de vinil magnesio en THF (típicamente 1.0M pero desde 0.25 hasta 3.0M) se agrega gota a gota a una solución de la nitro piridina en THF a -78° bajo una atmósfera inerte ya sea de nitrógeno o Argón. Después de que la adición se completó, la temperatura de reacción se permitió que se entibiara hasta -20° y luego se agitó por aproximadamente 12h antes de apagar con solución de cloruro de amonio acuosa al 20%. La reacción se extrajo con acetato de etilo y luego se trabajó en una manera típica usando un agente de secado tal como sulfato de magnesio o sulfato de sodio anhidro. Los productos se purifican generalmente usando cromatografía sobre gel de Sílice. Los mejores resultados se alcanzan generalmente usando bromuro de vinil magnesio recientemente preparado. En algunos casos, el cloruro de vinil magnesio puede substituirse por bromuro de vinil magnesio.

Los azaindoles substituidos pueden prepararse por métodos descritos en la literatura o pueden estar disponibles de fuentes comerciales. De esta manera, hay muchos métodos para llevar a cabo la etapa A en la literatura y los ejemplos específicos son muy numerosos para enlistarse. La síntesis alternativa de azaindoles y métodos generales para llevar a cabo la etapa A incluyen, pero no se limitan a, aquellos descritos en las siguientes referencias (a-k abajo): a) Prokopov, A. A.; Yakhontov, L. N. Khim.-Farm. Zh. 1994,

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28(7), 30-51; b) Lablache-Combier, A. Heteroaromatics. Photoinduced Electron Transfer 1988, Pt. C, 134-312; c) Saify, Zafar Said. Pak. J. Pharmacol. 1986, 2(2), 43-6; d) Bisagni, E. Jerusalem Symp. Quantum Chem. Biochem. 1972, 4, 439-45; e) Yakhontov, L. N. Usp. Khim. 1968, 37(7), 1258-87; f) Willette, R. E. Advan. Heterocycl. Chem. 1968, 9, 27-105; g) Mahadevan, I.; Rasmussen, M. Tetrahedron 1993, 49(33), 7337-52; h) Mahadevan, I.; Rasmussen, M. J. Heterocycl. Chem. 1992, 29(2), 359-67; i) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. J. Org. Chem. 1999, 64(26), 9430-9443; j) Spivey, A.C.; Fekner, T.; Adams, H. Tetrahedron Lett. 1998, 39(48), 8919-8922; k) Advances in Heterocyclic Chemistry (Academic press) 1991, Vol. 52, pg 235-236 y referencias en la presente.

Etapa B. El intermediario 3a puede prepararse por la reacción de aza-indol, el intermediario 2a, con un exceso de ClCOCOOMe en presencia de $AlCl_3$ (cloruro de aluminio) (Sycheva et al, Ref. 26, Sycheva, T. V.; Rubtsov, N. M.; Sheinker, Yu. N.; Yakhontov, L. N. Some reactions of 5-cyano-6-cloro-7-azaindoles and lactam-lactim tautomerism in 5-cyano-6-hidroxi-7-azaindolines. Khim. Geterotsikl. Soedin., 1987,100-106). Típicamente, un solvente inerte tal como CH_2Cl_2 se usa, pero otros tales como THF, Et_2O, DCE, dioxano, benceno, o tolueno pueden encontrar aplicabilidad ya sea solos o en mezclas. Otros ésteres de oxalato tales como mono ésteres de etilo o bencilo

de ácido oxálico también podrá ser suficiente para cualquier método mostrado arriba. Los ésteres lipofílicos son más fáciles de aislar durante las extracciones acuosas. Los ésteres fenólicos o fenólicos substituidos (tal como pentafluorofenol) son capaces de acoplarse directamente al grupo HW(C=O)A, tal como una piperazina, en la etapa D sin activación. Los catalizadores de ácido Lewis, tal como tetracloruro de estaño, cloruro de titanio IV, y cloruro de aluminio se emplean en la Etapa B con cloruro de aluminio siendo el más preferido. Alternativamente, el azaindol se trata con un reactivo Grignard tal como MeMgI (yoduro de metil magnesio), bromuro de metil magnesio o bromuro de etil magnesio y un haluro de zinc, tal como $ZnCl_2$ (cloruro de zinc) o bromuro de zinc, seguido por la adición de un mono éster de cloruro de oxalilo, tal como ClCOCOOMe (clorooxoacetato de metilo) u otro éster como arriba, para proporcionar el éster glioxilo aza-indol (Shadrina et al, Ref. 25). Se usan los ésteres de ácido oxálico tal como oxalato de metilo, oxalato de etilo o como arriba. Los solventes apróticos tal como CH_2Cl_2, Et_2O, benceno, tolueno, DCE, o similares pueden usarse solos o en combinación para esta secuencia. Además para los mono ésteres de cloruro de oxalilo, el cloruro de oxalilo por sí mismo puede hacerse reaccionar con el azaindol y luego se hace reaccionar además con una amina apropiada, tal como un derivado de piperazina (Ver Esquema de reacción 52, para ejemplo).

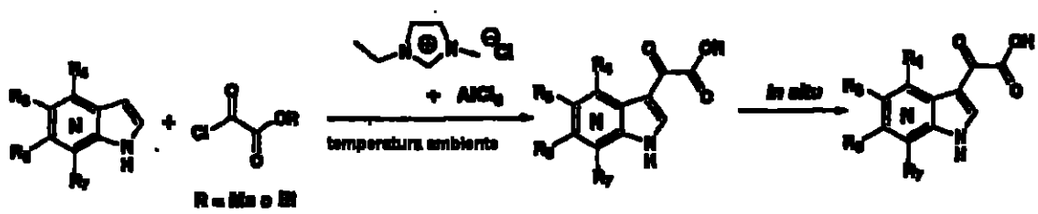
Etapa C. La hidrólisis del éster de metilo, (intermediario 3a, Esquema de reacción 1) proporciona una sal de potasio del intermediario 4a, que se acopla con derivados de piperazina mono-benzoilados como se muestra en la Etapa D del Esquema de reacción 1. Algunas condiciones típicas emplean hidróxido de sodio metanólico o etanólico seguido por acidificación cuidadosa con ácido clorhídrico acuoso de molaridad variable pero se prefiere HCl 1M. La acidificación no se utiliza en muchos casos como se describe arriba para las condiciones preferidas. También podrá emplearse hidróxido de litio o hidróxido de potasio y podrán agregarse cantidades variadas de agua a los alcoholes. Los propanoles o butanoles también podrán usarse como solventes. Pueden utilizarse temperaturas elevadas hasta los puntos de ebullición de los solventes si las temperaturas ambiente no son suficientes. Alternativamente, la hidrólisis puede llevarse a cabo en un solvente no polar tal como CH_2Cl_2 o THF en presencia de Triton B. Las temperaturas de -78°C hasta el punto de ebullición del solvente pueden emplearse, pero se prefiere -10°C. Otras condiciones para la hidrólisis del éster are se enlistan en la referencia 41 y tanto esta referencia y muchas de las condiciones para la hidrólisis del éster son bien conocidas para el químico de experiencia promedio en el arte.

Procedimientos alternativos para la etapa B y C:

Cloroaluminato de imidazolio:

Se ha encontrado que el cloroaluminato de 1-alquil-3-alquilimidazolio líquido iónico es generalmente útil para promover la acilación de tipo Friedel-Crafts de indoles y azaindoles. El líquido iónico se genera al mezclar cloruro de 1-alquil-3-alquilimidazolio con cloruro de aluminio a temperatura ambiente con agitación vigorosa. Se prefiere una relación molar de 1:2 ó 1:3 de cloruro de 1-alquil-3-alquilimidazolio al cloruro de aluminio. Un cloroaluminato de imidazolio particular útil para la acilación de azaindol con clorooxoacetato de metilo o etilo es el cloroaluminato de 1-etil-3-metilimidazolio. La reacción se realiza típicamente a temperatura ambiente y el éster de azaindolglioxilo puede aislarse. Más convenientemente, se ha encontrado que el éster de glioxilo puede hidrolizarse in situ a temperatura ambiente en un tiempo de reacción prolongado (típicamente durante la noche) para dar el correspondiente ácido glioxilo para formación de amida (Esquema de reacción 1).

Esquema de reacción 1

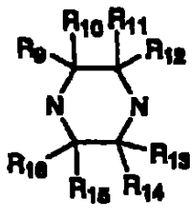


Un procedimiento experimental representativo es como sigue: el cloruro de 1-etil-3-metilimidazolio (2 equiv.; adquirido de TCI; pesado bajo una corriente de nitrógeno) se agitó en un matraz de fondo redondo secado en horno a temperatura ambiente bajo una atmósfera de nitrógeno, y se agregó cloruro de aluminio (6 equiv.; polvo anhidro empacado bajo argón en ampolletas adquirido de Aldrich preferido; pesado bajo una corriente de nitrógeno). La mezcla se agitó vigorosamente para formar un líquido, al que luego se agregó azaindol (1 equiv.) y se agitó hasta que una mezcla homogénea resultó. La mezcla de reacción se le agregó gota a gota clorooxoacetato de metilo o etilo (2 equiv.) y luego se agitó a t.a. durante 16 h. Después de ese tiempo, la mezcla se enfrió en un baño de agua con hielo y la reacción se apagó al agregar agua en exceso. Los precipitados se filtraron, se lavaron con agua y se secaron bajo alto vacío para dar el ácido azaindolglioxílo. Para algunos ejemplos, 3 equivalentes de cloruro de 1-etil-3-metilimidazolio and clorooxoacetato puede requerirse.

Referencias relacionadas: (1) Welton, T. Chem Rev. 1999, 99, 2071; (2) Surette, J. K. D.; Green, L.; Singer, R. D. Chem. Commun. 1996, 2753; (3) Saleh, R. Y. WO 0015594.

Etapa D. El intermediario ácido, 4a, de la etapa C del Esquema de reacción 1 se acopla con una amina A(C=O)WH preferiblemente en presencia de DEPBT (3-

(dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona) y N,N-diisopropiletilamina, conocida comúnmente como base Hunig, para proporcionar las diamidas de azaindol piperazina. El DEPBT se preparó según el procedimiento de Ref. 28, Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. Organic Lett., 1999, 1, 91-93. Típicamente un solvente inerte tal como DMF o THF se usa, pero otros solventes apróticos podrán usarse. El grupo W como se refiere en la presente es

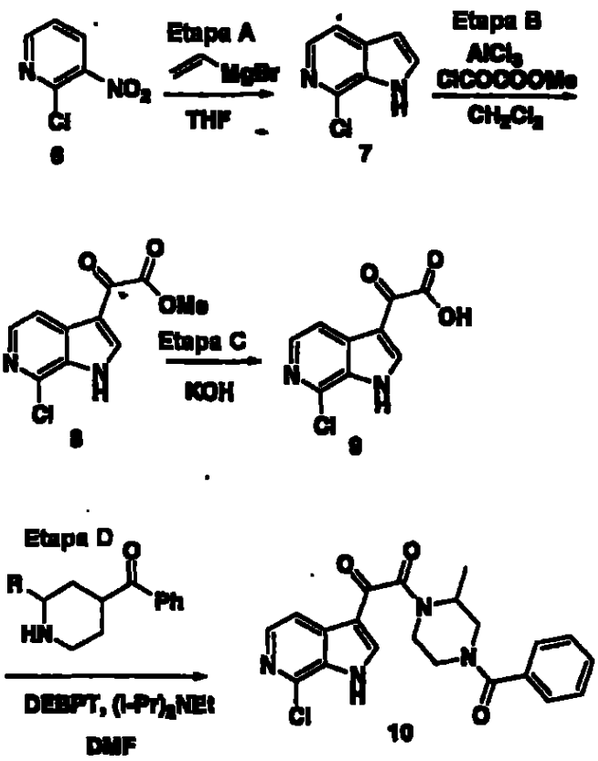


La reacción de construcción del enlace amida podría llevarse a cabo usando las condiciones preferidas descritas arriba, las condiciones EDC descritas abajo, otras condiciones de acoplamiento descritas en esta solicitud, o alternativamente al aplicar las condiciones o reactivos de acoplamiento para construcción de enlace amida descritos después en esta solicitud para construcción de substituyentes R_1-R_4. Algunos ejemplos no limitantes específicos se dan en esta solicitud.

Los derivados de piperazina mono-substituidos pueden prepararse de conformidad con procedimientos bien establecidos tal como aquellos descritos por Desai et al, Ref. 27(a), Adamczyk et al, Ref. 27(b), Rossen et al, Ref. 27(c), y Wang et al, 27(d).

Los procedimientos adicionales para sintetizar, modificar y enlazar grupos (C=O)M-WC(O)-A están contenidos en PCT WO 00/71535.

Esquema de reacción 2



El Esquema de reacción 2 proporciona un ejemplo más específico de las transformaciones previamente descritas en el Esquema de reacción 1. Los intermediarios 6-10 se preparan por las metodologías como se describe por los intermediarios 1a-5a en el Esquema de reacción 1. El Esquema de reacción 2A es otra modalidad de las transformaciones descritas en los Esquemas de reacción 1 y 2. La conversión del fenol al cloruro (Etapa S,

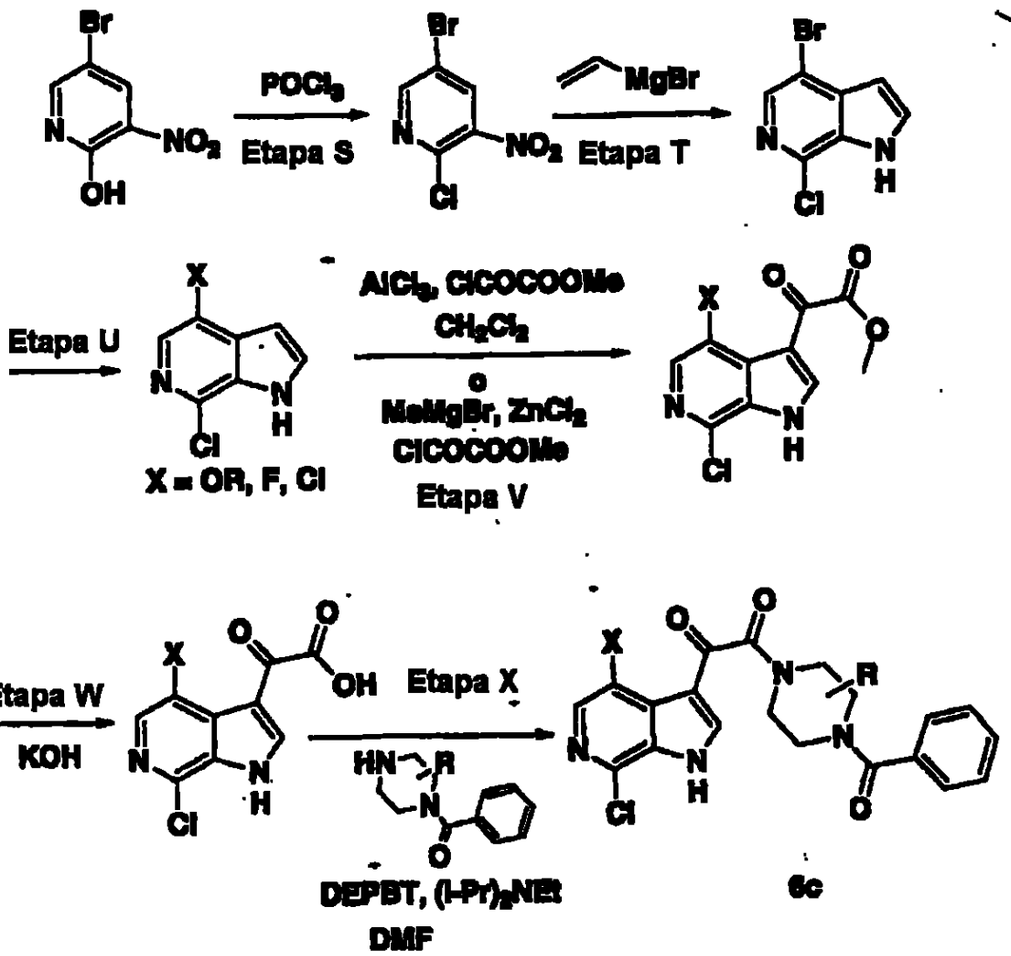
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Esquema de reacción 2A) puede realizarse según los procedimientos descritos en Reimann, E.; Wichmann, P.; Hoefner, G.; Sci. Pharm. 1996, 64(3), 637-646; y Katritzky, A. R.; Rachwal, S.; Smith, T. P.; Steel, P. J.; J. Heterocycl. Chem. 1995, 32 (3), 979-984. La etapa T del Esquema de reacción 2A puede llevarse a cabo como se describe por la Etapa A del Esquema de reacción 1. El intermediario de bromo puede entonces convertirse en intermediarios de alcoxi, cloro, o fluoro como se muestra en la Etapa U del Esquema de reacción 2A. El Esquema de reacción 2A describe el método preferido para preparar el intermediario 6c u otros compuestos cercanamente relacionados que contienen un grupo 4 metoxi en el sistema 6-azaindol. Cuando la etapa U es la conversión del bromuro en derivados alcoxi, la conversión puede llevarse a cabo al hacer reaccionar el bromuro con un exceso de metóxido de sodio en metanol con sales cuprosas, tal como bromuro de cobre I, yoduro de cobre I, y cianuro de cobre I. La temperatura puede llevarse a cabo a temperaturas de entre ambiente y 175° pero más posiblemente serán de alrededor de 115°C o 100°C. La reacción puede correrse en un recipiente a presión o un tubo sellado para prevenir el escape de volátiles tal como metanol. Las condiciones preferidas utilizan 3 equivalentes de metóxido de sodio en metanol, CuBr como el catalizador de reacción (0.2 hasta 3 equivalentes con el preferido siendo 1 eq o menos), y una temperatura de reacción de 115°C. La reacción se lleva a cabo

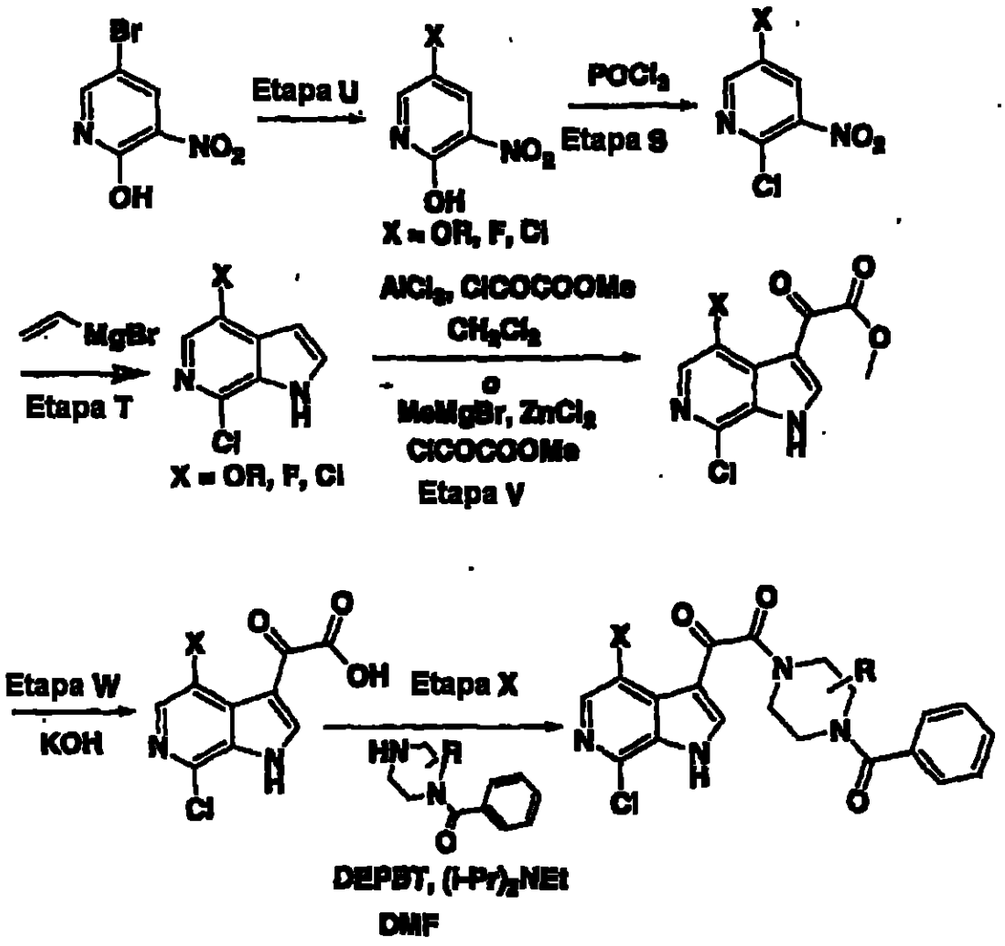
en un tubo sellado o un recipiente de reacción sellado. La conversión del bromuro en derivados de alcoxi también puede llevarse a cabo de acuerdo con los procedimientos descritos en Palucki, M.; Wolfe, J. P.; Buchwald, S. L.; J. Am. Chem. Soc. 1997, 119(14), 3395-3396; Yamato, T.; Komine, M.; Nagano, Y.; Org. Prep. Proc. Int. 1997, 29(3), 300-303; Rychnovsky, S.D.; Hwang, K.; J. Org. Chem. 1994, 59(18), 5414-5418. La conversión del bromuro al derivado fluoro (Etapa U, Esquema de reacción 2A) puede realizarse de conformidad con Antipin, I.S.; Vigalok, A.I.; Konovalov, A.I.; Zh. Org. Khim. 1991, 27(7), 1577-1577; y Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H.; Synlett. 1992, 4, 345-346. La conversión del bromuro al derivado cloro (Etapa U, Esquema de reacción 2A) puede realizarse de acuerdo con los procedimientos descritos en Gilbert, E.J.; Van Vranken, D. L.; J. Am. Chem. Soc. 1996, 118(23), 5500-5501; Mongin, F.; Mongin, O.; Trecourt, F.; Godard, A.; Queguiner, G.; Tetrahedron Lett. 1996, 37(37), 6695-6698; y O'Connor, K.J.; Burrows, C.J.; J. Org. Chem. 1991, 56(3), 1344-1346. Las Etapas V, W y X del Esquema de reacción 2A se llevan a cabo según los procedimientos previamente descritos por las Etapas B, C, y D del Esquema de reacción 1, respectivamente. La Etapas del Esquema de reacción 2A pueden llevarse a cabo en un orden diferente como se muestra en el Esquema de reacción 2B y el Esquema de reacción 2C.

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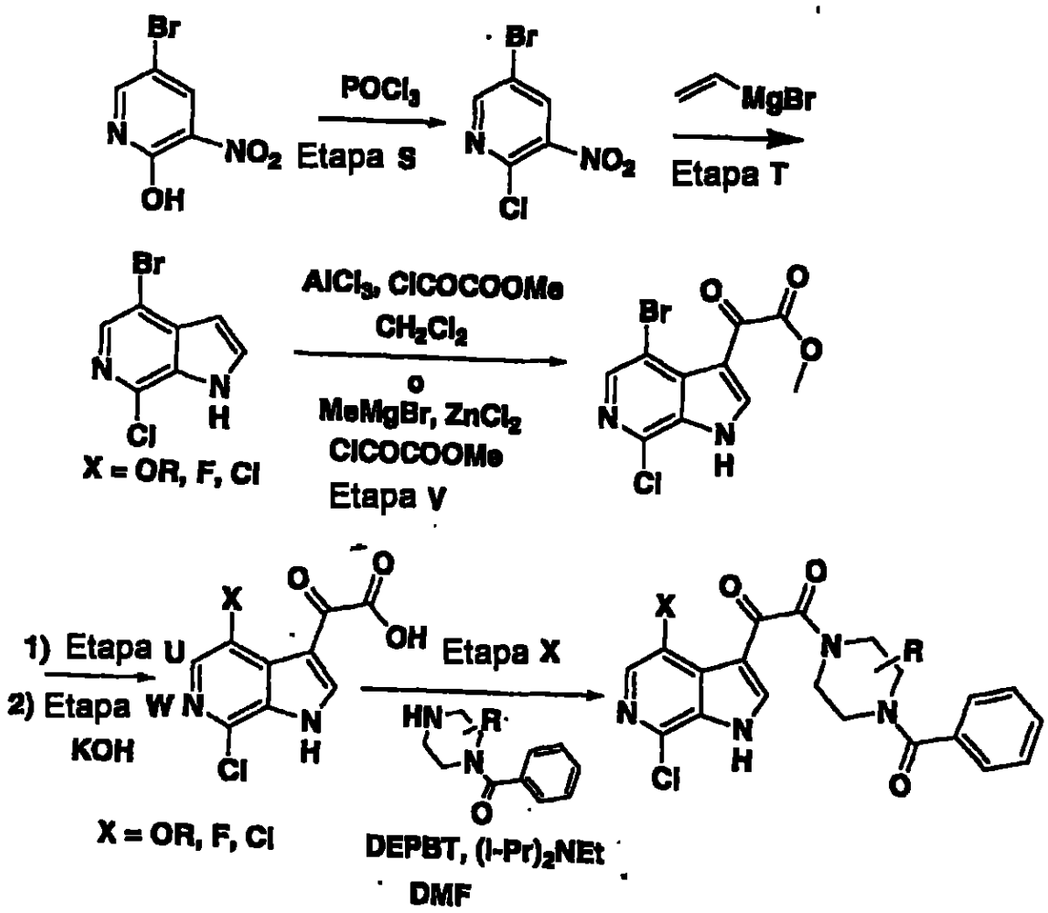
Esquema de reacción 2A



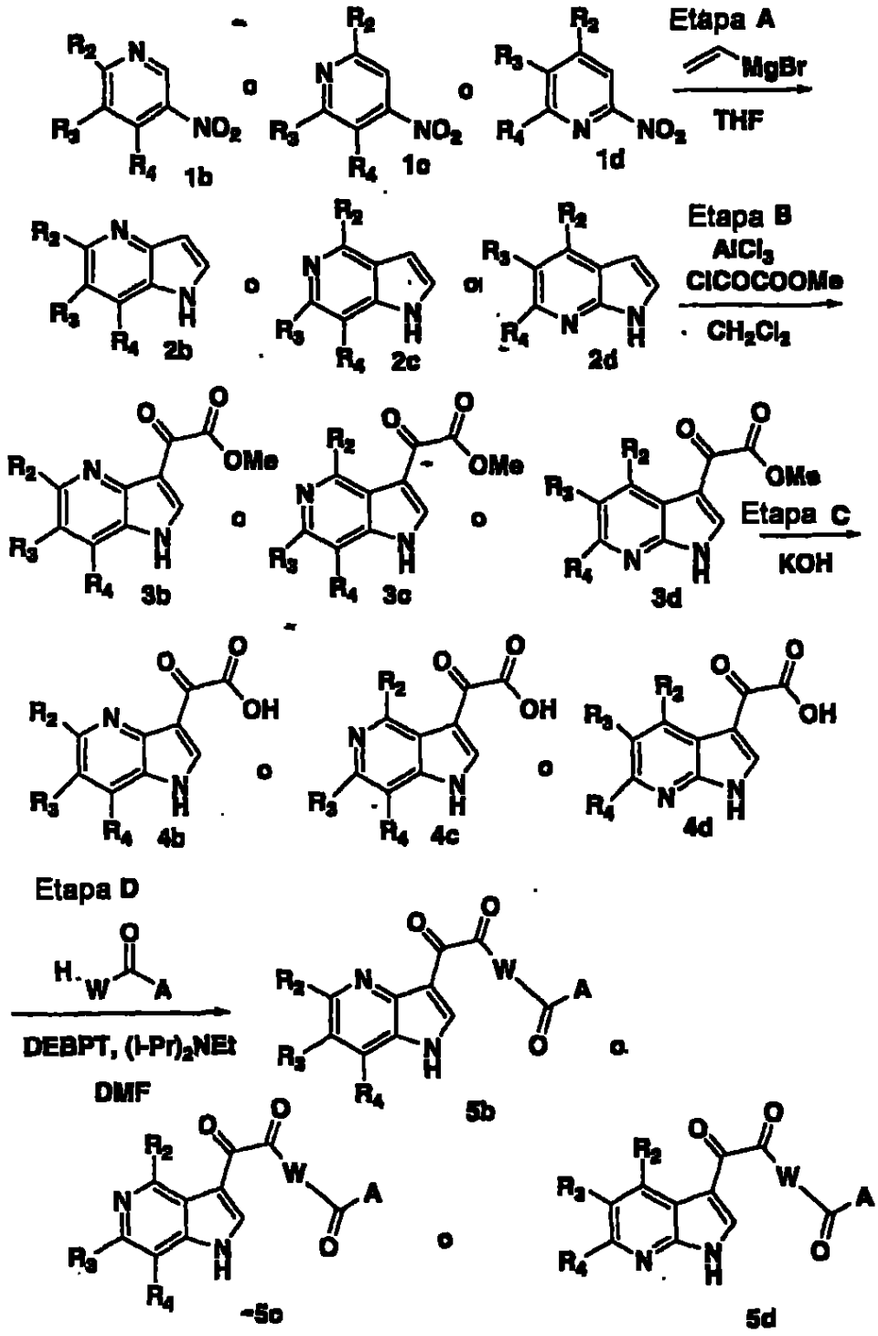
Esquema de reacción 2B



Esquema de reacción 2C



Esquema de reacción 3

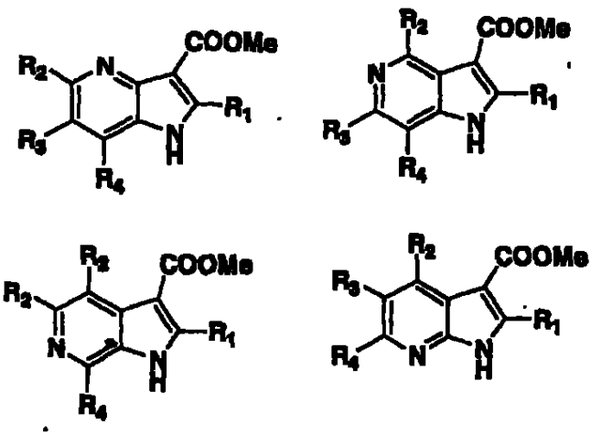


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El Esquema de reacción 3 muestra la síntesis de derivados de 4-azaindol 1b-5b, derivados de 5-azaindol 1c-5c, y derivados de 7-azaindol 1d-5d. Los métodos usados para sintetizar 1b-5b, 1c-5c, y 1d-5d son los mismos métodos descritos para la síntesis de 1a-5a como se describe en el Esquema de reacción 1. Se entenderá, para los propósitos del Esquema de reacción 3, que 1b se usa para sintetizar 2b-5b, 1c proporciona 2c-5c y 1d proporciona 2d-5d.

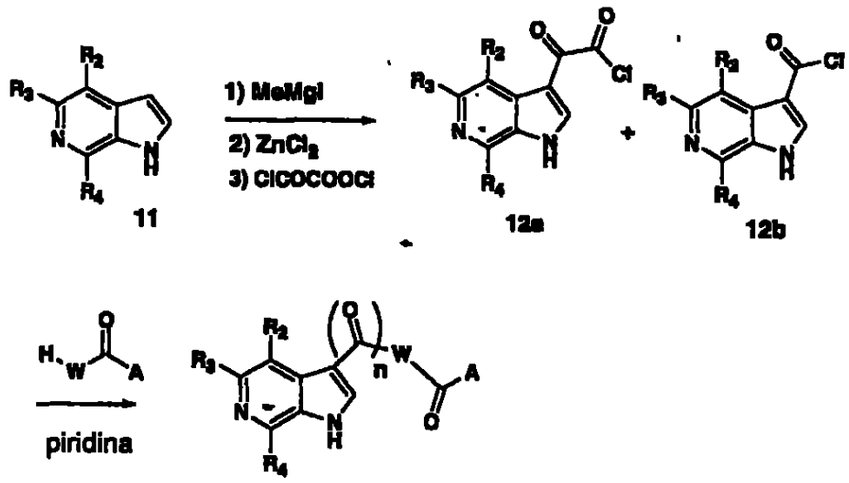
Los compuestos donde hay un carbonilo sencillo entre el azaindol y el grupo W pueden prepararse por el método de Kelarev, V. I.; Gasanov, S. Sh.; Karakhanov, R. A.; Polivin, Yu. N.; Kuatbekova, K. P.; Panina, M. E.; Zh. Org. Khim 1992, 28(12), 2561-2568. En este método los azaindoles reaccionan con cloruro de tricloroacetilo en piridina y luego posteriormente con KOH en metanol para proporcionar los 3- carbometoxi azaindoles mostrados en el Esquema de reacción 4 que pueden entonces hidrolizarse al ácido y llevarse a través de la secuencia de acoplamiento con HW(C=O)A para proporcionar los compuestos de la Fórmula I en donde un carbonilo sencillo enlaza la porción azaindol y el grupo W.

Esquema de reacción 4



Un método alternativo para llevar a cabo la secuencia resumida en la Etapas B-D (mostrada en el Esquema de reacción 5) involucra tratar un azaindol, tal como 11, obtenido por procedimientos descritos en la literatura o de fuentes comerciales, con MeMgI y $ZnCl_2$, seguido por la adición de ClCOCOCl (cloruro de oxalilo) ya sea en THF o Et_2O para proporcionar una mezcla de un cloruro de glioxilo azaindol, 12a, y un cloruro de acilo azaindol, 12b. La mezcla resultante de cloruro de glioxilo azaindol y cloruro de acilo azaindol se acopla entonces con derivados de piperazina mono-benzoilados bajo condiciones básicas para proporcionar los productos de la etapa D como una mezcla de compuestos, 13a y 13b, donde ya sea uno o dos grupos carbonilo enlazan el azaindol y el grupo W. La separación por medio de métodos cromatográficos que son bien conocidos en el arte, proporciona el 13a y 13b puro. Esta secuencia se resume en el Esquema de reacción 5, abajo.

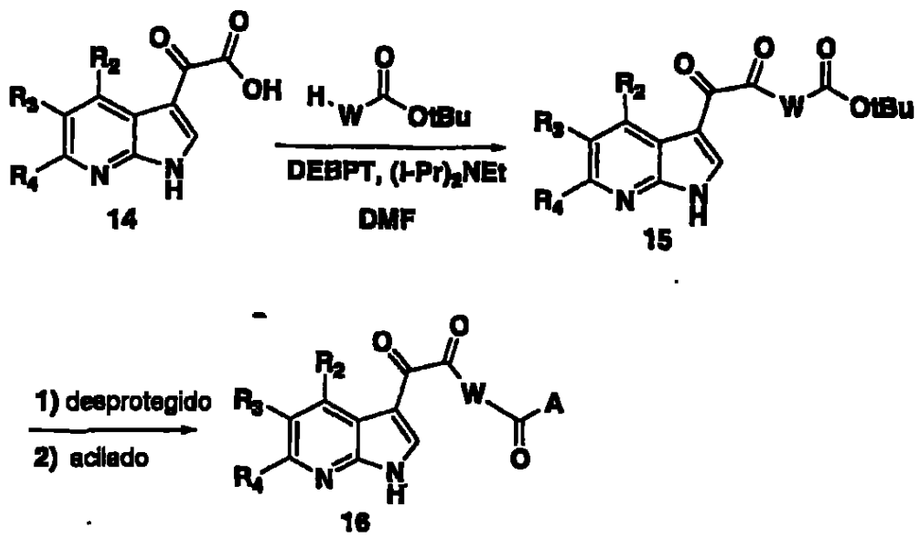
Esquema de reacción 5



11 12a 12b

12a y 13b
n = 1 o 2

Esquema de reacción 6



14 15 16

El Esquema de reacción 6 describe un método general para modificar el substituyente A. El acoplamiento de H-W-C(O)OtBu usando las condiciones descritas previamente para W en el Esquema de reacción 1, Etapa D proporciona el intermediario protegido por Boc, 15. El intermediario 15 se desprotege entonces por el tratamiento con un ácido tal como TFA, ácido clorhídrico o ácido fórmico usando solventes o aditivos estándar tal como CH_2Cl_2, dioxano, o anisol y temperaturas entre -78°C y 100°C. Otros ácidos tal como clorhídrico o perclórico acuoso también pueden usarse para la desprotección. Alternativamente otros grupos protegidos por nitrógeno en W tal como Cbz o TROC, pueden utilizarse y podrán removerse por medio de hidrogenación o tratamiento con zinc respectivamente. Un grupo protector de sililo estable tal como dimetilsilil fenilo también podrá emplearse como un grupo protector de nitrógeno en W y puede removerse con fuentes de fluoruro tal como fluóruro de tetrabutilamonio. Finalmente, la amina libre se acopla al ácido A-C(O)OH usando condiciones de acoplamiento amina-ácido estándar tal como aquellas usadas para enlazar el grupo W o como se muestra abajo para la formación de amida en las posiciones R_1-R_4 para proporcionar el compuesto 16.

Algunos ejemplos específicos de métodos generales para preparar azaindoles funcionalizados o para interconvertir la funcionalidad en aza indoles que serán útiles para preparar

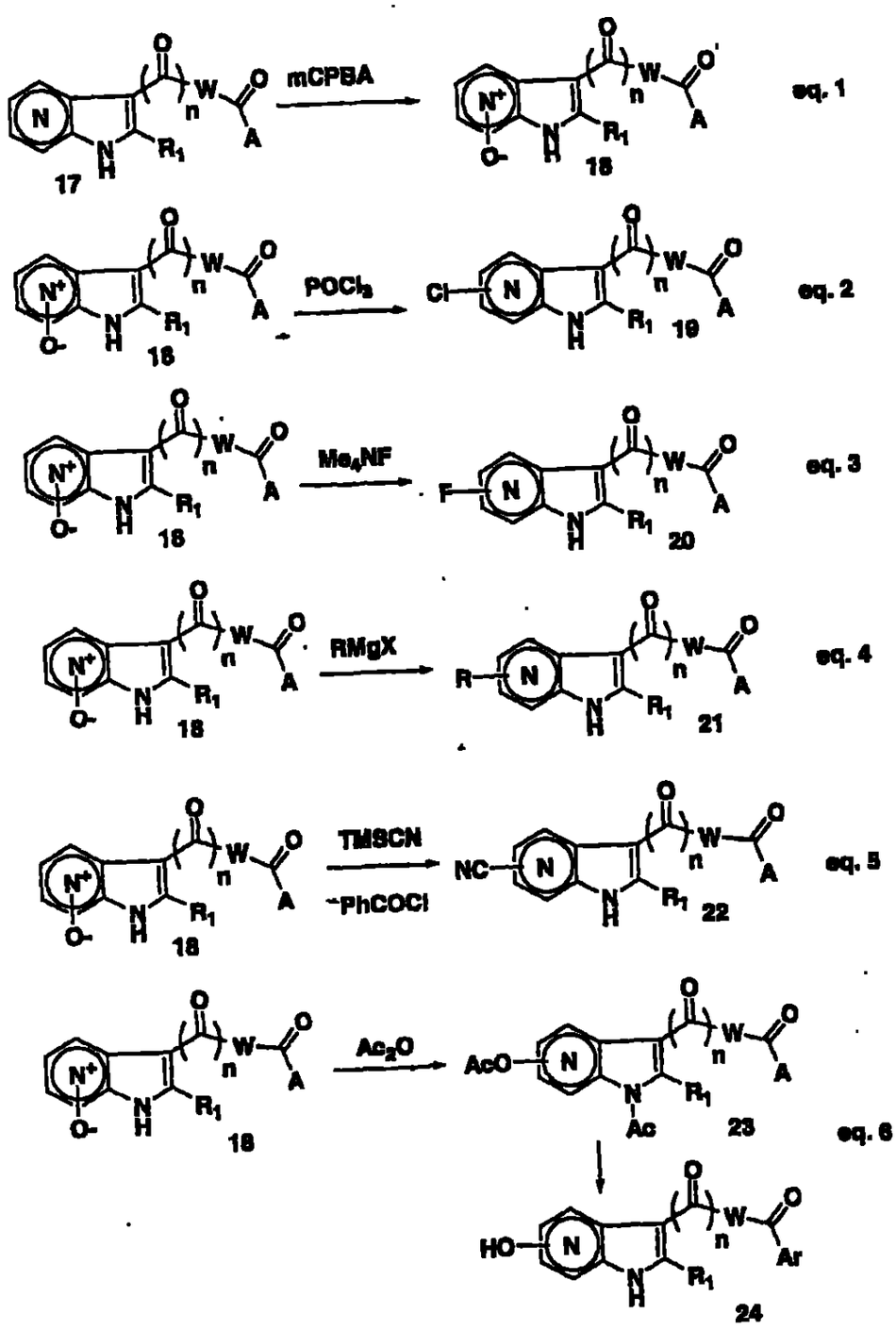
los compuestos de esta invención se muestran en las siguientes secciones para propósitos ilustrativos. Se entenderá que esta invención cubre los azaindoles 4, 5, 6, y 7 substituidos y que la metodología mostrada abajo puede aplicar a todas las series de abajo, aunque otras mostradas abajo serán específicas para una o más. Un practicante típico del arte puede hacer esta distinción cuando no se delinea específicamente. Se pretende que apliquen muchos métodos a todas las series, particularmente instalaciones o interconversiones de grupo funcional. Por ejemplo, una estrategia general para proporcionar una funcionalidad adicional de esta invención es colocar o instalar un haluro tal como bromo, cloro, o yodo, aldehído, ciano, o un grupo carboxi en el azaindol y luego convertir tal funcionalidad a los compuestos deseados. En particular, la conversión a los grupos heteroarilo, arilo, y amida substituidos en el anillo son de interés particular.

Las rutas generales para funcionalizar anillos de azaindol se muestran en los Esquemas de reacción 7, 8 y 9. Como se describe en el Esquema de reacción 7, el azaindol, 17, puede oxidarse al correspondiente derivado N-óxido, 18, usando MCPBA (ácido meta-cloroperbenzoico) en acetona o DMF (eq. 1, Harada et al, Ref. 29 y Antonini et al, Ref. 34). El N-óxido, 18, puede convertirse a una variedad de derivados de azaindol substituidos usando reactivos bien documentados tal como oxicloruro de

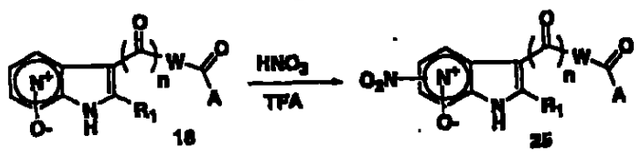
fósforo ($POCl_3$) (eq. 2, Schneller et al, Ref. 30), fluoruro de tetrametilamonio (Me_4NF) (eq. 3), reactivos Grignard RMgX (R = alquilo o arilo, X = Cl, Br o I) (eq. 4, Shiotani et al, Ref. 31), cianuro de trimetilsililo (TMSCN) (eq. 5, Minakata et al, Ref. 32) o Ac_2O (eq. 6, Klemm et al, Ref. 33). Bajo tales condiciones, un grupo cloro (en 19), flúor (en 20), nitrilo (en 22), alquilo (en 21), aromático (en 21) o hidroxilo (en 24) puede introducirse al anillo de piridina. La nitración de los N-óxidos de azaindol resulta en la introducción de un grupo nitro al anillo de azaindol, como se muestra en el Esquema de reacción 8 (eq. 7, Antonini et al, Ref. 34). El grupo nitro puede posteriormente desplazarse por una variedad de agentes nucleofílicos, tal como OR, NR^1R^2 o SR, en una manera química bien establecida (eq. 8, Regnouf De Vains et al, Ref. 35 (a), Miura et al, Ref. 35 (b), Profft et al, Ref. 35(c)). Los N-óxidos resultantes, 26, se reducen fácilmente al correspondiente azaindol, 27, usando tricloruro de fósforo (PCl_3) (eq. 9, Antonini et al, Ref. 34 y Nesi et al, Ref. 36). Similarmente, el N-óxido substituido con nitro, 25, puede reducirse al azaindol, 28, usando tricloruro de fósforo (eq. 10). El grupo nitro del compuesto 28 puede reducirse ya sea a hidroxilamina (NHOH), como en 29, (eq. 11, Walser et al, Ref. 37(a) y Barker et al, Ref. 37(b)) o un grupo amino (NH_2), como en 30, (eq. 12, Nesi et al, Ref. 36 y Ayyangar et al, Ref. 38) seleccionando cuidadosamente diferentes condiciones de reducción.

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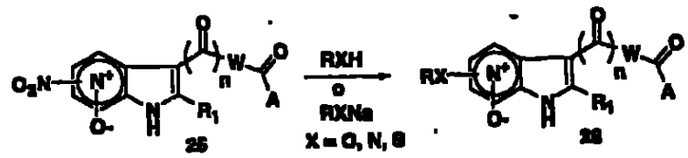
Esquema de reacción 7



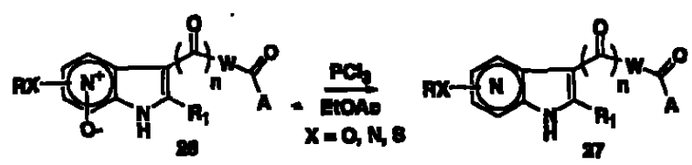
Esquema de reacción 8



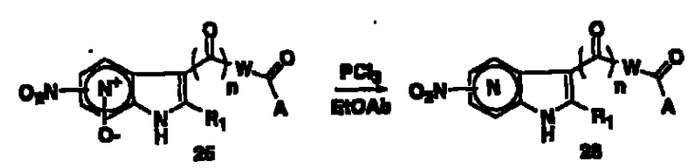
eq. 7



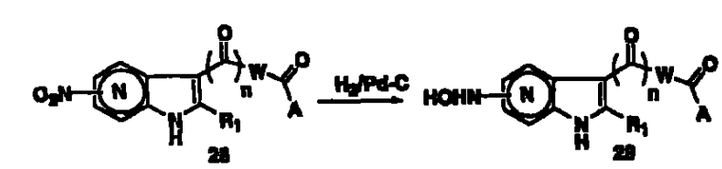
eq. 8



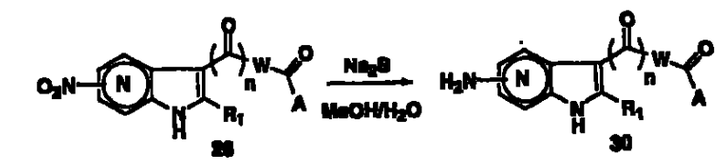
eq. 9



eq. 10



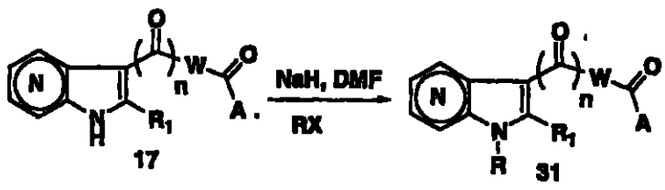
eq. 11



eq. 12

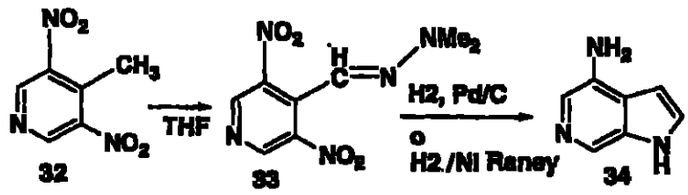
La alquilación del átomo de nitrógeno en la posición 1 de los derivados de azaindol puede realizarse usando NaH como la base, DMF como el solvente y un haluro de alquilo o sulfonato como el agente alquilante, de conformidad con un procedimiento descrito en la literatura (Mahadevan et al, Ref. 39) (Esquema de reacción 9).

Esquema de reacción 9



En las rutas generales para substituir el anillo azaindol descritas arriba, cada proceso puede aplicarse repetidamente y las combinaciones de estos procesos se permite con objeto de proporcionar azaindoles que incorporen substituyentes múltiples. La aplicación de tales procesos proporciona compuestos adicionales de la Fórmula I.

Esquema de reacción 10



La síntesis de 4-aminoazaindoles que son precursores útiles para 4,5, y/o 7-azaindoles substituidos se muestra en el Esquema de reacción 10 arriba. La síntesis of 3,5-dinitro-4-metilpiridina, 32, se describe en las siguientes dos referencias por Achremowicz et. al.: Achremowicz, Lucjan. Pr. Nauk. Inst. Chem. Org. Fiz. Politech. Wroclaw. 1982, 23, 3-128; Achremowicz, Lucjan. Synthesis 1975, 10, 653-4. En la

primera etapa del Esquema de reacción 10, la reacción con dimetilformamida dimetil acetal en un solvente inerte o puro bajo condiciones para formar precursores Batcho-Leimgruber, proporciona el precursor de ciclización, 33, como se muestra. No obstante que la etapa se anticipa al trabajo como se muestra, la piridina puede oxidarse al N-óxido antes de la reacción usando un perácido tal como MCPBA o un oxidante más potente tipo ácidos meta-trifluorometil o meta nitro peroxi benzoicos. En la segunda etapa del Esquema de reacción 10, la reducción del grupo nitro usando por ejemplo hidrogenación sobre catalizador Pd/C en un solvente tal como MeOH, EtOH, o EtOAc proporciona el producto ciclizado, 34. Alternativamente la reducción puede llevarse a cabo usando dicloruro de estaño y HCl, hidrogenación sobre níquel Raney u otros catalizadores, o usando otros métodos para reducción nitro tal como se describe en otro lugar en esta solicitud.

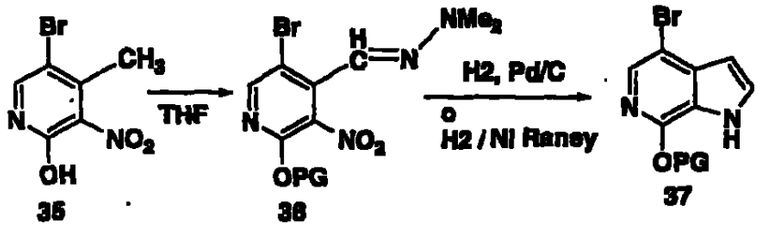
El amino indol, 34, puede ahora convertirse a compuestos de la Fórmula I por medio de, por ejemplo, diazotización del grupo amino, y luego la conversión de la sal de diazonio al fluoruro, cloruro o alcoxi. Ver la discusión de tales conversiones en las descripciones para los Esquemas de reacción 17 y 18. La conversión de la porción amino en la funcionalidad deseada podría seguirse entonces por la instalación de la porción oxoacetopiperazina por la metodología estándar descrita arriba. La substitución 5 6 7

del azaindol puede salir de la formación de N-óxido en la posición 6 y la conversión posterior al cloro por medio de condiciones tal como $POCl_3$ en cloroformo, anhídrido acético seguido por $POCl_3$ en DMF, o alternativamente TsCl en DMF. Las referencias de la literatura para estas y otras condiciones se proporcionan en alguno de los últimos Esquemas de reacción en esta solicitud. La síntesis de 4-bromo-7-hidroxi o hidroxi-4-azaindol protegido se describe abajo como un precursor útil para 6-azaindoles 4 y/o 7 substituidos.

La síntesis de 5-bromo-2-hidroxi-4-metil-3-nitro piridina, 35, puede llevarse a cabo como se describe en la siguiente referencia: Betageri, R.; Beaulieu, P. L.; Llinas-Brunet, M; Ferland, J. M.; Cardozo, M.; Moss, N.; Patel, U.; Proudfoot, J. R. Sol. Int. PCT WO 9931066, 1999. El intermediario 36 se prepara a partir de 35 de conformidad con el método como se describe por la Etapa 1 del Esquema de reacción 10. PG es un grupo protector hidroxi opcional tal como trialilsililo o similares. El intermediario 37 se prepara entonces a partir de 36 por la reducción selectiva del grupo nitro en presencia de bromuro y la posterior ciclización como se describe en la segunda etapa del Esquema de reacción 10. El $Fe(OH)_2$ en DMF con bromuro de tetrabutilamonio catalítico también puede utilizarse para la reducción del grupo nitro. El bromuro puede entonces convertirse al fluoruro por medio del desplazamiento con

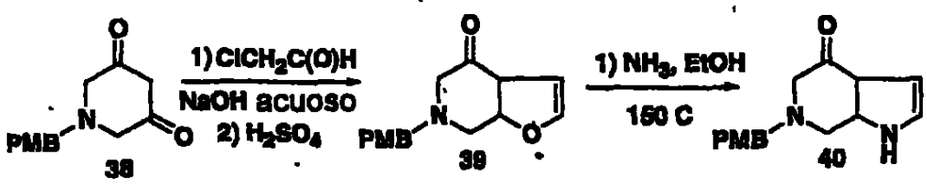
aniones de fluoruro o para otros substituyentes. Los compuestos se convierten entonces a los compuestos de la Fórmula I como arriba.

Esquema de reacción 11



Un método alternativo para preparar 6-azaindoles substituidos se muestra abajo en los Esquemas de reacción 12 y 13. Se reconocerá que son posibles modificaciones ligeras de la ruta descrita abajo. Por ejemplo, las reacciones de acilación de la posición 3 de la cual viene el anillo de cinco miembros azaindol, antes de la aromatización del azaindol, puede llevarse a cabo con objeto de obtener los rendimientos más altos. Además para el grupo para-metoxibencilo (PMB), un grupo bencilo puede llevarse a través de la secuencia y removerse durante la formación de azaindol usando TsOH, p-Cloranilo, en benceno como el oxidante si DDQ no es óptimo. El intermediario bencilo, 38, se ha descrito por Ziegler et al. en J. Am. Chem. Soc. 1973, 95(22), 7458. La transformación de 38 a 40 es análoga a la transformación descrita en Heterocycles 1984, 22, 2313.

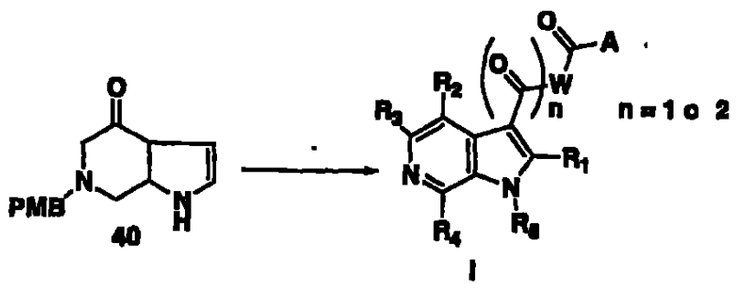
Esquema de reacción 12



El Esquema de reacción 13 describe varias transformaciones del intermediario 40 que por último proporcionan los compuestos de la Fórmula I. Las conversiones de la porción fenol a otra funcionalidad en la posición 4 (posición R_3 en el Esquema de reacción 13) puede llevarse a cabo por los siguientes métodos: 1) la conversión de un fenol a un grupo metoxi con óxido de plata y MeI o diazometano; 2) la conversión de un grupo hidroxi fenólico a cloro usando $ZnCl_2$ cat, y N,N dimetilanilina en CH_2Cl_2 o PCl_5 y $POCl_3$ en conjunto; 3) la conversión del grupo hidroxi fenólico a fluoro usando dietilamina-SF3 como en Org. Prep. Proc. Int. 1992, 24(1), 55-57. El método descrito en EP 427603, 1991, usando el cloroformiato y HF también será útil. Son posibles otras transformaciones. Por ejemplo el fenol puede convertirse a un triflato por métodos estándar y se usa en químicas de acoplamiento descritas después en esta solicitud.

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Esquema de reacción 13



1) Alquilación de cetona para instalar R_3

2) Oxidación DDQ para formar azaindol

3) Transformación de fenol (R_2 = OH) en éter de metilo, o Fluoro, cloro, etc

4) Uso del grupo de dirección C-7 para funcionalizar a R_4 o formación de N-óxido y $POCl_3$ para hacer R_4 = cloro

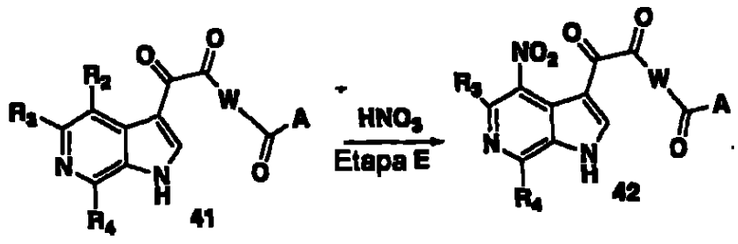
5) Conversión a compuestos de la Fórmula I como arriba

Etapa E. El Esquema de reacción 14 describe la nitración de un azaindol, 41, (R_2 = H). Numerosas condiciones para la nitración del azaindol pueden ser efectivas y se han descrito en la literatura. El N_2O_5 en nitrometano seguido por bisulfato de sodio acuoso de conformidad con el método de Bakke, J. M.; Ranes, E.; Synthesis 1997, 3, 281-283 podría utilizarse. El ácido nítrico en acético también puede emplearse como se describe en Kimura, H.; Yotsuya, S.; Yuki, S.; Sugi, H.; Shigehara, I.; Haga, T.; Chem. Pharm. Bull. 1995, 43(10), 1696-1700. El ácido sulfúrico seguido por ácido nítrico puede emplearse como en Ruefenacht, K.; Kristinsson, H.; Mattern, G.; Helv Chim Acta 1976, 59, 1593. Coombes, R. G.; Russell,

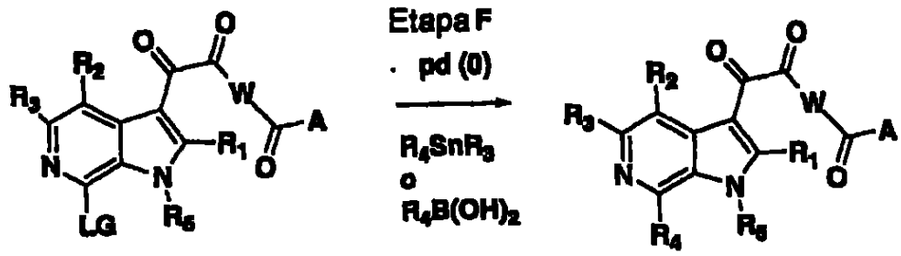
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L. W.; J. Chem. Soc., Perkin Trans. 1 1974, 1751 describe el uso de un sistema reactivo con base en titanio para nitración. Otras condiciones para la nitración del azaindol puede encontrarse en las siguientes referencias: Lever, O. W. J.; Werblood, H. M.; Russell, R. K.; Synth. Comm. 1993, 23 (9), 1315-1320; Wozniak, M.; Van Der Plas, H. C.; J. Heterocycl Chem. 1978, 15, 731.

Esquema de reacción 14



Esquema de reacción 15



Etapa F

Como se muestra arriba en el Esquema de reacción 15, Etapa F, los azaindoles substituidos que contienen un cloruro, bromuro, yoduro, triflato, o fosfonato experimentan reacciones de acoplamiento con

un boronato (reacciones tipo Suzuki) o un estanano para proporcionar azaindoles substituidos. Los estananos y boronatos se preparan por medio de procedimientos estándar de la literatura o como se describe en la sección experimental de esta solicitud. Los indoles substitutos pueden experimentar acoplamiento mediado por metal para proporcionar los compuestos de la Fórmula I en donde R_4 es arilo, heteroarilo, o heteroalicíclico por ejemplo. Los intermediarios de bromoazaindol, (o triflatos o yoduros de azaindol) pueden experimentar acoplamiento tipo Stille con heteroarilestananos como se muestra en el Esquema de reacción 15. Las condiciones para esta reacción son bien conocidos en el arte y los siguientes son tres ejemplos de referencia a) Farina, V.; Roth, G. P. Recent advances in the Stille reaction; Adv. Met.-Org. Chem. 1996, 5, 1-53. b) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille reaction; Org. React. (N.Y.) 1997, 50, 1-652. y c) Stille, J. K. Angew. Chem. Int. Ed. Engl. 1986, 25, 508-524. Otras referencias para condiciones generales de acoplamiento también están en la referencia por Richard C. Larock Comprehensive Organic Transformations 2nd Ed. 1999, John Wiley and Sons New York. Todas estas referencias proporcionan

numerosas condiciones a disposición de aquellos expertos en el arte además de los ejemplos específicos proporcionados en el Esquema de reacción 15 y en las modalidades específicas. Puede ser bien reconocido que un indol estanano también podrá acoplarse a un haluro o triflato heterocíclico o arilo para construir compuestos de la Fórmula I. El acoplamiento Suzuki (Norio Miyaura and Akiro Suzuki Chem Rev. 1995, 95, 2457.) entre un triflato, bromo, o cloro azaindol intermediario y un boronato apropiado también podrá emplearse y algunos ejemplos específicos están contenidos en esta solicitud. Los acoplamientos catalizados por paladio de estananos y boronates entre cloro azaindol intermediario, también son posibles y se han utilizado extensivamente por esta invención. Los procedimientos preferidos para el acoplamiento de un cloro azaindol y un estanano emplean dioxano, estequiométrico o un exceso del reactivo de estaño (hasta 5 equivalentes), 0.1 hasta 1 eq de tetraquis trifenil fosfina paladio (0) en dioxano calentado por 5 hasta 15 h a 110 hasta 120°. Otros solventes tal como DMF, THF, tolueno, o benceno podrán emplearse. Los procedimientos preferidos el acoplamiento Suzuki de un cloro azaindol y un boronato emplea 1:1 de DMF agua como solvente, 2

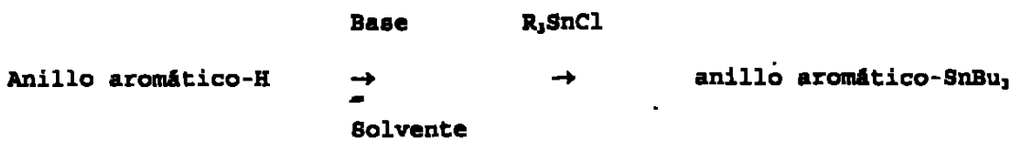
equivalentes de carbonato de potasio como base estequiométrica o un exceso del reactivo de boro (hasta 5 equivalentes), 0.1 hasta 1 eq de tetraquis trifenil fosfina paladio (0) calentado por 5 hasta 15 h a 110 hasta 120°. Si fallan las condiciones estándar, pueden emplearse nuevos catalizadores y condiciones especializadas. Algunas referencias (y las referencias en la presente) describen catalizadores que son útiles para acoplamiento con cloruros de arilo y heteroarilo son: Littke, A. F.; Dai, C.; Fu, G. C. J. Am. Chem. Soc. 2000, 122(17), 4020-4028; Varma, R. S.; Naicker, K. P. Tetrahedron Lett. 1999, 40(3), 439-442; Wallow, T. I.; Novak, B. M. J. Org. Chem. 1994, 59(17), 5034-7; Buchwald, S.; Old, D. W.; Wolfe, J. P.; Palucki, M.; Kamikawa, K.; Chieffi, A.; Sadighi, J. P.; Singer, R. A.; Ahman, J Sol. Int. PCT WO 0002887 2000; Wolfe, J. P.; Buchwald, S. L. Angew. Chem., Int. Ed. 1999, 38(23), 3415; Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. J. Am. Chem. Soc. 1999, 121(41), 9550-9561; Wolfe, J. P.; Buchwald, S. L. Angew. Chem., Int. Ed. 1999, 38(16), 2413-2416; Bracher, F.; Hildebrand, D.; Liebigs Ann. Chem. 1992, 12, 1315-1319; y Bracher, F.; Hildebrand, D.; Liebigs Ann. Chem. 1993, 8, 837-839.

Alternativamente, el boronato o estanano se puede formar en el azaindol por medio de métodos conocidos en el arte y el acoplamiento se realiza de manera inversa con halógenos o triflatos basados en arilo o heteroarilo.

Los agentes de boronato o estanano podrían ya sea adquirirse de distribuidores comerciales o prepararse siguiendo los documentos descritos. Los ejemplos adicionales para la preparación de reactivos de estaño o reactivos de boro están contenidos en la sección experimental.

Los agentes de estanano novedosos podrán prepararse a partir de una de las siguientes rutas.

Esquema de reacción Estaño-01

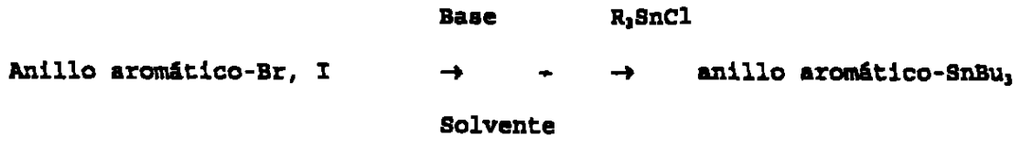


Base=LDA, TMP-Li, n-BuLi, S-BuLi, t-BuLi

Solvente=THF, éter, DME

R=Me, Bu

Esquema de Reacción Estaño-02



Base=n-BuLi, S-BuLi, t-BuLi

Solvente=THF, éter, DME

R=Me, Bu

Esquema de Reacción Estaño-03

R_3SnLi

Anillo aromático-F, Cl, Br, I → anillo aromático-$SnBu_3$

Solvente

Solvente=THF, éter, DME

R=Me, Bu

Esquema de Reacción Estaño-04

$R_3Sn\text{-}SnR_3$

Anillo aromático-Cl, Br, I, OTf → anillo aromático-$SnBu_3$

Solvente

Pd(0)

Solvente=diozano, tolueno

R=Me, Bu

Esquema de Reacción Estaño-05

Anillo Aromático	Anillo NH o aromático -XH	Base / Solvente	Anillo arimático N-E	o	Anillo aromático X-E
R_3Sn	R_3Sn	Electrofilos	R_3Sn		R_3Sn

E=Electrófilo = R'-haluro, R'COCl, R'OCOCl, R'R"NCOCl, RSO_2Cl, R'NCO, R'NSO, R'NCNR"

Solvente = CH_2Cl_2, THF, Éter, DMF

R = Me, Bu

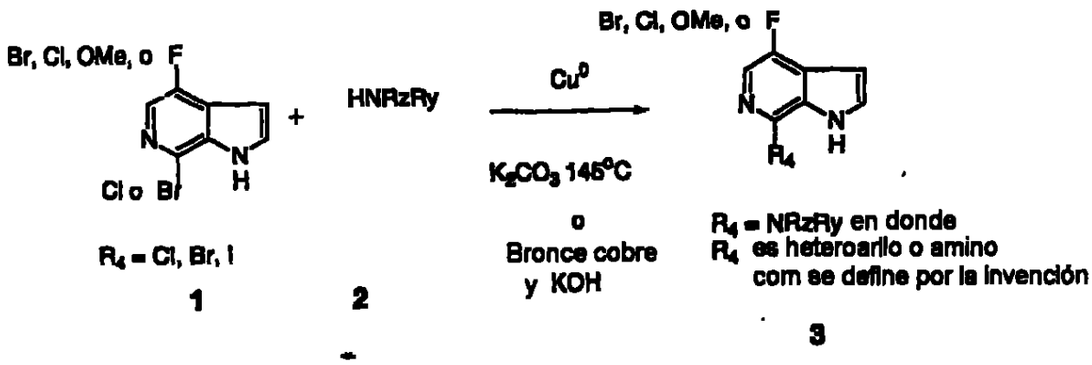
Base = NaH, BuLi, LDA, K_2CO_3, Et_3N, DBU, DMAP, NaHMDS

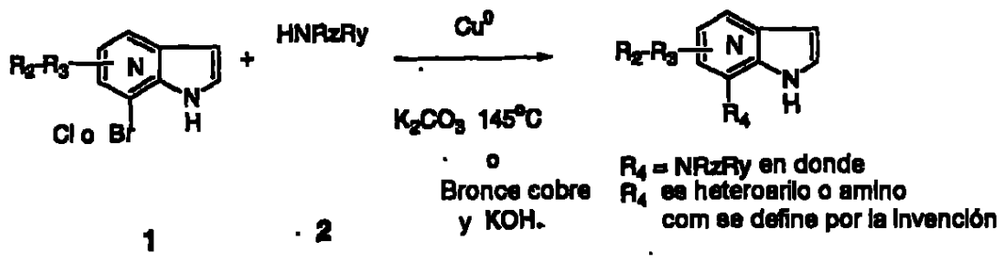
Los reactivos de boronato se preparan como se describe en la referencia 71. La reacción de reactivos de litio o Grignard con trialquil boratos, genera boronatos. Alternativamente, los acoplamientos catalizados por paladio de reactivos de alcoxi diboro o alquil diboro con haluros de arilo o heteroarilo puede proporcionar reactivos de boro para usarse en acoplamientos tipo Suzuki. Algunas condiciones de ejemplo para acoplar un haluro con (MeO)BB(OMe)2 utiliza PDCl2 (dppf), KOAc, DMSO, a 80°C hasta que la reacción se completa cuando se sigue por CCD o análisis de CLAR.

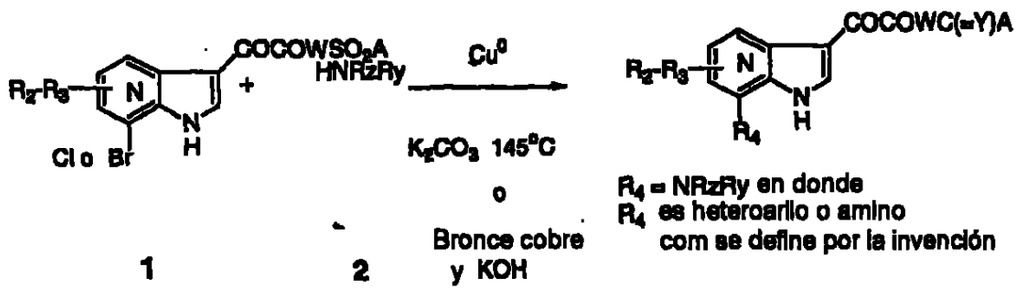
Se proporcionan ejemplos relacionados en la siguiente sección experimental.

Los métodos para la adición directa de reactivos organometálicos de arilo o heteroarilo a heterociclos que contienen alfa cloro nitrógeno o los N-óxidos de heterociclos que contienen nitrógeno se conocen y aplican a los azaindoles. Algunos ejemplos son Shiotani et. al. J. Heterocyclic Chem. 1997, 34 (3), 901-907; Fourmigue et. al. J. Org. Chem. 1991, 56(16), 4858-4864.

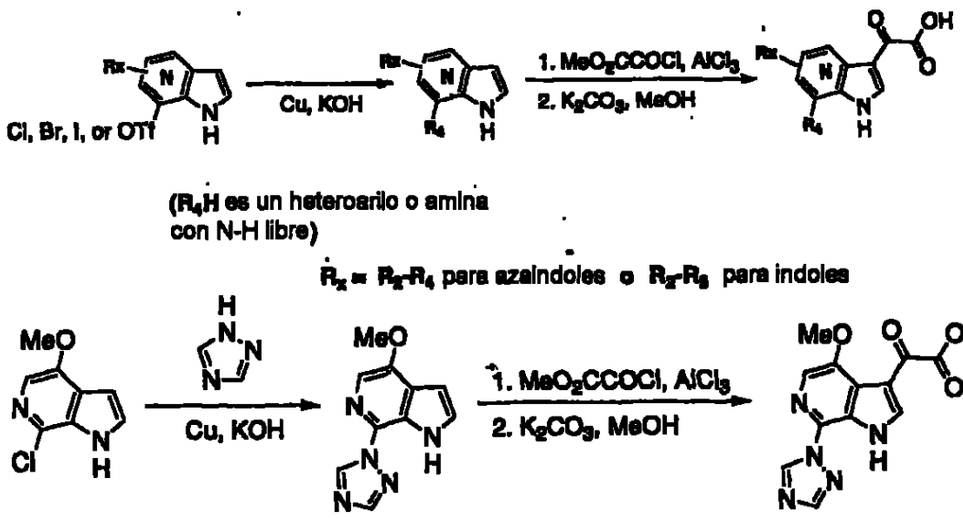
Esquema de reacción 15aa







Esquema de reacción 15bb



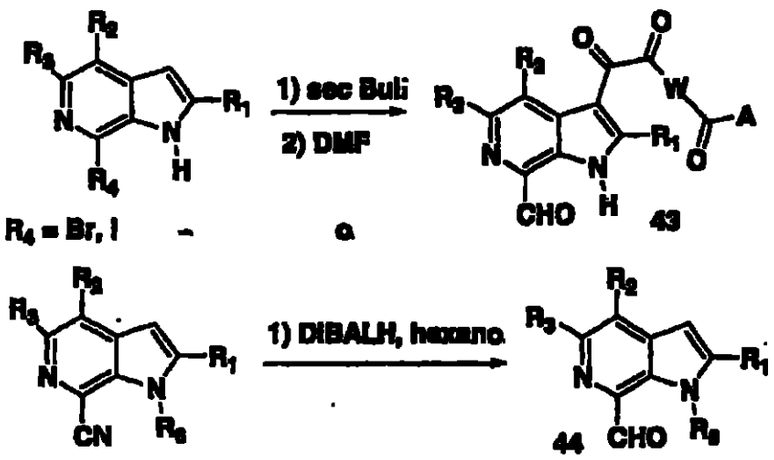
Los desplazamientos directos para instalar la amina o los substituyentes heteroarilo enlazados a N también pueden usarse para preparar compuestos de la Fórmula I. Como se muestra en los Esquemas de reacción 15aa y 15bb, una mezcla de intermediario halo-indol o halo-azaindol, 1-2 equivalentes de polvo de cobre, con 1 equivalente preferido para la serie 4-F,6-azaindol y 2 equivalentes para la serie 4-metoxi, 6-azaindol; 1-2 equivalentes de carbonato de potasio, con 1 equivalente preferido para la serie 4-F,6-azaindol y 2 equivalentes para la serie 4-metoxi,6-azaindol; y 2-30 equivalentes del correspondiente reactivo heterocíclico, con 10 equivalentes preferido; se calentó a 135-160°C por 4 hasta 9 horas, con 5 horas a 160°C preferido para la serie 4-F,6-azaindol y 7 horas a 135°C preferido para la serie 4-

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metoxi,6-azaindol. La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de papel filtro. El filtrado se diluyó con metanol y se purificó ya sea por CLAR preparativa o gel de sílice. En muchos casos no es necesaria la cromatografía, el producto puede obtenerse por cristalización con metanol.

Alternativamente, la instalación de aminas o heteroarilos enlazados a N puede llevarse a cabo al calentar 1 hasta 40 equivalentes de la amina apropiada y un equivalente del cloruro, bromuro o yoduro de aza indol apropiado, con bronce cobre (a partir de 0.1 hasta 10 equivalentes (preferiblemente alrededor de 2 equivalentes) y a partir de 1 hasta 10 equivalentes de hidróxido de potasio finamente pulverizado (preferiblemente alrededor de 2 equivalentes). Las temperaturas de 120° hasta 200° puede emplearse con 140-160° generalmente preferido. Para materiales de partida volátiles puede emplearse un reactor sellado. La reacción se usa más comúnmente cuando el halógeno se desplaza en la posición 7 del 6-aza (o 4-azaindol, no se muestra) pero el método puede trabar en la serie 5-aza o cuando el halógeno está en una posición diferente (posición posible 4-7). Como se muestra arriba, la reacción puede emplearse en azaindoles no substituidos en la posición 3 ó intermediarios que contienen el dicarbonilo o urea o tioureas de dicarbonil piperazina intacta contenida en los compuestos de la Fórmula I.

Esquema de reacción 16



La preparación de un intermediario aldehído clave, 43, usando un procedimiento adaptado a partir del método de Gilmore et. al. Synlett 1992, 79-80. Se muestra en el Esquema de reacción 16 arriba. El substituyente aldehído se muestra sólo en la posición R_4 por motivo de claridad, y no deberá considerarse como limitación de la metodología. El intermediario de bromuro o yoduro se convierte en un intermediario aldehído, 43, por intercambio metal-halógeno y reacción posterior con dimetilformamida en un solvente aprótico apropiado. Se incluyen bases típicas, pero no se limitan a, bases de alquil litio tal como n-butil litio, sec butil litio o tert butil litio o un metal tal como metal de litio. Un solvente aprótico preferido es THF. Típicamente la transmetalación se inicia a -78°C. La reacción puede permitirse que se entibie para permitir que la transmetalación se complete dependiendo de la reactividad del

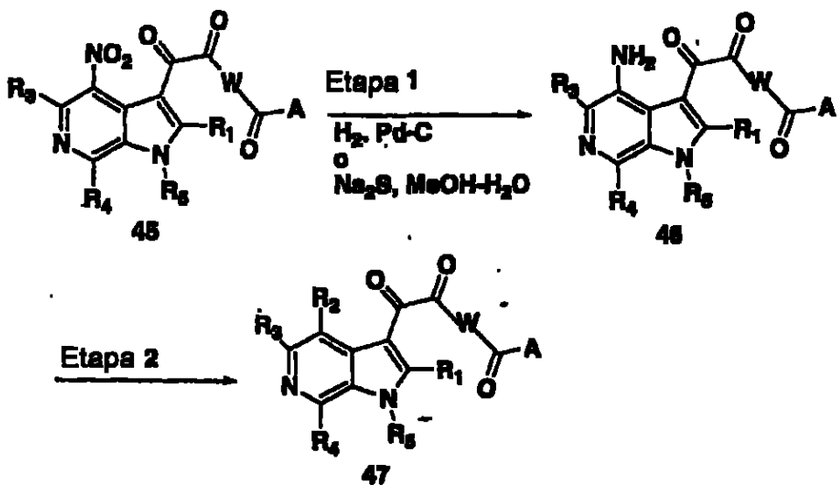
intermediario de bromuro. La reacción se vuelve enfriar entonces hasta -78°C y se permite que reaccione con dimetilformamida (permitiendo que la reacción se entibie como se requiera para hacer la reacción completa) para proporcionar un aldehído que se elabora para los compuestos de la Fórmula I. Otros métodos para la introducción de un grupo aldehído para formar los intermediarios de la Fórmula 43 incluyen las reacciones de carbonilación catalizadas por un metal de transición de bromo, trifluorometano sulfonilo, o azaindoles de estanilo apropiados. Alternativamente, los aldehídos pueden introducirse al hacer reaccionar aniones de indolilo o reactivos Grignard de indolilo con formaldehído y luego oxidar con MnO_2 o TPAP/NMO u otros oxidantes apropiados para proporcionar el intermediario 43.

La metodología descrita en T. Fukuda et. al. Tetrahedron 1999, 55, 9151 y M. Iwao et. Al. Heterocycles 1992, 34(5), 1031 proporciona métodos para preparar indoles con substituyentes en la posición 7. Las referencias de Fukuda proporciona métodos para funcionalizar la posición C-7 de indoles ya sea al proteger el nitrógeno indole con un grupo 2,2-dietil propanoilo y luego desprotonar la posición 7 con sec/Buli en TMEDA para dar un anion. Este anión puede apagarse con DMF, formaldehído, o dióxido de carbono para dar el aldehído, alcohol bencílico, ácido carboxílico respectivamente y el grupo protector removerse con t butóxido acuoso. Pueden realizarse

transformaciones similares al convertir indoles a indolina, litiación en C-7 y luego reoxidación al indol tal como la descrita en la referencia de Iwao arriba. El nivel de oxidación de cualesquiera de estos productos puede ajustarse por métodos bien conocidos en el arte como la interconversión de alcohol, aldehído, y grupos ácido se ha estudiado bien. También es bien entendido que el grupo ciano puede convertirse fácilmente a un aldehído. El agente reductor tal como DIBALH en hexano como se usa en Weyerstahl, P.; Schlicht, V.; Liebigs Ann/Recl. 1997, 1, 175-177 o alternativamente catecolalano en THF tal como el usado en Cha, J. S.; Chang, S. W.; Kwon, O. O.; Kim, J. M.; Synlett. 1996, 2, 165-166 se alcanza rápidamente esta conversión para proporcionar intermediarios tal como el 44 (Esquema de reacción 16). Los métodos para sintetizar los nitrilos se muestran después en esta solicitud. También se entenderá que el grupo alcohol, aldehído, o ácido protegido podrá estar presente en el azaindol de partida y llevarse a través de la etapas sintéticas a un compuesto de la Fórmula I en una forma protegida hasta que puedan convertirse en el substituyente deseado en R_1 hasta R_4. Por ejemplo, un alcohol bencílico puede protegerse como un éter de bencilo o éter de sililo ou otro grupo protector de alcohol; un aldehído puede llevarse como un acetal, y un ácido puede protegerse como un ester o éster orto hasta que se desea la desprotección y se lleva a cabo por métodos de la literatura.

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Esquema de reacción 17



Etapa G. La Etapa 1 del Esquema de reacción 17 muestra la reducción de un grupo nitro en 45 al grupo amino de 46. No obstante que se muestra en la posición 4 del azaindol, la química aplica a otros isómeros nitro. El procedimiento descrito en Ciurla, H.; Puszko, A.; Khim Geterotsikl Soedin 1996, 10, 1366-1371 usa níquel Raney hidrazina para la reducción del grupo nitro a la amina. Robinson, R. P.; DonahueO, K. M.; Son, P. S.; Wagy, S. D.; J. Heterocycl. Chem. 1996, 33 (2), 287-293 describe el uso de hidrogenación y níquel Raney para la reducción del grupo nitro a la amina. Se describen condiciones similares por Nicolai, E.; Claude, S.; Teulon, J. M.; J. Heterocycl. Chem. 1994, 31 (1), 73-75 para la misma transformación. Las siguientes dos referencias describen algunos reactivos con base en azufre o cloruro de trimetilsililo que pueden usarse para la reducción de un

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grupo nitro a una amina. Hwu, J. R.; Wong, F. F.; Shiao, M. J.; J. Org. Chem. 1992, 57(19), 5254-5255; Shiao, M. J.; Lai, L. L.; Ku, W. S.; Lin, P. Y.; Hwu, J. R.; J. Org. Chem. 1993, 58(17), 4742-4744.

La Etapa 2 del Esquema de reacción 17 describe métodos generales para la conversión de grupos amino en azaindoles en otra funcionalidad. El Esquema de reacción 18 también describe transformaciones de un amino azaindol en varios intermediarios y compuestos de la Fórmula I.

El grupo amino en cualquier posición del azaindol, tal como 46 (Esquema de reacción 17), puede convertirse a un grupo hidroxi usando nitrato de sodio, ácido sulfúrico, y agua por medio del método de Klemm, L. H.; Zell, R.; J. Heterocycl. Chem. 1968, 5, 773. Bradsher, C. K.; Brown, F. C.; Porter, H. K.; J. Am. Chem. Soc. 1954, 76, 2357 describe como el grupo hidroxi puede alquilarse bajo condiciones estándar o Mitsonobu para formar éteres. El grupo amino puede convertirse directamente en un grupo metoxi por diazotización (nitrato de sodio y ácido) y atraparse con metanol.

El grupo amino del azaindol, tal como 46, puede convertirse a fluoro por medio del método de Sanchez usando HPF_6, $NaNO_2$, y agua por el método descrito en Sanchez, J. P.; Gogliotti, R. D.; J. Heterocycl. Chem.

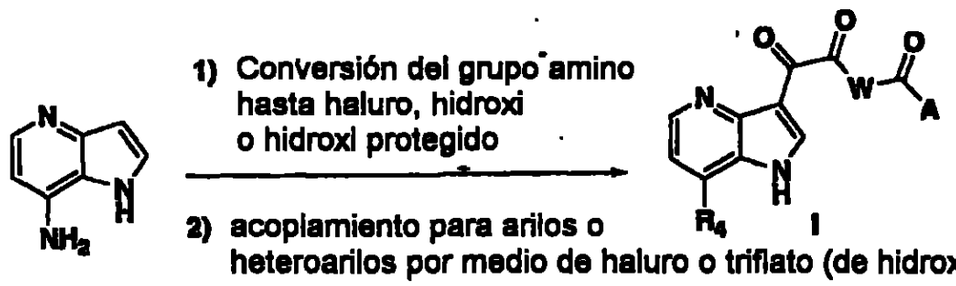
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1993, 30(4), 855-859. Otros métodos útiles para la conversión del grupo amino a fluoro se describen en Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G.; Tetrahedron Lett. 1993, 34(18), 2937-2940 y Sanchez, J. P.; Rogowski, J. W.; J. Heterocycl. Chem. 1987, 24, 215.

El grupo amino del azaindol, 46, también puede convertirse a un cloruro por medio de diazotización y desplazamiento de cloruro como se describe en Ciurla, H.; Puszko, A.; Khim Geterotsikl Soedin 1996, 10, 1366-1371 o los métodos en Raveglia, L. F.; Giardina, G. A.; Grugni, M.; Rigolio, R.; Farina, C.; J. Heterocycl. Chem. 1997, 34(2), 557-559 o los métodos en Matsumoto, J. I.; Miyamoto, T.; Minamida, A.; Mishimura, Y.; Egawa, H.; Mishimura, H.; J. Med. Chem. 1984, 27(3), 292; o como en Lee, T. C.; Salemnick, G.; J. Org. Chem. 1975, 24, 3608.

El grupo amino del azaindol, 46, también puede convertirse a un bromuro por medio de diazotización y desplazamiento por bromuro como se describe en Raveglia, L. F.; Giardina, G. A.; Grugni, M.; Rigolio, R.; Farina, C.; J. Heterocycl. Chem. 1997, 34(2), 557-559; Talik, T.; Talik, Z.; Ban-Oganowska, H.; Synthesis 1974, 293; y Abramovitch, R. A.; Saha, M.; Can. J. Chem. 1966, 44, 1765.

Esquema de reacción 18



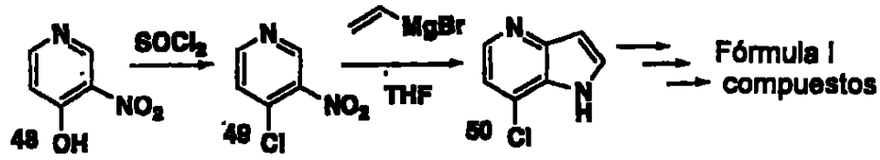
La preparación de 4-amino 4-azaindol y 7-metil-4-azaindol se describe por Mahadevan, I.; Rasmussen, M. J. Heterocycl. Chem. 1992, 29(2), 359-67. El grupo amino del 4-amino 4-azaindol puede convertirse a halógenos, hidroxi, hidroxi protegido, triflato, como se describe arriba en los Esquemas de reacción 17-18 para los compuestos 4-amino o por otros métodos conocidos en el arte. La protección del nitrógeno indol del 7-metil-4-azaindol por medio de acetilación u otra estrategia seguido por oxidación del grupo 7-metilo con permanganato de potasio o ácido crómico proporciona el ácido 7/4-N-óxido. La reducción del N-óxido, como se describe abajo, proporciona un intermediario a partir de del cual se instalan varios subetituyentes en la posición R_4. Alternativamente el 4-azaindol precursor el cual se

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preparó como se describe en Mahadevan, I.; Rasmussen, M. J. Heterocycl. Chem. 1992, 29(2), 359-67 podrá derivarse en nitrógeno para proporcionar el 1-(2,2-dietilbutanoil)azaindol que podrá entonces litiarse usando TMEDA/sec BuLi como se describe en T. Fukuda et. Al. Tetrahedron 1999, 55, 9151-9162; seguido por la conversión de la especie litio al ácido 7-carboxílico o 7-halógeno como se describe. La hidrólisis de la N-amida usando tert-butóxido acuoso en THF regenera el indol NH libre el cual puede ahora convertirse a compuestos de la Fórmula I. La química usada para funcionalizar la posición 7 también puede aplicarse a la serie indol 5 y 6.

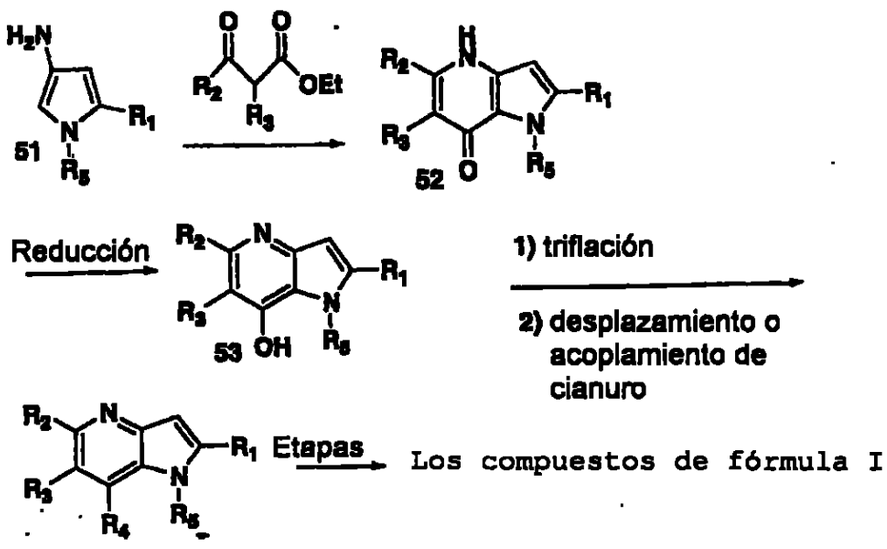
El Esquema de reacción 19 muestra la preparación de un 7-cloro-4-azaindol, 50, el cual puede convertirse a compuestos de la Fórmula I por la química previamente descrita, especialmente la metodología de acoplamiento basada en estaño y boro catalizada por paladio descrita arriba. El cloro nitro indol, 49, está disponible comercialmente o puede prepararse a partir de 48 de conformidad con el método de Delarge, J.; Lapiere, C. L. Pharm. Acta Helv. 1975, 50(6), 188-91.

Esquema de reacción 19



El Esquema de reacción 20, abajo, muestra otra ruta sintética para 4-aza indoles susbtituidos. El 3-aminopirrol, 51, se hace reaccionar para proporcionar la pirrolopiridinona, 52, que se reduce entonces para dar el hidroxi azaindol, 53. Las pirrolo[2,3-b]piridinas descritas se preparan de conformidad con el método de Britten, A. Z.; Griffiths, G. W. G. Chem. Ind. (Londres) 1973, 6, 278. El hidroxi azaindol, 53, pueden entonces convertirse al triflato luego se hace reaccionar además para proporcionar compuestos de la Fórmula I.

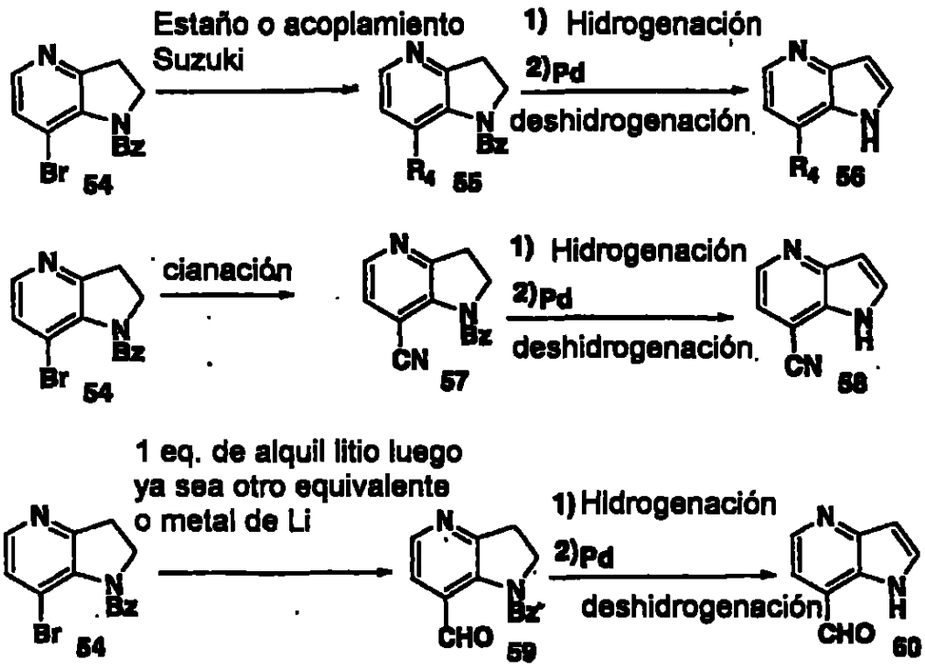
Esquema de reacción 20



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Las siguientes referencias describen la síntesis de ácido 7-halo o 7 carboxílico, o derivados de 7-amido de 5-azaindolina que se pueden usar para construir compuestos de la Fórmula I. Bychikhina, N. N.; Azimov, V. A.; Yakhontov, L. N. Khis. Geterotsikl. Soedin. 1983, 1, 58-62; Bychikhina, N. N.; Azimov, V. A.; Yakhontov, L. N. Khim. Geterotsikl. Soedin. 1982, 3, 356-60; Azimov, V. A.; Bychikhina, N. N.; Yakhontov, L. N. Khim. Geterotsikl. Soedin. 1981, 12, 1648-53; Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. J. Org. Chem. 1999, 64(26), 9430-9443; Spivey, A. C.; Fekner, T.; Adams, H. Tetrahedron Lett. 1998, 39(48), 8919-8922. Los métodos descritos en Spivey et al. (dos referencias precedentes) para la preparación de 1-metil-7-bromo-4-azaindolina se pueden usar para preparar la 1-bencilo-7-bromo-4-azaindolina, 54, mostrada abajo en el Esquema de reacción 21. Esta puede utilizarse en acoplamientos Stille o Suzuki para proporcionar el 55, el cual se desprotege y deshidrogena para proporcionar el 56. Otros intermediarios de azaindol útiles, tal como los derivados ciano, 57 y 58, y los derivados de aldehído, 59 y 60, pueden entonces elaborarse además para compuestos de la Fórmula I.

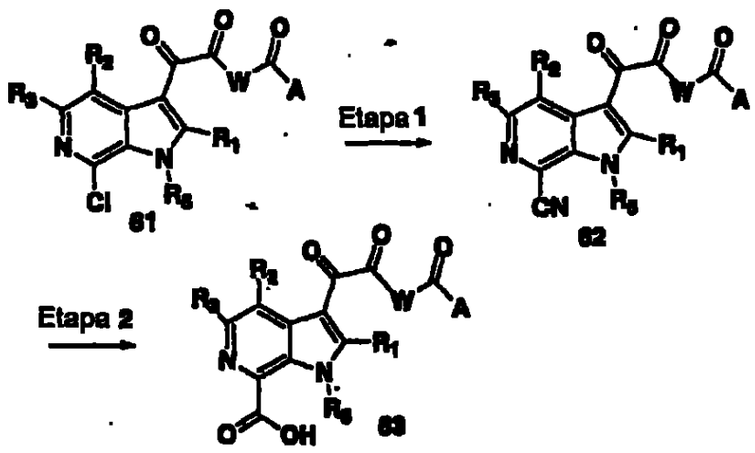
Esquema de reacción 21



Alternativamente los derivados de 5-azaindol 7-funconalizados pueden obtenerse por la funcionalización usando las metodologías de T. Fukuda et. al. Tetrahedron 1999, 55, 9151 y M. Iwao et. AL. Heterocycles 1992, 34(5), 1031 descrito como arriba para los 4 ó 6 azaindoles. Las posiciones 4 ó 6 de los 5 aza indoles pueden funcionalizarse usando el azaindol N-óxido.

La conversión de indoles a indolinas es bien conocida en el arte y puede llevarse a cabo como se muestra o por los métodos descritos en Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. Chem. Pharm. Bull. 1987, 35(8), 3146-54; M. Iwao et. Al. Heterocycles 1992, 34(5), 1031; y Akagi, M.; Ozaki, K. Heterocycles 1987, 26(1), 61-4.

Esquema de reacción 22



La preparación de oxoacetil azaindol u oxo piperidinas con ácidos carboxílicos puede llevarse a cabo a partir de precursores nitrilo, aldehído, o anión por medio de hidrólisis, oxidación, o atrapado con CO_2 respectivamente. Como se muestra en el Esquema de reacción 22, Etapa 1, o el esquema de reacción abajo, la etapa a12, un método para formar el intermediario nitrilo, 62, es por el desplazamiento de cianurode un haluro en el anillo aza-indol. El reactivo de cianuro uasdo puede ser cianuro de sodio, o más preferiblemente cianuro de cobre o zinc. Las reacciones pueden llevarse a cabo en numerosos solventes que son bien conocidos en el arte. Por ejemplo DMF se usa en el caso de cianuro de cobre. Los procedimientos adicionales útiles para llevar a cabo la etapa 1 del Esquema de reacción 24 son Yamaguchi, S.; Yoshida, M.; Miyajima, I.; Araki, T.; Hirai, Y.; J. Heterocycl. Chem. 1995, 32(5), 1517-1519 que describen métodos para cianuro de cobre; Yutilov, Y. M.; Svertilova, I. A.; Khim Geterotsikl Soedin 1994, 8,

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1071-1075 que utiliza cianuro de potasio; y Prager, R. H.; Tsopelas, C.; Heisler, T.; Aust. J. Chem. 1991, 44(2), 277-285 que utiliza cianuro de cobre en presencia de $MeOS(O)_2F$. El cloruro o más preferiblemente el bromuro en el azaindol puede desplazarse por cianuro de sodio en dioxano por medio del método descrito en Synlett. 1998, 3, 243-244. Alternativamente, dibromuro de níquel, zinc, y trifenil fosfina se pueden usar para activar los cloruros aromático y heteroarilo para desplazamiento por medio de cianuro de potasio en THF u otro solvente apropiado por los métodos descritos en Sol. de Pat. Eur., 831083, 1998.

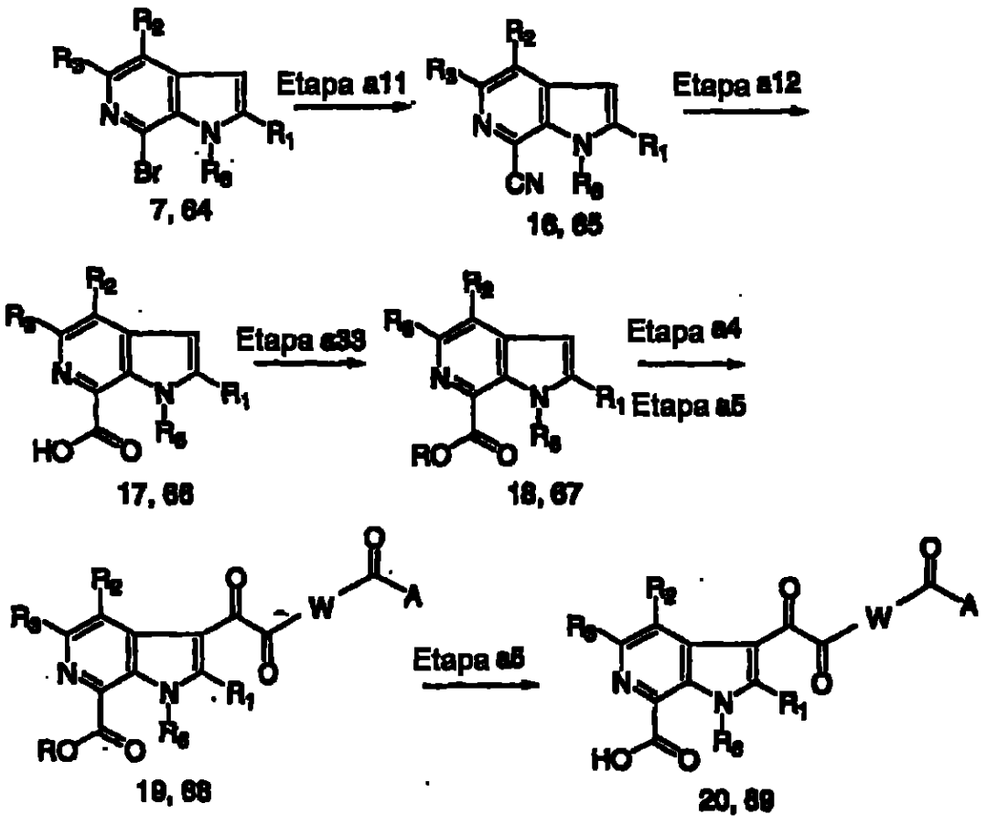
La conversión del intermediario ciano, 62, al ácido carboxílico intermediario, 63, se describe en la Etapa 2, Esquema de reacción 22 o en la Etapa a12, Esquema de reacción 23. Muchos métodos para la conversión de nitrilos a ácidos son bien conocidos en el arte y pueden emplearse. Las condiciones adecuadas para la etapa 2 del Esquema de reacción 22 o la conversión del intermediario 65 al intermediario 66 abajo emplea hidróxido de potasio, agua, y un alcohol acuoso tal como etanol. Típicamente la reacción deberá calentarse a temperaturas de reflujo por una hasta 100 horas. Otros procedimientos para la hidrólisis incluyen aquellos descritos en:

Shiotani, S.; Taniguchi, -K.; J. Heterocycl. Chem. 1997, 34(2), 493-499; Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J.; Tetrahedron 1994, 50(8), 2551-2560; Rivalle, C.; Bisagni, E.; Heterocycles 1994, 38(2), 391-397; Macor, J. E.; Post, R.; Ryan, K.; J. Heterocycl. Chem. 1992, 29(6), 1465-1467.

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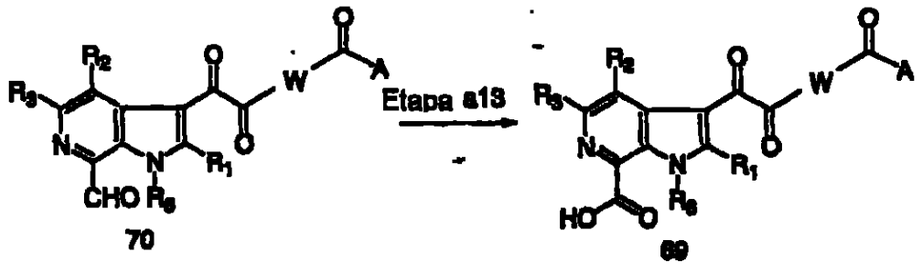
El intermediario ácido, 66 (Esquema de reacción 23), puede entonces esterificarse usando condiciones bien conocidas en el arte. Por ejemplo, la reacción del ácido con diazometano en un solvente inerte tal como éter, dioxano, o THF podría dar el éster de metilo. El intermediario 67 puede entonces convertirse al intermediario 68 de conformidad con el procedimiento descrito en el Esquema de reacción 2. El intermediario 68 puede entonces hidrolizarse para proporcionar el intermediario 69.

Esquema de reacción 23



Como se muestra en el Esquema de reacción 24, Etapa a13 otra preparación de los ácidos indoloxoacetilpiperazin 7-carboxílicos, 69, se lleva a cabo por la oxidación del correspondiente 7-carboxaldehído, 70. Son apropiados numerosos oxidantes para la conversión del aldehído al ácido y muchos de estos están descritos en textos de química orgánica estándar tal como: Larock, Richard C., Comprehensive organic transformations: a guide to functional group preparations 2nd ed. New York: Wiley-VCH, 1999. Un método preferido es el uso de nitrato de plata u óxido de plata en un solvente tal como metanol acuoso o anhidro a una temperatura de 25°C o tan alta como reflujo. La reacción típicamente se lleva a cabo por una hasta 48 horas y se observa típicamente por CCD o CL/EM hasta que la conversión completa del producto al material de partida se ha presentado. Alternativamente, $KmnO_4$ o CrO_3/H_2SO_4 podría utilizarse.

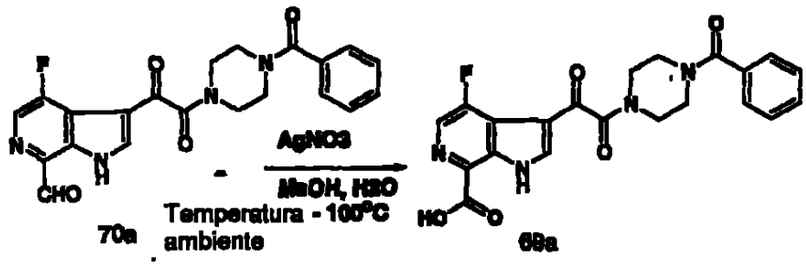
Esquema de reacción 24



70 69

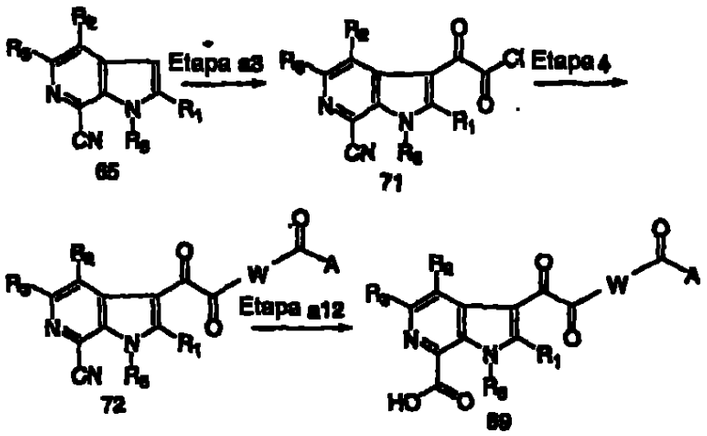
El Esquema de reacción 25 da un ejemplo específico de la oxidación de un intermediario aldehído, 70a, para proporcionar él ácido carboxílico intermediario, 69a.

Esquema de reacción 25

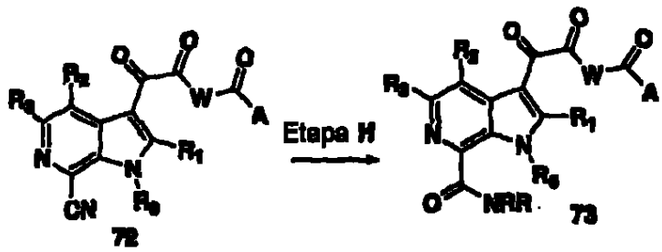


Alternativamente, el intermediario 69 puede prepararse por el método nitrilo de síntesis llevado a cabo en un orden alternativo como se muestra en el Esquema de reacción 26. La etapa de hidrólisis nitrilo puede retardarse y el nitrilo llevarse a través de la síntesis para proporcionar un nitrilo el cual puede hidrolizarse para proporcionar el ácido libre, 69, como arriba.

Esquema de reacción 26



Esquema de reacción 27



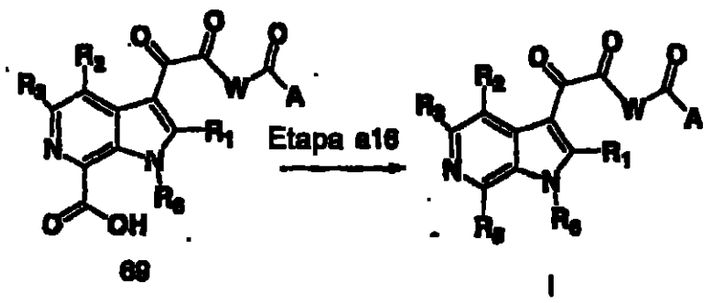
Etapa H. La conversión directa de nitrilos, tal como 72, a amidas, tal como 73, mostrada en el Esquema de reacción 27, Etapa H, puede llevarse a cabo usando las condiciones como se describe en Shiotani, S.; Taniguchi, K.; J. Heterocycl. Chem. 1996, 33(4), 1051-1056 (que describe el uso de ácido sulfúrico acuoso); Memoli, K. A.; Tetrahedron Lett. 1996, 37(21), 3617-3618 ; Adolfsson, H.; Waernmark, K.; Moberg, C.; J. Org. Chem. 1994, 59(8), 2004-2009; y El Hadri, A.; Leclerc, G.; J. Heterocycl. Chem. 1993, 30(3), 631-635.

Etapa I. Para NH2

Shiotani, S.; Taniguchi, K.; J. Heterocycl. Chem. 1997, 34(2), 493-499; Boogaard, A. T.; Pandit, U.K.; Koomen, G.-J.; Tetrahedron 1994, 50(8), 2551-2560; Rivalle, C.; Bisagni, E.; Heterocycles 1994, 38(2), 391-397; Macor, J.E.; Post, R.; Ryan, K.; J. Heterocycl. Chem. 1992, 29(6), 1465-1467.

Etapa J.

Esquema de reacción 28

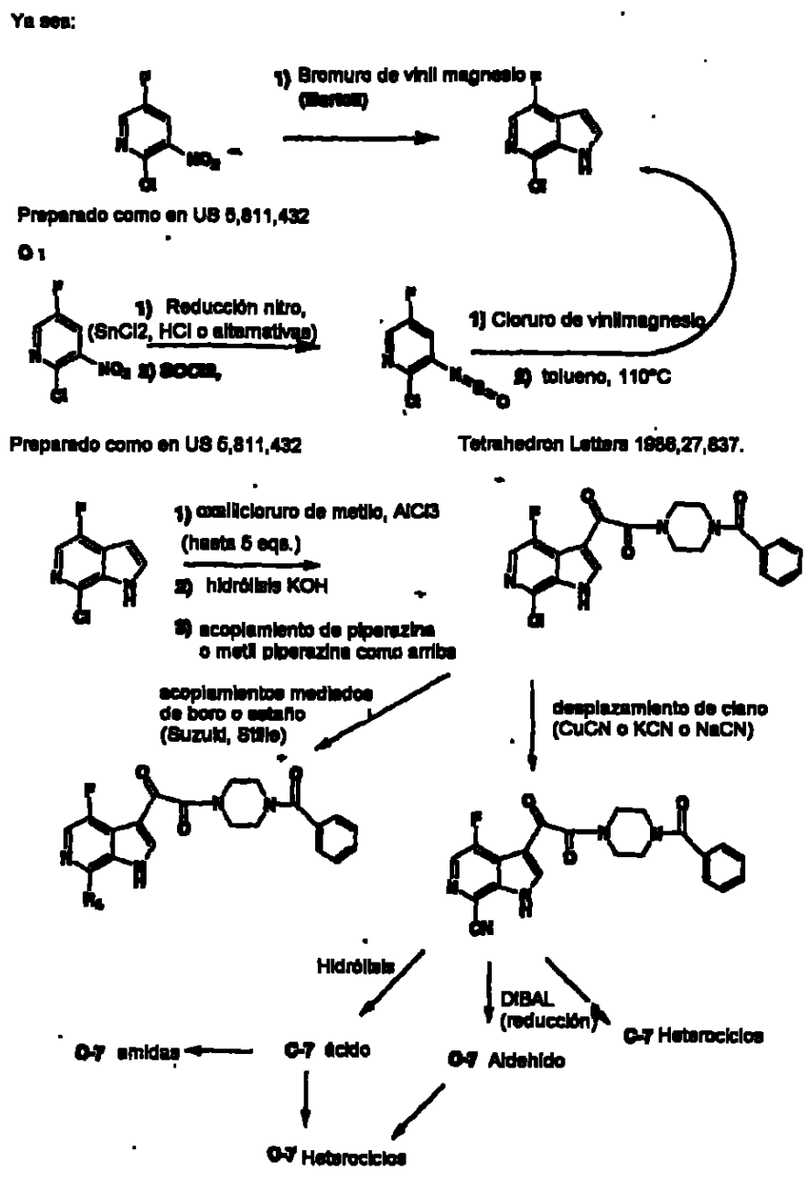


69 I

El siguiente esquema de reacción (28A) muestra un ejemplo para la preparación de 4-fluoro-7azaindoles substituidos a partir de

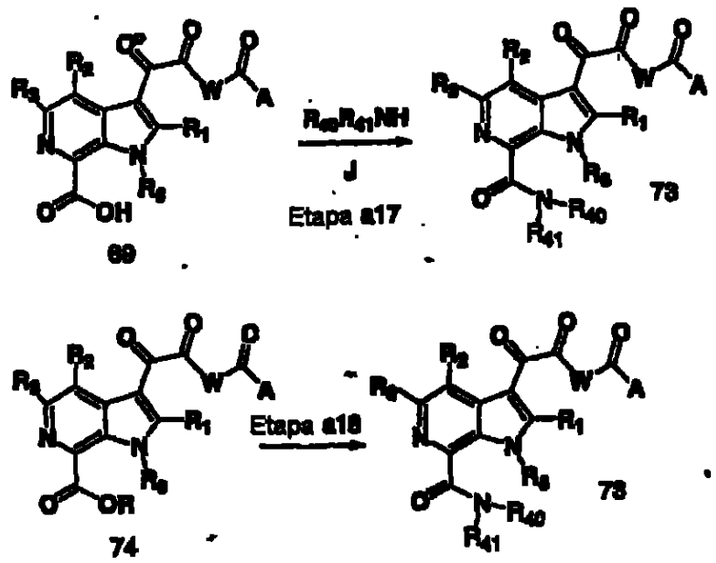
materiales de partida conocidos. Las referencias para la síntesis de indol de Bartoli se mencionan previamente. Las condiciones para la transformación a los nitrilos, ácidos, aldehídos, heterociclos y amidas también se han descrito en esta solicitud.

Esquema de reacción 28A



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Esquema de reacción 29

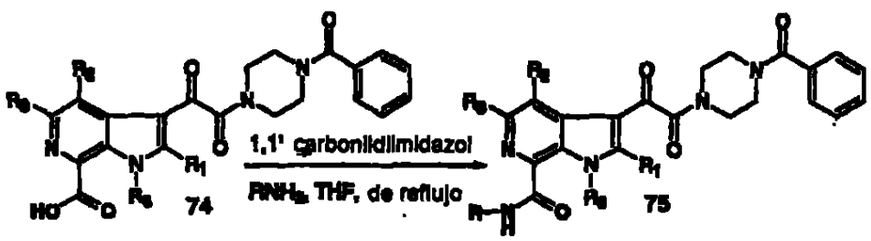


La etapas a16, a17, y a18 abarcan las reacciones y condiciones para la 1°, 2° y 3° formación de enlace amida como se muestra en los Esquemas de reacción 28 y 29 que proporcionan compuestos tal como aquellos de la Fórmula 73.

Las condiciones de reacción para la formación de enlaces amida abarcan cualesquiera de los reactivos que generan el intermediario reactivo para la activación del ácido carboxílico para la formación amida, por ejemplo (pero no se limita a), haluro de acilo, a partir de carbodiimida, sal de acil iminio, anhídridos simétricos, anhídridos mezclados (incluyendo anhídridos mezclados fosfónico/fosfínico), ésteres activos (incluyendo éster de sililo, éster de metilo y tioéster), carbonato de acilo, acil azida, sulfonato de acilo y sal aciloxi N-fosfonio. La reacción de los ácidos

indol carboxílicos con aminas para formar amidas puede mediarse por condiciones de formación de enlace amida estándar descritas en el arte. Algunos ejemplos para formación de enlace amida se enlistan en la referencias 41-53 pero esta lista no es limitante. Algún ácido carboxílico para reactivos de amina de acoplamiento que son aplicables son EDC, Diisopropilcarbodiimida u otras carbodiimidas, PyBop (hexafluorofosfato de benzotriazoliloxitris(dimetilamino)fosfonio), hexafluorofosfato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametil uronio (HBTU). Un método particularmente útil para las reacciones del ácido azaindol 7-carboxílico a la amida es el uso de carbonil imidazol como el reactivo de acoplamiento como se describe en la referencia 53. La temperatura de esta reacción puede ser menos que en la referencia citada, a partir de 80°C (o posiblemente menor) hasta 150°C o mayor. Una aplicación más específica se describe en el Esquema de reacción 30.

Esquema de reacción 30



Los siguientes cuatro métodos generales proporcionan una descripción más detallada para la preparación de indolcarboamidas y estos métodos se emplean para la síntesis de compuestos de la Fórmula I.

Método 1:

A una mezcla de un intermediario ácido, tal como 69, (1 equiv., 0.48 mmol), una amina apropiada (4 equiv.) y DMAP (58 mg, 0.47 mmol) CH_2Cl_2 disuelto (1 mL) se le agregó EDC (90 mg, .0.47 mmol). La mezcla resultante se agitó a temperatura ambiente durante 12 horas, y luego se evaporó in vacuo. El residuo se disolvió en MeOH, y se sometió a purificación CLAR de fase inversa preparativa.

Método 2:

A una mezcla de una amina apropiada (4 equiv.) y HOBT (16 mg, 0.12 mmol) en THF (0.5 mL) se le agregó un intermediario ácido, tal como 69, (25 mg, 0.06 mmol) y NMM (50 µl, 0.45 mmol), seguido por EDC (23 mg, 0.12 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 12 horas. Los volátiles se evaporaron in vacuo; y el residuo se disolvió en MeOH y se sometió a purificación CLAR de fase inversa preparativa.

Método 3:

A una mezcla de un intermediario ácido, tal como 69, (0.047 mmol), amina (4 equiv.) y DEPBT (preparado de conformidad con Li, H.; Jiang, X. Ye, Y.; Fan, C.; Todd, R.; Goodman, M. Organic Letters 1999, 1, 91; 21 mg, 0.071 mmol) en DMF (0.5 mL) se le agregó TEA (0.03 mL, 0.22 mmol). La mezcla resultante se agitó a temperatura ambiente durante 12 horas; y luego se diluyó con MeOH (2 mL) y se purificó por CLAR de fase inversa preparativa.

Método 4:

Una mezcla de un intermediario ácido, tal como 69, (0.047mmol) y 8.5 mg (0.052 mmol) de 1,1-carbonildiimidazol en THF anhidro (2 mL) se calentó a reflujo bajo nitrógeno. Después de 2.5 horas, 0.052 mmol de la amina se agregó y el calentamiento continuó. Después de un periodo adicional de 3-20 horas a reflujo, la mezcla de reacción se enfrió y se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para proporcionar el compuesto de la Fórmula I.

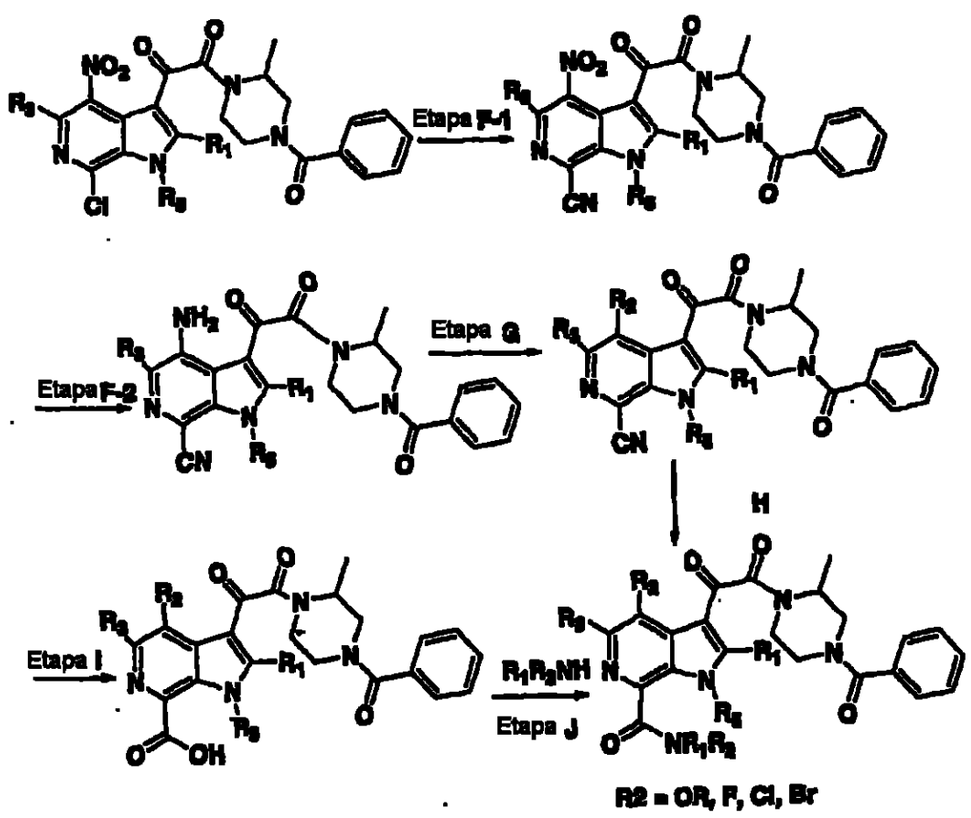
Además, el ácido carboxílico puede convertirse a un cloruro ácido usando reactivos tal como cloruro de tionilo (puro o en un solvente inerte) o el cloruro de oxalilo en un solvente tal como benceno, tolueno, THF, o CH_2Cl_2. Las amidas pueden alternativamente, formarse por la reacción del cloruro ácido con un exceso de

amoniaco, amina primaria, o secundaria en un solvente inerte tal como benceno, tolueno, THF, o CH_2Cl_2 o con cantidades estequiométricas de aminas en presencia de una amina terciaria tal como trietilamina o una base tal como piridina o 2,6-lutidina. Alternativamente, el cloruro ácido puede hacerse reaccionar con una amina bajo condiciones básicas (usualmente hidróxido de sodio o potasio) en mezclas de solventes que contienen agua y posiblemente un co-solvente miscible tal como dioxano o THF. El Esquema de reacción 25B describe una preparación típica de un cloruro ácido y la derivación a una amida de la Fórmula I: Adicionalmente, el ácido carboxílico puede convertirse a un éster preferiblemente un éster de metilo o etilo y luego hacerse reaccionar con una amina. El éster se puede formar por la reacción con diazometano o alternativamente trimetilsilil diazometano usando condiciones estándar que son bien conocidas en el arte. Las referencias y procedimientos para usar estas u otras reacciones que forman el éster, pueden encontrarse en la referencia 52 ó 54.

Las referencias adicionales para la formación de amidas a partir de ácidos son: Norman, M. H.; Navas, F. III; Thompson, J. B.; Rigdon, G. C.; J. Med. Chem. 1996, 39(24), 4692-4703; Hong, F.; Pang, Y.-P.; Cusack,

B.; Richelson, E.; J. Chem. Soc., Perkin Trans 1 1997, 14, 2083-2088; Langry, K. C.; Org. Prep. Proc. Int. 1994, 26(4), 429-438; Romero, D. L.; Morge, R. A.; Biles, C.; Berrios-Pena, N.; May, P. D.; Palmer, J. R.; Johnson, P. D.; Smith, H. W.; Busso, M.; Tan, C.-K.; Voorman, R. L.; Reuşser, F.; Althaus, I. W.; Downey, K. M.; et al.; J. Med. Chem. 1994, 37(7), 999-1014; Bhattacharjee, A.; Mukhopadhyay, R.; Bhattacharjya, A.; Indian J. Chem., Sect B 1994, 33(7), 679-682.

Esquema de reacción 31



El Esquema de reacción 31 muestra transformaciones sintéticas en un cloro nitro azaindol. La etapa F-1 del Esquema de reacción 31 puede llevarse a cabo de conformidad con los siguientes procedimientos: Yamaguchi, S.; Yoshida, M.; Miyajima, I.; Araki, T.; Hirai, Y.; J. Heterocycl. Chem. 1995, 32(5), 1517-1519;

Yutilov, Y. M.; Svertilova, I. A.; Khim Geterotsikl Soedin 1994, 8, 1071-1075; y Prager, R. H.; Tsopelas, C.; Heisler, T.; Aust. J. Chem. 1991, 44(2), 277-285. La etapa F-2 del Esquema de reacción 31 puede realizarse según los procedimientos establecidos en: Ciurla, H.; Puszko, A.; Khim Geterotsikl Soedin 1996, 10, 1366-1371; Robinson, R. P.; Donahue, K. M.; Son, P. S.; Wagy, S. D.; J. Heterocycl. Chem. 1996, 33(2), 287- 293; Nicolai, E.; Claude, S.; Teulon, J. M.; J. Heterocycl. Chem. 1994, 31(1), 73-75; Hwu, J. R.; Wong, F. F.; Shiao, M.-J.; J. Org. Chem. 1992, 57(19), 5254-5255; Shiao, M.-J.; Lai, L.-L.; Ku, W.-S.; Lin, P.-Y.; Hwu, J. R.; J. Org. Chem. 1993, 58(17), 4742-4744.

La introducción de un substituyente alcoxi o ariloxi en el azaindol (Etapa G, Esquema de reacción 31, R_2 es alcoxi o ariloxi) puede realizarse por los procedimientos descritos en Klemm, L. H.; Zell, R.; J. Heterocycl. Chem. 1968, 5, 773; Bradsher, C. K.; Brown, F. C.; Porter, H. K.; J. Am. Chem. Soc. 1954, 76, 2357; y Hodgson, H. H.; Foster, C. K.; J. Chem. Soc. 1942, 581.

La introducción de un substituyente flúor en el azaindol (Etapa G, Esquema de reacción 31) puede realizarse según los procedimientos como se describe en Sanchez, J. P.; Gogliotti, R. D.; J. Heterocycl. Chem. 1993, 30(4), 855-859; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G.; Tetrahedron Lett. 1993, 34(18), 2937-2940; y Sanchez, J. P.; Rogowski, J. W.; J. Heterocycl. Chem. 1987, 24, 215.

La introducción de un substituyente cloro en el azaindol (Etapa G, Esquema de reacción 31) puede realizarse según los procedimientos como se describe en Ciurla, H.; Puszko, A.; Khim Geterotsikl Soedin 1996, 10, 1366-1371; Raveglia, L. F.; GiardinaI, G.A.M.; Grugni, M.; Rigolio, R.; Farina, C.; J. Heterocycl. Chem. 1997, 34(2), 557-559; Matsumoto, J. I.; Miyamoto, T.; Minamida, A.; Mishimura, Y.; Egawa, H.; Mishimura, H.; J. Med. Chem. 1984, 27(3), 292; Lee, T.-C.; Salemnick, G.; J. Org. Chem. 1975, 24, 3608.

La introducción de un substituyente bromo en el azaindol (Etapa G, Esquema de reacción 31) puede realizarse según los procedimientos como se describe en Raveglia, L. F.; Giardina, G. A. M.; Grugni, M.; Rigolio, R.; Farina, C.; J. Heterocycl. Chem. 1997, 34 (2), 557-559; Talik, T.; Talik, Z.; Ban-Oganowska, H.; Synthesis 1974, 293; Abramovitch, R. A.; Saha, M.; Can. J. Chem. 1966, 44, 1765.

Es bien conocido en el arte que los heterociclos pueden prepararse a partir de un aldehído, ácido carboxílico, éster

de ácido carboxílico, amida del ácido carboxílico, haluro del ácido carboxílico, o porción ciano o enlazarse a otro carbono substituido por un bromuro u otro grupo de partida tal como un triflato, mesilato, cloruro, yoduro, o fosfonato. Los métodos para preparar tales intermediarios a partir de los intermediarios tipificados por el ácido carboxílico intermediario, 69, bromo intermediario, 76, o aldehído intermediario, 70 descritos arriba, son bien conocidos por un practicante de la química típico. Los métodos o tipos de heterociclos que pueden construirse se describen en la literatura química. Algunas referencias representativas para encontrar tales heterociclos y su construcción se incluyen en la referencia 55 hasta 67 pero no se construirá como limitante. Sin embargo, el examen de estas referencias muestra que están disponibles muchos métodos versátiles para sintetizar diversamente heterociclos substituidos y son aparentes para alguien de habilidad en el arte que estos pueden aplicarse para preparar compuestos de la Fórmula I. Los químicos bien versados en el arte pueden ahora fácilmente, rápidamente, y rutinariamente encontrar numerosas reacciones para preparar heterociclos, amidas, oximas u otros susbtituyentes a partir del material de partida arriba mencionado al hacer la búsqueda para reacciones o preparaciones usando la base de datos electrónica convencional tal como Scifinder (American Chemical Society),

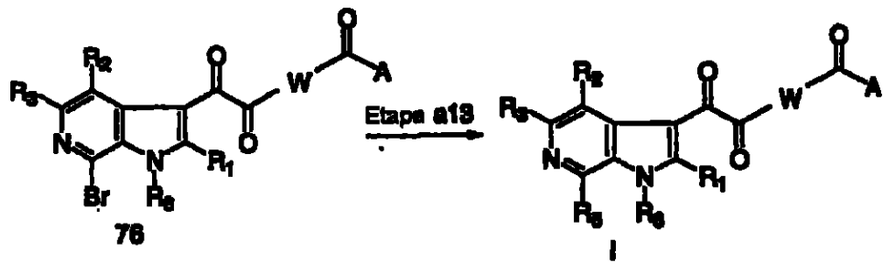
Crossfire (Beilstein), Theilheimer, o Reaccs (MDS). Las condiciones de reacción identificadas por tal búsqueda pueden entonces emplearse usando los substratos descritos en esta solicitud para producir todos los compuestos divisados y cubiertos por esta invención. En el caso de amidas, se pueden usar aminas comercialmente disponibles en la síntesis. Alternativamente, los programas de búsqueda arriba mencionados se pueden usar para localizar preparaciones de la literatura de aminas conocidas o procedimientos para sintetizar aminas nuevas. Estos procedimientos se llevan a cabo entonces por alguien con experiencia típica en el arte para proporcionar los compuestos de la Fórmula I para usar como agentes antivirales.

Como se muestra abajo en el Esquema de reacción 32, Etapa a13, los azaindoles substituidos apropiados, tal como el bromoazaindol intermediario, 76, pueden experimentar acoplamiento mediado por metales con grupos arilo, heterociclos, o vinil estananos para proporcionar compuestos de la Fórmula I en donde R_5 es arilo, heteroarilo, o heteroalicíclico por ejemplo. Los intermediarios bromoazaindol, 76 (o azaindol triflatos o yoduros) pueden experimentar acoplamiento tipo Stille con heteroarilestananos como se muestra en el Esquema de reacción 32, Etapa a13. Las condiciones para esta reacción son bien conocidas en el arte y las referencias 68-70 así como la referencia 52 proporciona

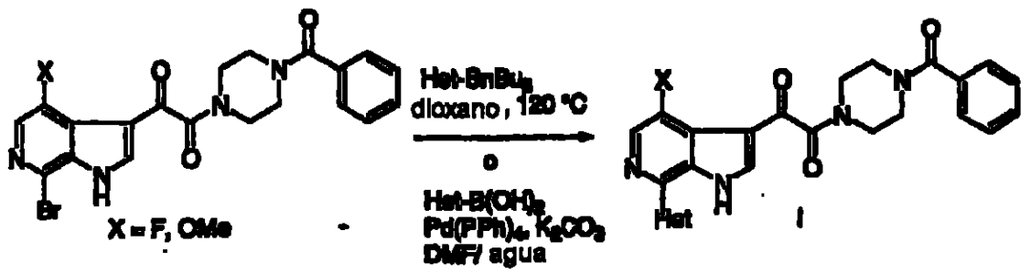
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numerosas condiciones además de los ejemplos específicos proporcionados en el Esquema de reacción 14 y en las modalidades específicas. Puede ser bien reconocido que un indol estanano también podrá acoplarse a un haluro o triflato heterocíclico o arilo para construir compuestos de la Fórmula I. El acoplamiento Suzuki (referencia 71) entre el intermediario de bromo, 76, y un boronato apropiado también podrá emplearse y algunos ejemplos específicos están contenidos en esta solicitud.

Esquema de reacción 32

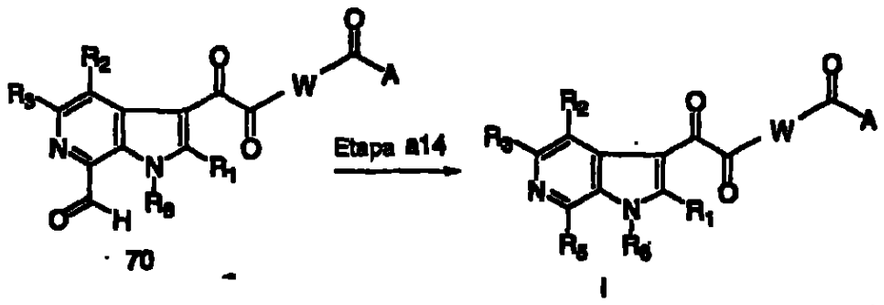


Esquema de reacción 33



Como se muestra en el Esquema de reacción 34, Etapa a14, los intermediarios aldehído, 70, pueden usarse para generar numerosos compuestos de la Fórmula I. El grupo aldehído puede ser un precursor para cualesquiera de los substituyentes R_1 hasta R_5 pero la transformación para R_5 se describe arriba por simplicidad. El intermediario aldehído 70, puede hacerse reaccionar para incorporarlo en el anillo

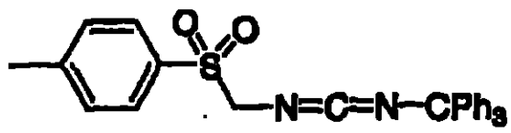
Esquema de reacción 34



70 I

como se describe en las reivindicaciones o se convierte en un grupo acíclico. El aldehído, 70, puede hacerse reaccionar con un reactivo de base Tósmico para generar oxazoles (referencias 42 y 43 por ejemplo). El aldehído, 70, puede hacerse reaccionar con un reactivo tósmico y entonces una amina para dar imidazoles como en la referencia 72 o el intermediario aldehído, 70, puede hacerse reaccionar con hidroxilamina para dar una oxima la cual es un compuesto de la Fórmula I como se describe abajo. La oxidación de la oxima con NBS, hipoclorito de t-butilo, o los otros reactivos

conocidos proporcionaría el N-óxido que reacciona con alquinos o ésteres de 3 alcoxi vinilo para dar isoxazoles de substituición variada. La reacción del aldehído intermediario 70, con el reactivo conocido, 77 (referencia 70) mostrada abajo bajo condiciones básicas proporcionaría 4-aminotritil oxazoles.



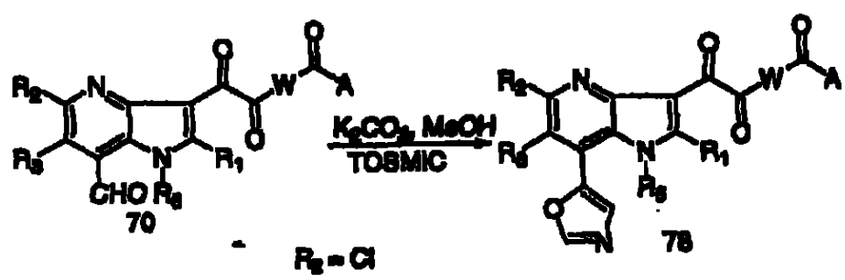
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La remoción del grupo tritilo proporcionaría 4-amino oxazoles que podrán substituirse por acilación, alquilación reductiva o reacciones de alquilación o reacciones que forman heterociclo. El tritilo podrá reemplazarse con un grupo protector alternativo tal como un tritil monometoxi-, CBZ, bencilo, o un grupo sililo apropiado si se desea. La referencia 73 demuestra la preparación de oxazoles que contienen una porción triflouorometilo y las condiciones descritas en la presente demuestra la síntesis de oxazoles con grupos metilo fluorados adjuntos a estos.

El aldehído también podrá hacerse reaccionar con un metal o Grignard (alquilo, arilo, o heteroarilo) para generar alcoholes secundarios. Estos serán eficacez o podrán oxidarse para la cetona con TPAP o MnO_2 o PCC por

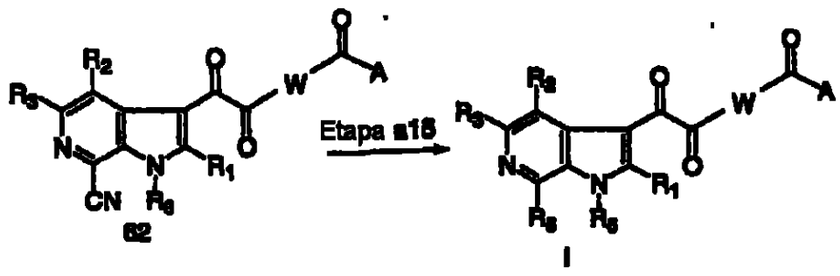
ejemplo para proporcionar cetonas de la Fórmula I las cuales podrían utilizarse para el tratamiento o hacerse reaccionar con reactivos de metal para dar alcoholes terciarios o alternativamente convertirse a oximas por la reacción con clorohidratos de hidroxilamina en solventes etanólicos. Alternativamente el aldehído podrá convertirse a bencil aminas por medio de aminación reductiva. Un ejemplo de la formación oxazol por medio de un reactivo tósmico se muestra abajo en el Esquema de reacción 35. La misma reacción podrá trabajar con aldehídos en otras posiciones y también en la serie 5 y 6 aza indol.

Esquema de reacción 35



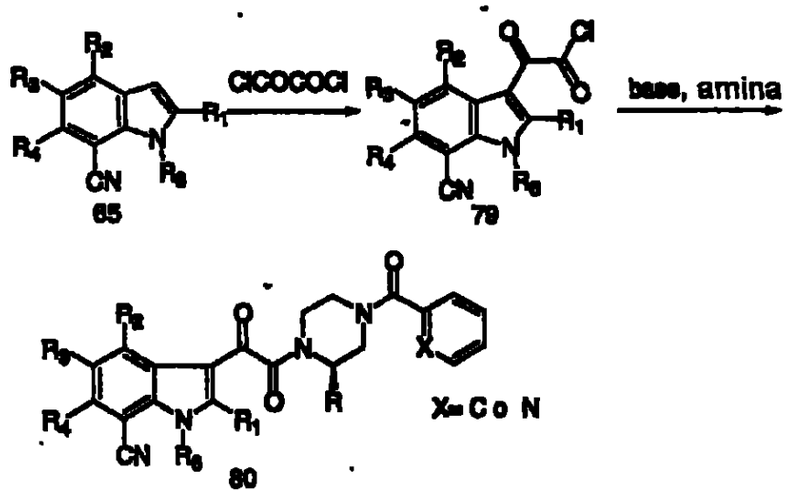
El Esquema de reacción 36 muestra en la Etapa a15, un ciano intermediario, tal como 62, el cual podrá convertirse directamente a compuestos de la Fórmula I por medio de formación heterociclo o la reacción con reactivos organometálicos.

Esquema de reacción 36



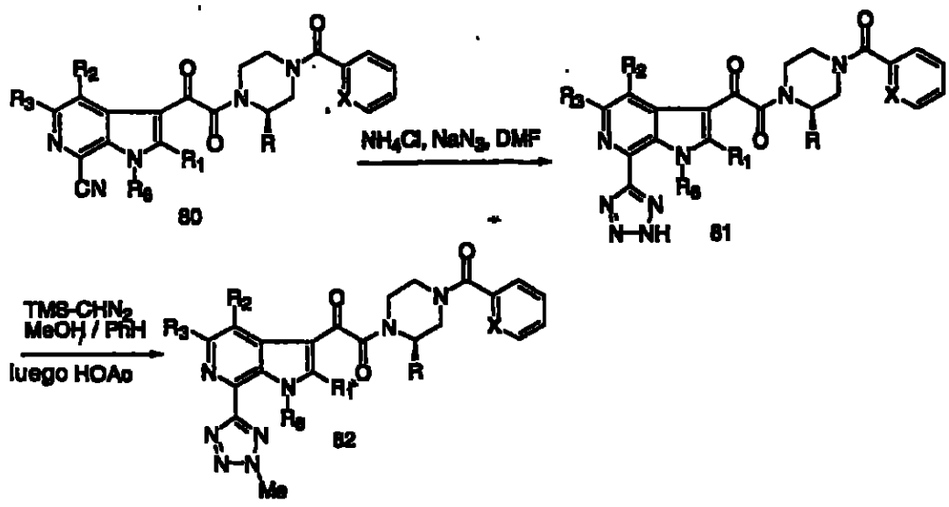
El Esquema de reacción 37 muestra un método para la acilación de un cianoindol intermediario de la Fórmula 65 con el cloruro de oxalilo que podrá dar el cloruro ácido, 79, que podrá entonces acoplarse con la amina apropiada en presencia de una base para proporcionar 80.

Esquema de reacción 37



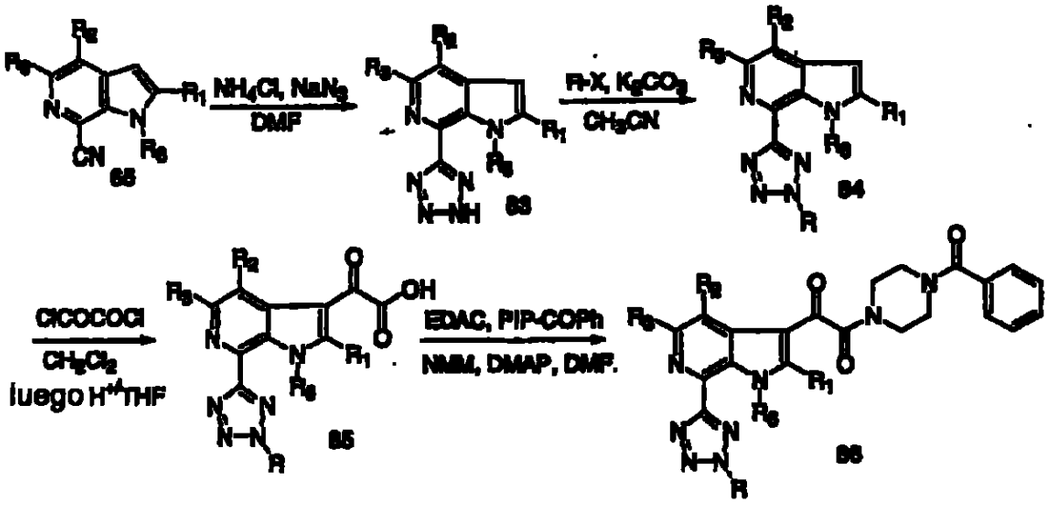
El intermediario nitrilo, 80, podrá convertirse al tetrazol de la Fórmula 81, que podrá entonces alquilarse con trimetilsilildiazometano para dar el compuesto de la Fórmula 82 (Esquema de reacción 38).

Esquema de reacción 38



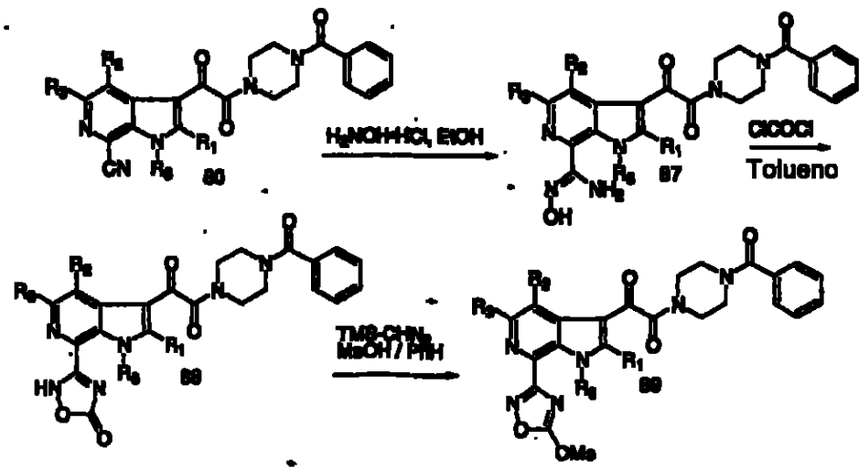
La alquilación de tetrazol con alquil haluros se llevará a cabo antes de la acilación de azaindol como se muestra en el Esquema de reacción 39. El intermediario 65 podrá convertirse a tetrazol, 83, que podrá alquilarse para proporcionar 84. El intermediario 84 podrá entonces acilarse e hidrolizarse para proporcionar 85 el cual podrá someterse a condiciones de formación amida para proporcionar 86. El grupo adjunto al tetrazol puede ser completamente diverso y todavía exhibir potencia de impresión.

Esquema de reacción 39



El Esquema de reacción 40 muestra que un oxadiazol tal como 88, puede prepararse por la adición de hidroxilamina al nitrilo, 80, seguido por cerrado del anillo ddel intermediario 87 con fosgeno. La alquilación de oxadiazol, 88, con trimetilsilildiazometano dará el compuesto de la Fórmula 89.

Esquema de reacción 40



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Un 7-cianoindol, tal como en 80 se puede convertir eficientemente al éster de imidato bajo condiciones convencionales de Pinner usando 1,4-dioxano como el solvente. El éster de imidato puede reaccionar con nucleófilos de nitrógeno, oxigeno, y azufre para proporcionar C7-indoles substituidos, por ejemplo: imidazolinas, bencimidazoles, azabencimidazoles, oxazolinas, oxadiazoles, tiazolinas, triazoles, pirimidinas y amidinas etc. Por ejemplo, el imidato puede reaccionar hidrazida de acetilo con calentamiento en un solvente no participante tal como dioxano, THF o benceno por ejemplo (base acuosa o base acuosa en un solvente alcohólico se puede requerir para efectuar una ciclización final deshidratante en algunos casos) para formar una metil triazina. Se puede usar otras hidracinas. Las triazinas también se pueden instalar por medio de acoplamiento de triasinas de estanilo con 4, 5, 6 o 7 bromo o cloro azaindoles. Los ejemplos dan un ejemplo de la formación de muchos de estos heterociclos.

Referencias:

(1) Das, B. P.; Boykin, D. W. J. Med. Chem. 1977, 20, 531.

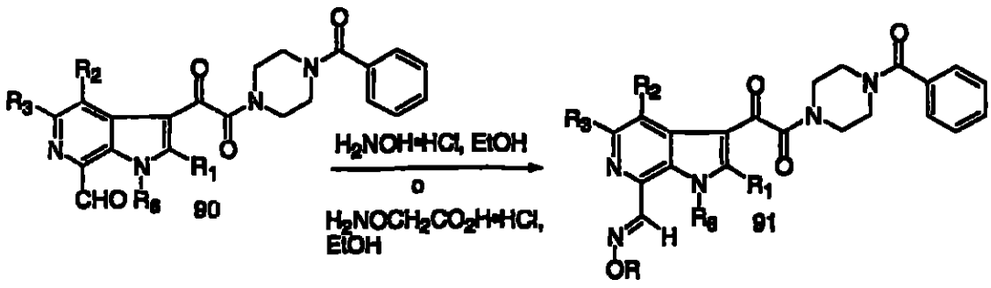
(2) Czany, A.; Wilson, W. D.; Boykin, D. W. J. Heterocyclic Chem 1996, 33, 1393.

(3) Francesconi, I.; Wilson, W. D.; Tanious, F. A.; Hall, J. E.; Bender, B. C.; Tidwell, R. R.; McCurdy, D.; Boykin, D. W. J. Chem. 1999, 42, 2260.

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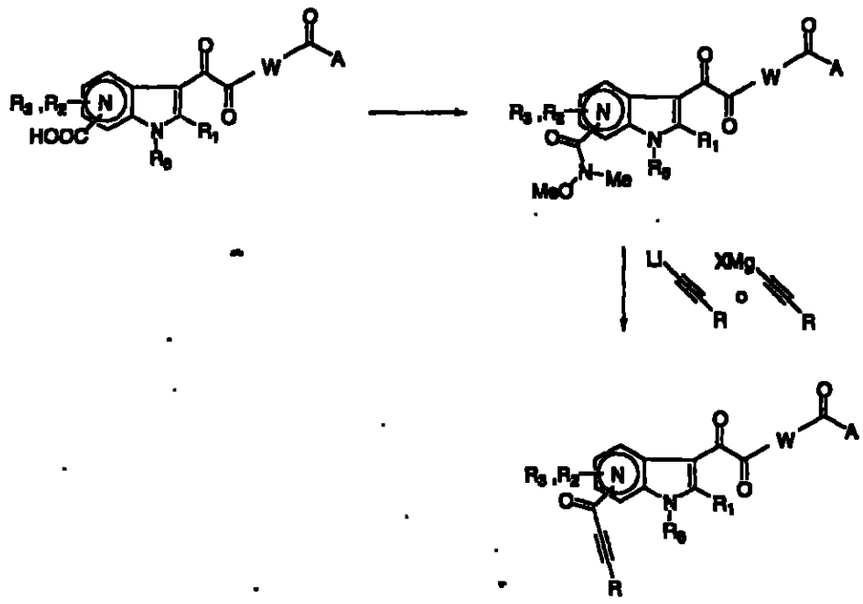
El esquema de reacción 41 muestra la adición de hidroxilamina o ácido hidroxilamina acetico el intermediario de aldehído 90 que puede dar la oxima de formula 91.

Esquema de reacción 41



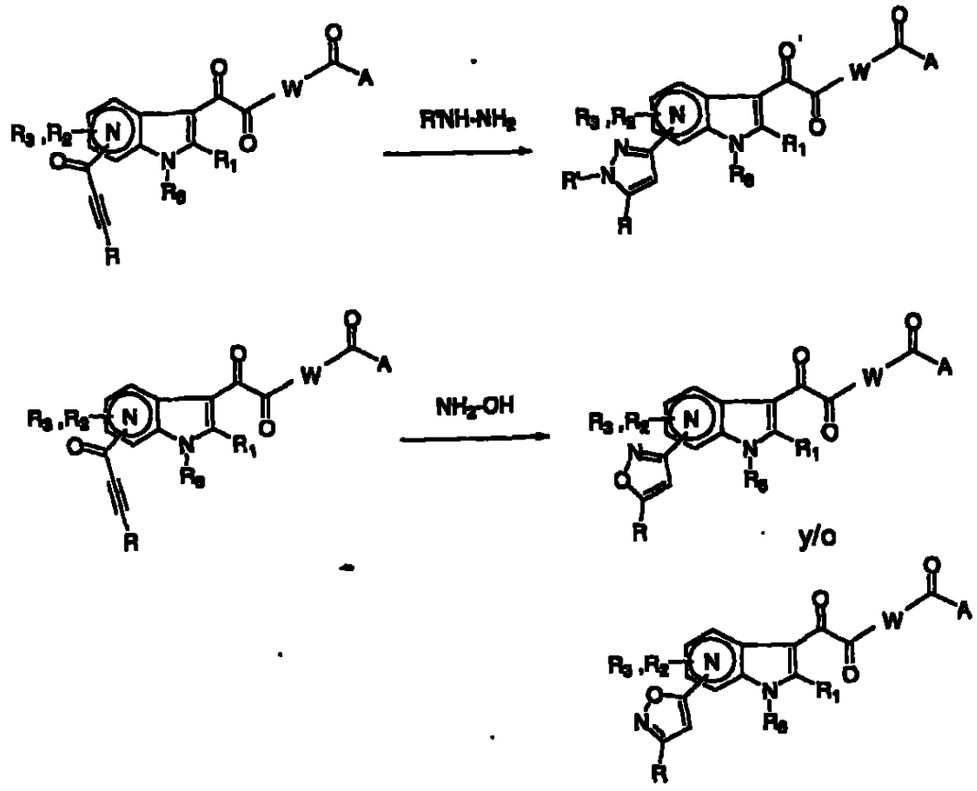
Un ácido puede ser un precursor para los substituyentes R_1 hasta R_5 cuando ocupa la posición correspondiente tal como R_5 como se muestra en el esquema de reacción 42.

Esquema de reacción 41a

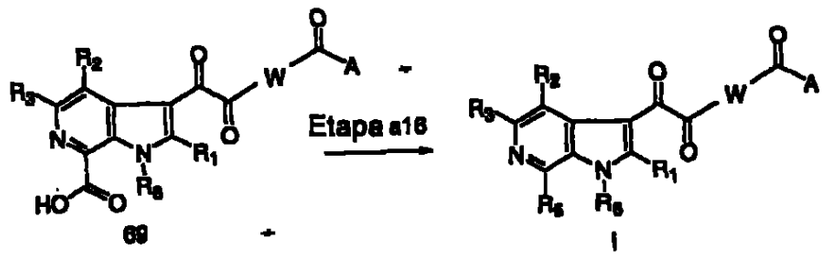


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Esquema de reacción 41a (continuación)



Esquema de reacción 42



Un intermediario ácido tal como 69 se puede usar como un precursor versátil para generar diversos compuestos substituidos. El ácido se puede convertir al bromuro de

hidrazonilo y luego a un pirazol por medio de la referencia 74. Un método para la síntesis general de heterociclos sería convertir el ácido a una alfa bromo cetona (ref 75) por conversión al cloruro ácido usando métodos estándar, reacción con diazometano y finalmente reacción con HBr. La alfa bromo cetona se puede usar para preparar muchos compuestos diferentes de fórmula 1 ya que se puede convertir a muchos heterociclos u otros compuestos de fórmula 1. Las alfa amino cetona se pueden preparar por desplazamiento del bromuro con cetona. Alternativamente la alfa bromo cetona se puede usar para preparar heterociclos que no están disponibles directamente del aldehído o del ácido. Por ejemplo, al usar las condiciones de Hulton en la referencia 76 para reaccionar con la alfa bromo cetona proporcionaría oxazoles. La reacción de alfa bromo cetona con urea por medio de los métodos de referencia 77 proporcionaría 2-amino oxazoles. La alfa bromo cetona se puede también usar para generar furanos usando betas ceto ésteres (ref 78-80) u otros métodos, pirroles (a partir de beta dicarbonilos como en ref 81 o por los métodos de Hantsch (ref 82) tiazoles, isoxazoles e imidazoles (ref 83) de ejemplo usando los procedimientos de literatura. el acoplamiento del cloruro ácido antes mencionado con N-metil-O-metil hidroxil amina proporcionaría una "amina Weinreb" que se puede usar para reaccionar con alquil

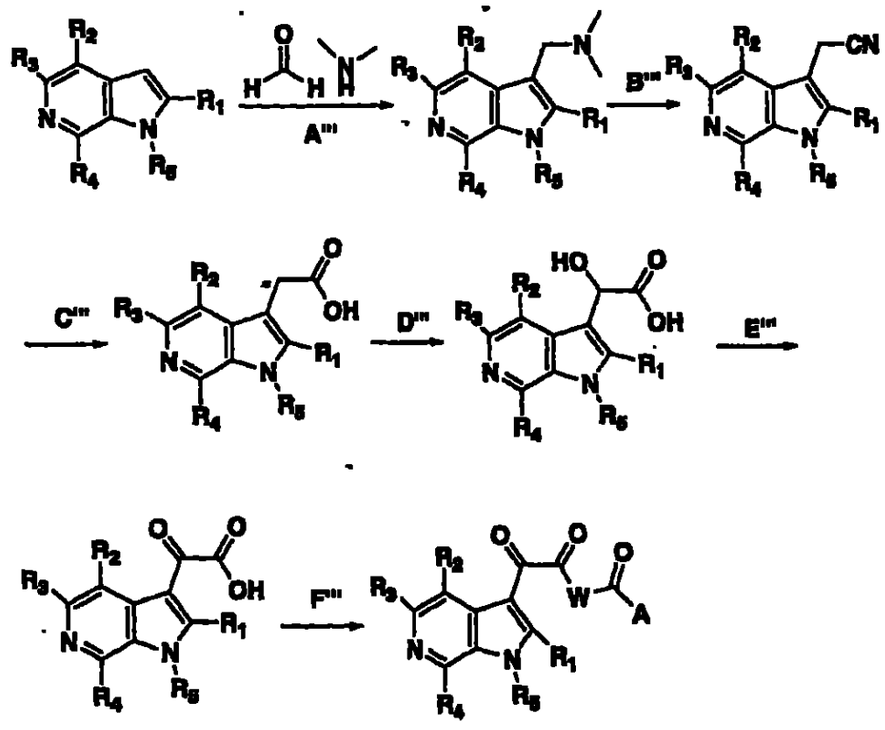
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litios o reactivos de Grignard para generar cetona. La reacción de la anión Weinreb de un dianion de una hidroxi amina generaría isoxazoles (ref 84). La reacción con un litio acetilénico u otro carbanión generaría alquinil indol cetona. La reacción de este intermediario alquinilo con diazometano u otros compuestos diazo daría pirazoles (ref 85). La reacción con azida o hidroxil amina daría heterociclos después de la eliminación de agua. Los óxidos de nitrilo reaccionarían con la alquinil cetona para dar isoxazoles (ref 86). La reacción del ácido inicial para proporcionar un cloruro ácido usando por ejemplo cloruro de oxalilo o cloruro de tionilo trifenil fosfina/tetracloruro de carbono, proporciona un intermediario útil como se señala arriba. La reacción del cloruro ácido con un isocianuro substituido con alfa éster y una base daría 2-oxazoles substituidos (ref 87). Estos se pueden convertir a aminas, alcoholes, o haluros usando reducciones estándar o reconfiguraciones del tipo Hoffman/Curtius.

El esquema de reacción 43 describe la química alternativa para instalar la porción de oxoacetil piperazina sobre la posición 3 de los azaindoles. La etapa "A" en el esquema de reacción 43 detalla la reacción formaldehido y dimetilaminia usando las condiciones en Frydman, B; Despuy, M. E.; Rapoport, H.; J. Am. Chem. Soc. 1965, 87, 3530 proporcionará el compuesto de dimetilamino que se muestra.

La etapa "B" muestra que el displazamiento con cianuro de potasio proporcionaría el derivado ciano según el método descrito Miyashita, K.; Kondoh, K.; Tsuchiya, K.; Miyabe, H.; Imanishi, T.; Chem. Pharm. Bull. 1997, 45(5), 932-935 o en Kawase, M.; Sinhababu, A. K.; Borchardt, R. T.; Chem. Pharm. Bull. 1990, 38(11), 2939-2946. La misma transformación también se puede efectuar usando TMSCN y una fuente de fluoruro de tetrabutilamonio como en Iwao, M.; Motoi, O.; Tetrahedron Lett. 1995, 36 (33), 5929-5932. También se puede utilizar cianuro de sodio.

Esquema de reacción 43



La etapa "C" del esquema de reacción 43 detalla la hidrólisis de nitrilo con hidróxido de sodio y metanol proporcionaría el ácido por medio de los métodos descritos en Iwao, M.; Motoi, O.; Tetrahedron Lett. 1995, 36(33), 5929-5932 por ejemplo. Otras condiciones básicas de hidrólisis usando cualquiera de NaOH o KOH como se describe en Thesing, J.; et al.; Chem. Ber. 1995, 88, 1295 y Geissman, T. A.; Armen, A.; J. Am. Chem. Soc. 1952, 74, 3916. El uso de una encima nitrilasa para lograr la misma transformación se describe por Klempier N, de Raadt A, Griengl H, Heinisch G, J. Heterocycl. Chem., 1992 29, 93 y puede ser aplicables.

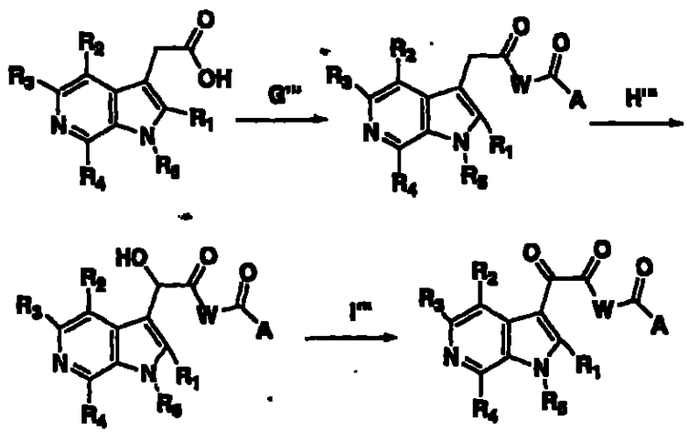
La etapa "D" del esquema de reacción 43 detalla una alfa hidroxilación que se puede lograr por los métodos como se describen en Hanessian, S.; Wang, W.; Gai, Y.; Tetrahedron Lett. 1996, 37(42), 7477-7480; Robinson, R. A.; Clark, J. S.; Holmes, A. B.; J. Am. Chem. Soc. 1993, 115(22), 10400-10401 ($KN(TMS)_2$ y luego camforsulfoniloxaziridina u otra oxasziridina y Davis, F.A.; Reddy, R. T.; Reddy, RE.; J. Org. Chem. 1992, 57(24), 6387-6389.

La etapa "E" del esquema de reacción de 43 muestra métodos para la oxidación del éster alfa hidroxi a la cetona que se puede lograr según los métodos descritos en Mohand, S.A.; Levina, A.; Muzart, J.; Synth. Comm. 1995, 25(14), 2051-2059. Un método preferido para la etapa "E" es aquel de Ma, Z.; Bobbitt, J. M.; J. Org. Chem. 1991, 56(21), 6110-6114

que utiliza 4-(NH-Ac)-TEMPO en un solvente tal comoCH_2Cl_2 en presencia de ácido toluensulfonico. El método descrito en Corson, B. B.; Dodge, R. A.; Harris, S. A.; Hazen, R. K.; Org Synth 1941, I, 241 para la oxidación de éster alfa hidroxi a la cetona usa $KmnO_4$ como oxidante. Otros métodos para la oxidación del éster alfa hidroxi a la cetona incluyen aquellos descritos en Hunaeus,; Zincke,; Ber. Dtsch Chem. Ges. 1877, 10, 1489; Acree,; Am. Chem. 1913, 50, 391; y Claisen; Ber. Dtsch. Chem. Ges. 1877, 10, 846.

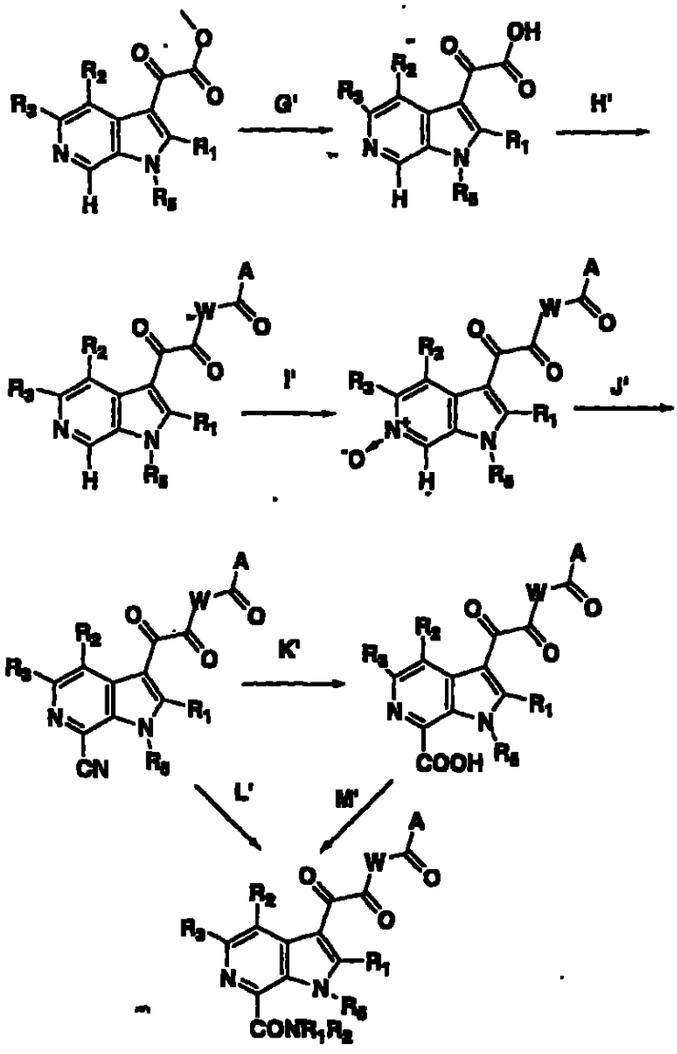
La etapa "F" del esquema de reacción 43 detalla las reacciones de acoplamiento que se pueden efectuar como se describió en la solicitud y por un método preferido que se describe en Li, H.; Jiang, X.; Ye, Y.-H-; Fan, C.; Romoff, T.; Goodman, M. Organic Lett, 1999, 1, 91-93 y emplea 3-(Dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)ona (DEPBT); un nuevo reactivo de acoplamiento con resistencia notable a la racemización.

Esquema de reacción 44



El esquema de reacción 44 detalla la preparación de compuestos de fórmula I por acoplamiento de HWC(O)A al ácido como se describe en la Etapa "F" del esquema de reacción 43, seguido por la hidroxilación como en la etapa "D" del esquema de reacción 43 y la oxidación como se describe en la etapa "E" del esquema de reacción 43.

Esquema de reacción 45

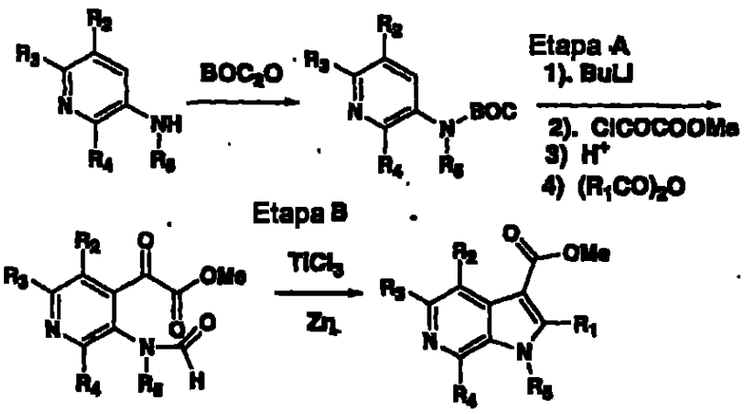


El esquema de reacción 45 detalla un método para la preparación que se puede usar para obtener compuestos amido de fórmula I. La etapa G' representa la hidrólisis de éster seguido por la formación de amidas (etapa H' como se describe en la etapa F" del esquema 43). La etapa I' del esquema 45 detalla la preparación del N-óxido que se puede lograr según los procedimientos en Suzuki, H.; Itawa, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y.; Tetrahedron 1997, 53(5), 1593-1606; Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y.; Chem. Pharm. Bull. 1991, 39(8), 2170-2172; and Ohmato, T.; Koike, K.; Sakamoto, Y.; Chem. Pharm. Bull. 1981, 29, 390. La cianación del N-óxido se muestra en la etapa J' del esquema de reacción 45 que se puede lograr según con Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y.; Tetrahedron 1997, 53(5), 1593-1606 and Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y.; Chem. Pharm. Bull. 1991, 39(8), 2170-2172. La hidrólisis al ácido se detalla en la etapa K' del esquema de reacción 45 de acuerdo con los procedimiento tales como Shiotani, S.; Tanigucchi, K.; J. Heterocycl. Chem. 1996, 33(4), 1051-1056; Memoli, K. A.; Tetrahedron Lett. 1996, 37(21), 3617-3618; Adolfsson, H.; Waernmark, K.; Moberg, C.; J. Org. Chem. 1994, 59(8), 2004-2009; and El Hadri, A.; Leclerc, G.; J. Heterocycl. Chem.

1993, 30(3), 631-635. La etapa L' del esquema de reacción 45 detalla un método que se puede utilizar para la preparación de los amido de fórmula 1 a partir del derivado ciano que se puede lograr según los procedimientos descritos en Shiotani, Shiotani, S.; Taniguchi, K.; J. Heterocycl. Chem. 1997, 34(2), 493-499; Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J.; Tetrahedron 1994, 50(8), 2551-2560; Rivalle, C.; Bisagni, E.; Heterocycles 1994, 38(2), 391-397; and Macor, J. E.; Post, R.; Ryan, K.; J. Heterocycl. Chem. 1992, 29(6), 1465-1467. La etapa M' del esquema de reacción 45 muestra un método que se puede utilizar para la preparación de compuestos de amido de fórmula 1 a partir del derivado ácido que se puede lograr según los procedimientos descritos en Norman, M.H.; Navas, F. III; Thompson, J.B.; Rifdon, G.C.; J. Med. Chem. 1996, 39(24), 4692-4703; Hong, F.; Pang, Y.-P.; Cusack, B.; Richelson, E.; J. Chem. Soc., Perkin Trans 1 1997, 14,, 2083-2088; Langry, K. C.; Org. Prep. Proced. Int. 1994, 26(4), 429-438; Romero, D.L.; Morge, R.A.; Biles, C.; Berrios-Pena, N.; May, P.D.; Palmer, J.R.; Johnson, P.D.; Smith, H.W.; Busso, M.; Tan, C.-K.; Voorman, R.L.; Reusser, F.; Althaus, LW.; Downey, K.M.; et al.; J. Med. Chem. 1994, 37(7), 999-1014 and Bhattacharjee, A.; Mukhopadhyay, R.; Bhattacharjya, A.; Indian J. Chem., Sect B 1994, 33(7), 679-682.

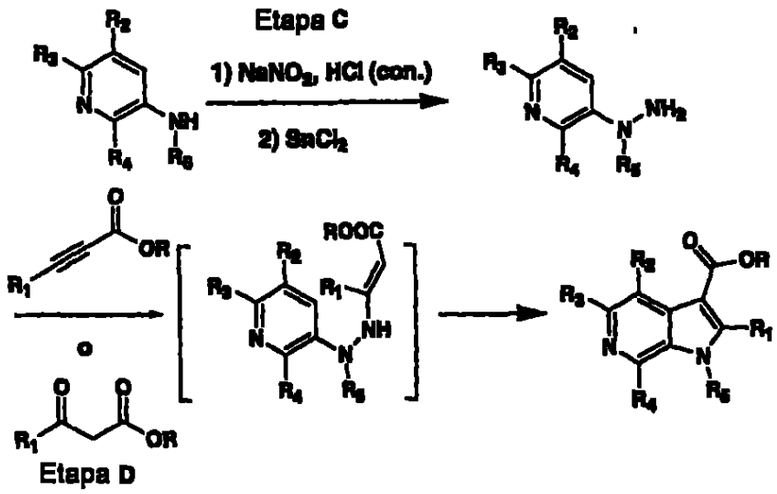
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Esquema de reacción 46



El esquema de reacción 46 muestra un método que se puede usar para la síntesiš de un derivado del ácido azaindol acetico. La protección del grupo amina se puede efectuar con el tratamiento de di-tert-butildicarbonato para introducir el grupo t-Butoxicarbonil (BOC). Luego se puede lograr la introducción de la porción oxalato como se muestra en la etapa A del esquema de reacción 46 según los procedimientos escritos en Hewawasam, P.; Meanwell, N. A.; Tetrahedron Lett. 1994, 35(40), 7303-7306 (usando t-Buli, o t-buli, THF); o Stanetty, P.; Koller, H.; Mihovilovic, M.; J. Org. Chem. 1992, 57(25), 6833-6837 (usando t-Buli). El intermediario así formado luego se puede ciclizar para formar el azaindol como se muestra en la etapa B en el esquema de reacción 46 según los procedimientos descritos en Fuerstner, A.; Ernst, A.; Krause, H.; Ptock, A.; Tetrahedron 1996, 52(21), 7329-7344 (usando TiCl3, Zn, DME) O Fuerstner, A.; Hupperts, A.; J. AM. Chem. Soc. 1995, 117(16), 4468-4475 (usando Zn, exceso de Tms-Cl, TiCl3 (cat), MeCN).

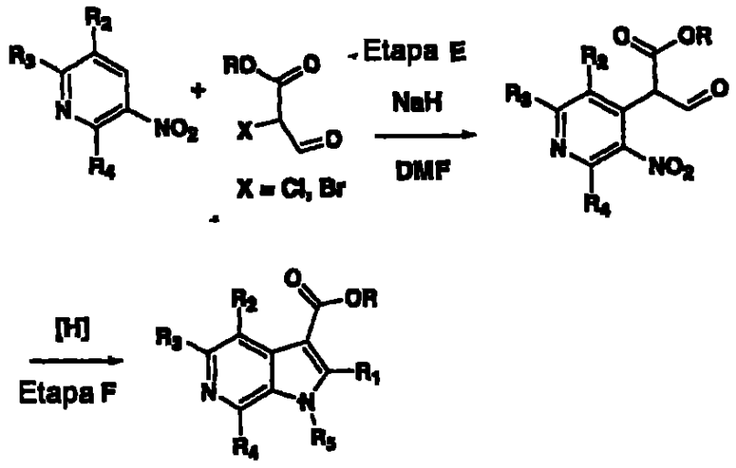
Esquema de reacción 47



El esquema de reacción 47 describe una síntesis alterna que se puede usar para preparar derivados del azaindol acético. La etapa C del esquema de reacción 47 se puede efectuar al usar los procedimientos descritos en Harden, F.A.; Quinn, R.J.; Scammells, P.J.; J. Med. Chem. 1991, 34(9), 2892-2898 [uso de 1. $NaNO_2$, HCl concentrado 2. $SnCl_2$, HCl concentrado (cat.)]. Típicamente, 10 equivalentes de $NaNO_2$ y un equivalente del substracto reaccionan a 0°C durante 0.25 hasta 1 hora y a esta mezcla de reacción se agregan 3.5 equivalentes de $SnCl_2$. Alternativamente, el procedimiento descrito en De Roos, K.B.; Salemink, C.A.; Recl. Trav. Chim. Pays-Bas 1971, 90, 1181 (uso de $NaNO_2$, AcOH, H_2O) se puede usar. El intermediario así formado se puede además reaccionar y ciclizar para proporcionar los derivados del ácido azaindol acético como se muestran en la

etapa D del esquema de reacción 47 y según los procedimientos descritos en Atkinson, C.M.; Mattocks, A. R.; J. Chem. Soc, 1957, 3722; Ain Khan, M.; ferreira Da Rocha, J.; Heterocicles 1978, 9, 1617; Fusco, R.; Sannicolo, F.; tetrahedron 1908, 36, 161 (uso de HCL (conc)]; Abramovitch, R.A.; Spenser, I. D.; Adv. Heterocicl. Chem. 1964, 3, 79(uso de $ZnCl_2$, p-Cymene); and Clemo, G. R.; Holt, R.J.W.; J. Chem. Soc. 1953, 1313; (uso de $ZnCl_2$, EtOH, Sealed tube).

Esquema de reacción 48



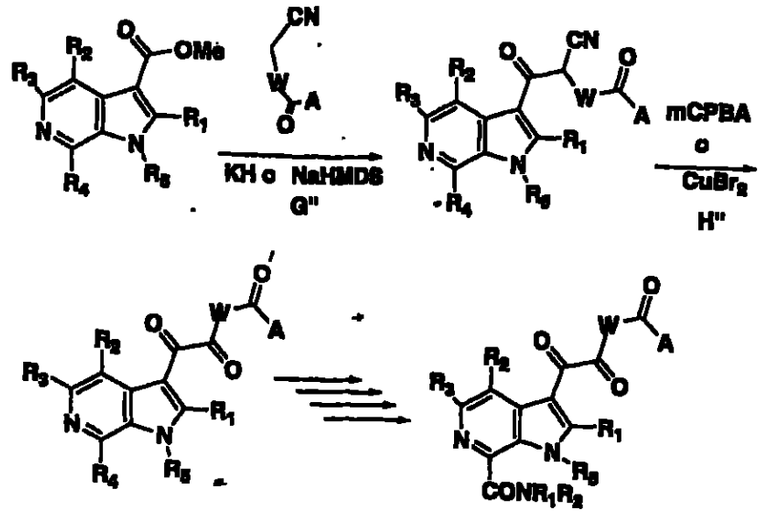
El esquema de reacción 48 detalla otra vía posible para los derivados del ácido azaindol acético. La etapa D del esquema de reacción 48 se puede efectuar como se muestra o según los procedimientos tales como aquellos descritos en Yurovskaya, M.A.; Khamlova, L.G.; Nesterov, V.N.; Shishkin, O.V.; Struchkov, T.; Khim Geterotsikl Soedin 1995, 11, 1543-1550; Grzegozek, M.; Wozniak, M.; Baranski, A.; Van Der Plas,

H.C.; J. Heterocycl.. Chem. 1991, 28(4), 1075-1077 (uso de NaOH, DMSO); Lawrence, N.J.; Liddle, J.; Jackson, D.A.; Tetrahedron Lett. 1995, 36(46), 8477-8480 (uso de NaH, DMSO); Haglund, O.; Nilsson, M.; Synthesis 1994, 3, 242-244; (uso de 2.5 equiv. CuCl, 3.5 equiv, TBu-OK, DME, Py); Makosza, M.; Sienkiewicz, K.; Wojciechowski, K.; Synthesis 1990, 9, 850-852; (uso de KO-tBu, DMF); Makosza, M.; Nizamov, S.; Org. Prep. Proceed. Int. 1997, 29(6), 707-710; (uso de tBu-OK-THF). La etapa F del esquema de reacción 48 muestra la reacción de ciclización que puede suministrar los derivados del ácido azaindol acético. Esta reacción se puede lograr según los procedimientos tales como aquellos descritos en Frydman, B.; Baldain, G.; Reppetto, J. C.; J. Org. Chem. 1973, 38, 1824 (uso de H_2, Pd-C, EtOH); Bistryakova, I.D.; Smirnova, N.M.; Safonova, T.S.; Khim Geterotsikl Soedin 1993, 6, 800-803 (uso de H_2, Pd-C (cat), MeOH);Taga, M.; Ohtsuka, H,; Inoue, I.; Kawaguchi, T.; Nomura, S.; Yamada, K.; Date, T.; Hiramatsu, H.; Sato, Y.; Heterocycles 1996, 42(1), 251-263 (uso de $SnCl_2$, HCl, Et_2O); Arcari, M.; Aveta, R.; Brandt, A.; Cecchetelli, L.; Corsi, G.B.;Dirella, M.; Gazz, Chim. Ital. 1991, 121(11), 499-504. [uso de $Na_2S_2O_6$, THF/EtOH/H_2O (2:2:1)]; Moodoy, C.J.;Rahimtoola, K.F.; J. Chem. Soc.,Perkin Trans 1 1990, 673 (uso de $TiCl_3$, NH_4Oac, acetone, H_2O).

El esquema de reacción 49 proporciona otra vía para los intermediarios de azaindol que luego se puede además elaborar

para proporcionar para compuestos de fórmula 1, tales como los derivados de amido mostrados. Las etapas G y H del esquema de reacción 49 se puede efectuar según los procedimientos descritos en Takahashi, K.; Shibasaki, K.; Shibasaki, K.; Ogura, K.; Lida, H.; Chem. Lett. 1983, 859; y Itoh, N.; Chem. Pharm. Bull. 1962, 10, 55. La eliminación del intermediario para el compuesto amido de fórmula I luego se puede lograr como se describe previamente para las etapas I'-M' del esquema de reacción 45.

Esquema de reacción 49



El esquema de reacción 50 muestra la preparación de derivados del ácido azaindol oxálico. Los materiales de partida en el esquema 50 se puede preparar de acuerdo con Tetrahedron Lett. 1995, 336, 2389-2392. Las etapas A', B', C', y D' del esquema de reacción 50 se puede efectuar de acuerdo con los procedimientos descritos en Jones, R.A; Pastor, J.; Siro, J;

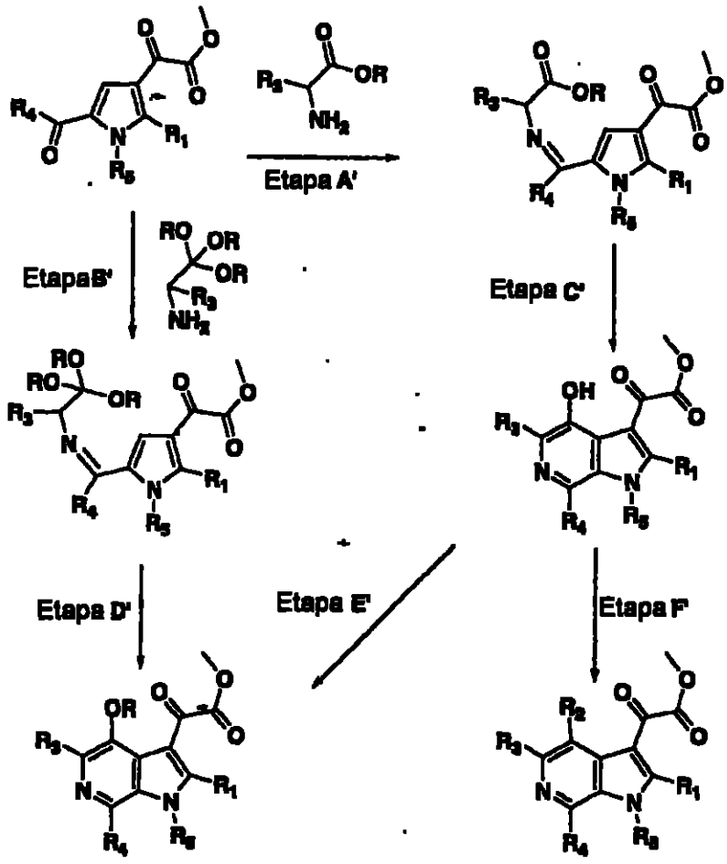
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Voro, T.N.; Tetrahedron 1997, 53(2), 479-486; and Singh, S.K.; Dekhane, M.; Le Hyaric, M.; Potier, P.; Dodd, R.H.; Heterocycles 1997, 44(1), 379-391. Etapa E' del esquema de reacción 50 se puede efectuar de acuerdo con los procedimientos descritos en Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y.; Tetrahedron 1997, 53(5), 1593-1606; Suzuki, H.; Yokoyama, Y.; Miyagi, C.; Murakami, Y.; Chem. Pharm. Bull. 1991, 39(8), 2170-2172; Hagen, T.J.; Narayanan, K.; Names, J.; Cook, J.M.; J. Org. Chem. 1989, 54, 2170; Murakami, Y.; Yokoyama, Y.; Watanabe, T.; Aoki, C.; et al.; Heterocycles 1987, 26, 875; and Hagen, T.J.; Cook, J.M.; Tetrahedron Lett. 1988, 29(20), 2421. La etapa F' del esquema de reacción 50 muestra la conversión del fenol al derivado de fluoro, cloro, o bromo. La conversión del fenol al derivado fluoro se puede efectuar según los procedimientos descritos en Christe, K.O.; Pavlath, A,E.; J.Org. Chem. 1965, 30, 3170; Murakami, Y.; Aoyama, Y.; Nakanoishi, S.; Chem. Lett. 1976, 857; Christe, K.O.;Pavlath, A.E.;J.Org. Chem. 1965, 30, 4104; and Christe, K.O.; Pavlath, A.E.; J. Org. Chem. 1966, 31, 559. La conversión del fenol al derivado del cloro se puede efectuar según los procedimientos descritos en Wright; S.W.; Org. Prep. Proc. Int. 1997, 29(1), 128-131; Hartmann, H.; Schulze, M.; Guenther, R.; Dyes Pigm 1991, 16(2), 119-136; Bay, E.; Bak, D.A.; Tomony, P.E.; Leone-Bay, A.; J. Org. Chem. 1990, 55, 3415; Hoffmann, H.; et al.; Chem. Ver 1962, 95, 523; and Vanallan,

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J.A.; Reynolds, G.A.; J.Org.Chem.1963, 28, 1022. La conversión del fenol al derivado de bromo se puede efectuar según los procedimientos descritos en Katritzky, A.R.; Li, J.; Stevens, C.V.; Ager, D.J; Org. Prep. Proc. Int. 1994, 26(4), 439-444, Judice, J.K.; Keipert, S.J.; Cram, D.J.;J. Chem. Soc., Chem. Commun. 1993, 17, 1323-1325; Schaeffer, J.P.;Higgins, J.; J. Org. Chem. 1967, 32, 1607; Wiley, G.A; Hershokowitz, R.L.;Rein, R.M.; Chung, B.C.; J. Am. Chem. Soc. 1964, 86, 964; and Tayaka, H.; Akutagawa, S.; Noyori, R.; Org. Syn. 1988, 67, 20.

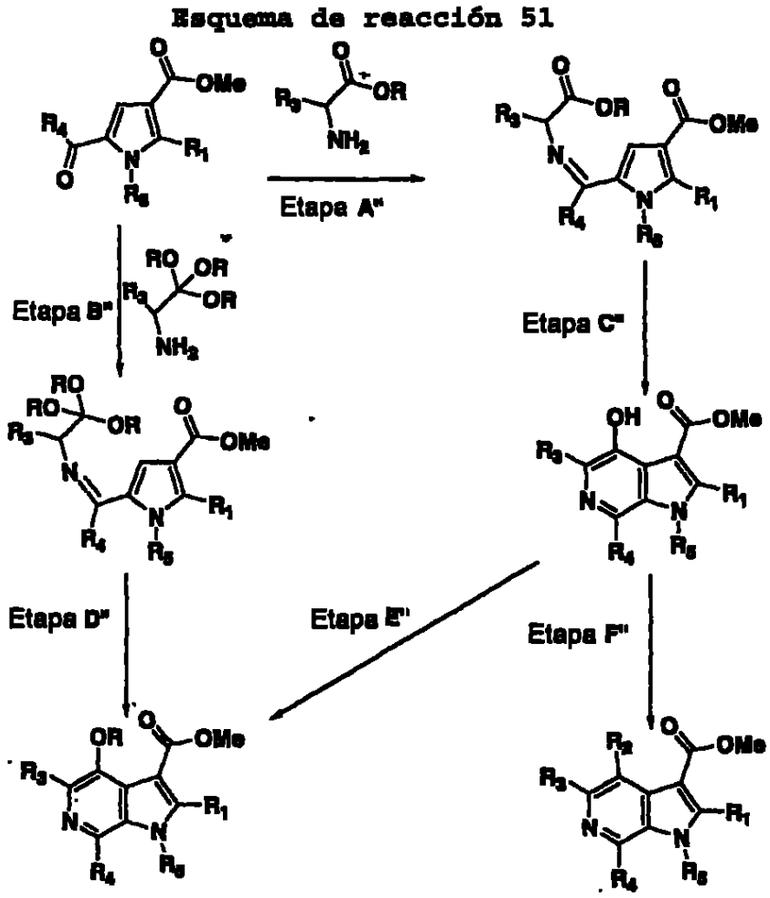
Esquema de reacción 50



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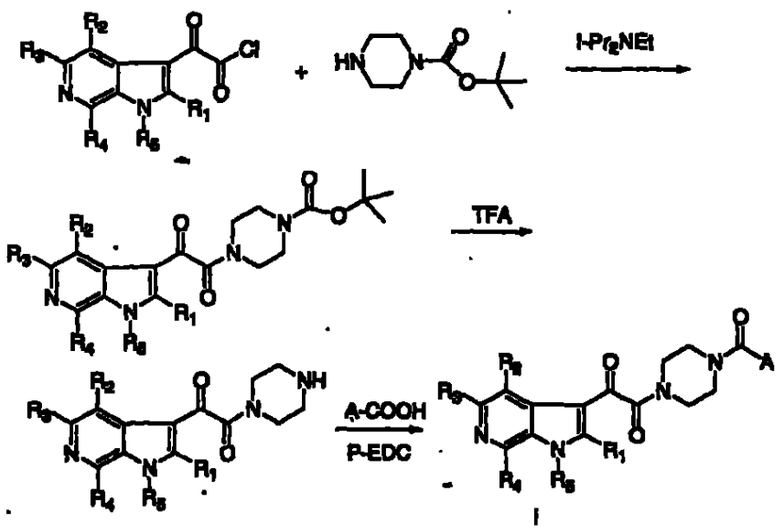
El esquema de reacción 51 describe métodos para la preparaciones de derivados de ácido azaindol acético por los mismos métodos empleados para preparación de los derivados del ácido azaindol oxálico como se muestra y describe en el esquema de reacción 50 anterior. El material de partida empleado en el esquema de reacción 51 se puede preparar según J. Org. Chem. 1999, 64, 7788-7801. Las etapas A", B", C", D", y E" del esquema de reacción 51 se pueden efectuar de la misma manera como se describe previamente para las etapas A', B', C', D' y E' del esquema de reacción 50.

Esquema de reacción 51



Los esquemas de reacción restantes proporcionan antecedentes adicionales, ejemplos y condiciones para efectuar esta invención. Los métodos específicos para la preparación de W y la modificación de A se presentan. Como se muestra en el esquema de reacción 52, los azaindoles se pueden tratar con cloruro de oxalilo y con THF o éter para efectuar los cloruros de glioxilo deseados según los procedimientos de la literatura (Lingens, F.; Lange, J. Justus Liebigs Ann. Chem. 1970, 738, 46-53). Los cloruros de glioxilo intermediarios se puede acoplar con benzoilo piperazinas (Desai, M.; Watthey. J. W. Org. Prep. Proc. Int. 1976, 8, 85-86) bajo condiciones básicas para resultar los compuestos de fórmula I directamente.

Esquema de reacción 52



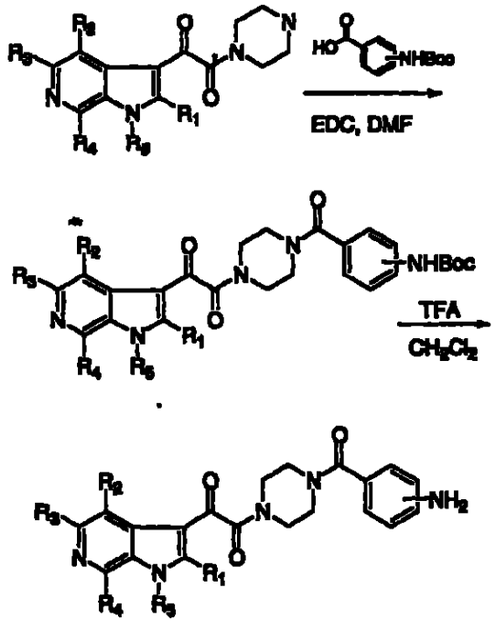
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Alternativamente, el esquema de reacción 52 tratamiento del cloruro de azaindol-3-glioxilo (esquema de reacción 52) con tert-

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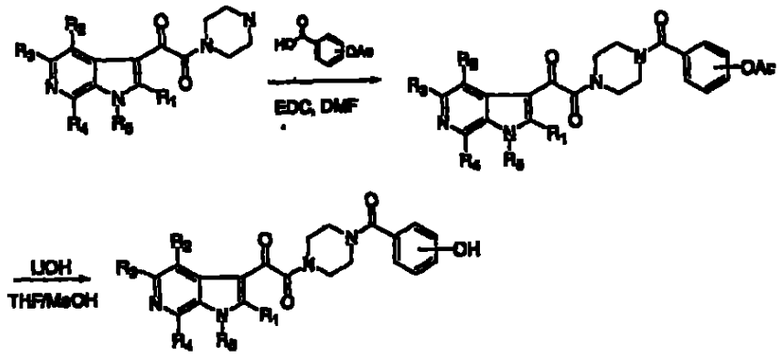
butil 1-piperazincarboxilato resulta en el producto acoplado de piperazina. Es evidente para alguien experto en la técnica que el uso de una piperazina Boc protegida alternativa que se sintetiza como se muestra a continuación proporcionaría compuestos de fórmula I con grupos alternativos de fórmula W. Como se discutió previamente otros grupos protectores de aminas que no requieren condiciones de desprotección ácidas se pueden utilizar si se desean. La desprotección del grupo Boc se efectúan con 20% TFA/CH_2Cl_2 para producir la piperazina libre. Este producto luego se acopla con ácido carboxílico en presencia de polímero soportado 1-(3-Dimetilaminopropil)-3-etilcarboimida (P-EDC) para producir productos de la fórmula I. Esta secuencia proporciona un método general para sintetizar compuestos de A variados en fórmula I.

Esquema de reacción 53



Un ejemplo para la preparación de compuestos de fórmula I que poseen substituyentes en A (o otras partes de la molécula) que pudieran interferir con los esquemas de reacción estándar, muestran las reacciones en el esquema de reacción 53. El derivado de piperazina (esquema de reacción 53) se trata con el ácido amino benzoico protegido para Boc en presencia de EDC para producir la piperazina de amida. Se separo una porción del producto resultante y se sometió a TFA con objeto de eliminar el grupo Boc, produciendo así los derivados amino.

Esquema de reacción 54

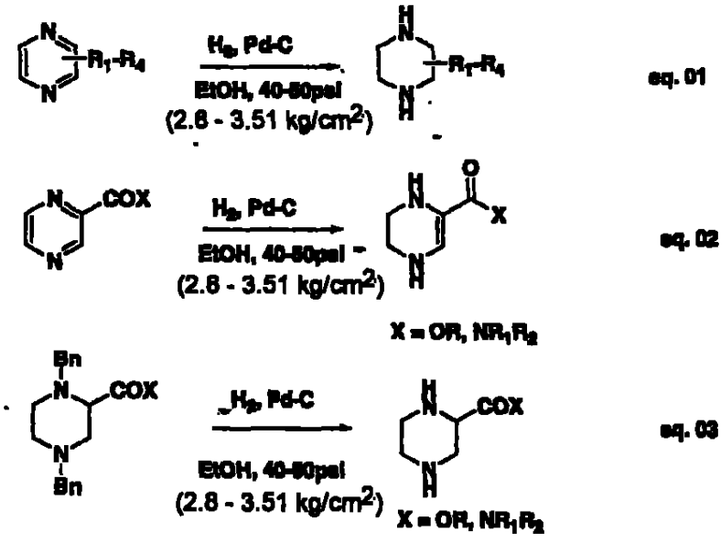


Similarmente, los substituyentes que poseen un alcohol reactivo se pueden incorporar como a continuación. El derivado de piperazina (esquema de reacción 54) se trató con el ácido acetoxibenzoico en presencia de EDC para producir el derivado de piperazina diamida. Se separó una porción del producto resultante y se sometió a una hidrólisis por LiOH con objeto de retirar el objeto acetato, produciendo así los derivados hidroxi.

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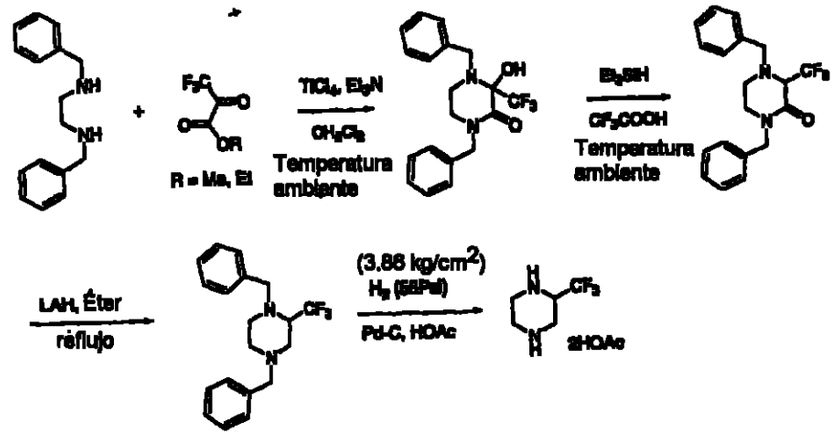
Los ejemplos que tiene piperazina substituidas se preparan usando los procedimientos generales detallados en los esquemas de reacción 55-38. Las piperazinas substituidas están comercialmente disponibles de Aldrich, Co., o se preparan según los procedimientos de la literatura (Behun et al, Ref. 88(a), esquema de reacción 31, eq. 01). La hidrogenación de las pirazinas substituidas con alquilo bajo una presión de 40 a 50 psi (2.81 a 3.51 kg/cm^2) en EtOH resultan en las piperazinas substituidas. Cuando el substituyente es un éster de amida los sistemas de piperazinas se pueden reducir parcialmente a la tetrahidropirazina (Rossen et al. Ref. 88(b), esquema de reacción 55, eq. 02). Las piperasinas substituidas con carbonilo se pueden obtener bajo las mismas condiciones antes descritas al usar dibencil piperazinas comercialmente disponibles (esquema de reacción 55, eq. 03).

Esquema de reacción 55



Se preparó la 2-trifluorometilpiperazina (Jenneskens et al., Ref. 88c) a través de una vía de cuatro etapas (esquema de reacción 56). Usando el ácido de Lewis $TiCl_4$, N, N'-dibenciletilendiamina reaccionó con trifluoropiruvatos para producir el hemiacetal, que redujo a temperatura ambiente por Et_3SiH en TFA para resultar la lactama. El tratamiento con $LiAlH_4$ luego redujo la lactama a 1,4-dibencil-2-trifluorometilpiperazina. Finalmente, la hidrogenación de dibencil-2-trifluorometilpiperazina en HOAc dio el producto deseado 2-trifluorometilpiperazina.

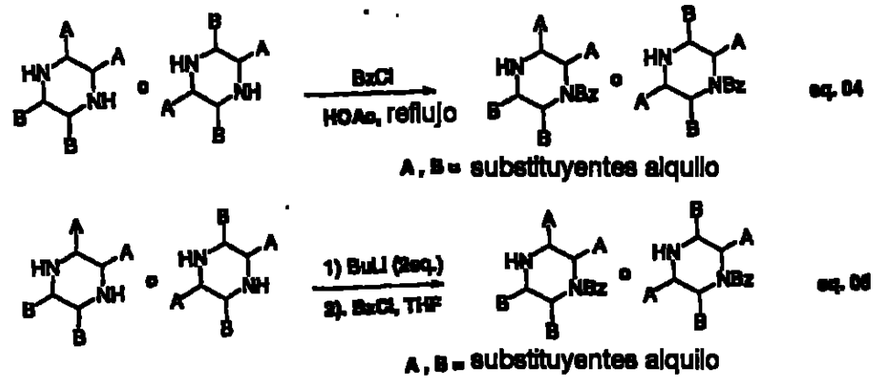
Esquema de reacción 56



La monobenzoilación de piperazina substituida simétrica se puede lograr al usar uno de los siguientes procedimientos (esquema de reacción 57). (a) Tratamiento de una solución de

piperazina en ácido acético con cloruro de acetilo resulta en la piperazina monobenzoilada deseada (Desai et al. Ref. 27, esquema de reacción 57, eq. 04). (b) Se trataron piperazinas simétricas con dos equivalentes de n-butilitio, seguido por la adición de cloruro de benzoilo a temperatura ambiente (Wang et al. Ref. 89, esquema de reacción 57, eq. 05).

Esquema de reacción 57

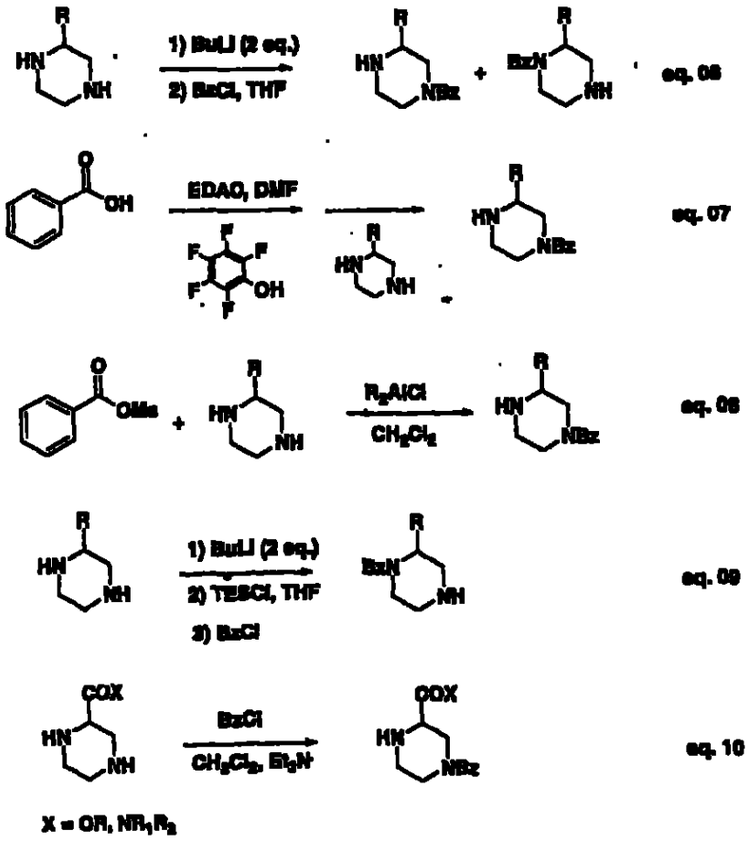


La monobenzoilación de las piperazinas substituidas no simétricas se puede lograr al usar uno de los siguientes procedimientos (esquema de reacción 57) en el cual se ejemplifican todos los métodos por piperazinas monoalquil substituidas. (a) se trataron las piperazinas no simétricas con dos equivalentes de n-butillitio seguido por la adición de cloruro de benzoilo a temperatura ambiente para resultar una mezcla de dos regioisómeros que se

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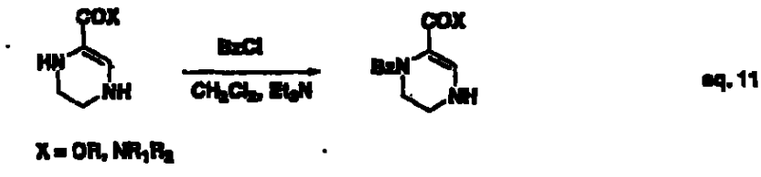
pueden separar por cromatografía (Wang et al. Ref, 89 y 90(b), esquema de reacción 58 eq. 06); (b) Se convirtió el ácido benzoico a su éster de pentafluorfenilo y luego la reacción adicional con 2-alquilpiperazina para suministrar las mono benzoilpiperazinas con el grupo benzoilo en el nitrógeno menos obstaculizado (Adamczyk et al, Ref. 90(a), esquema de reacción 58, eq. 07); (c) Se trató una mezcla de piperazina y benzoato de metilo con cloruro de dialquil aluminio en cloruro de metileno por dos a cuatro días para producir la monobenzoil piperazina con el grupo benzoilo en el nitrógeno menos obstaculizado (esquema de reacción 58 eq. 08); (d) Se trataron las piperazinas no simétricas con dos equivalentes de n-butillitio seguido por la adición subsecuente de cloruro de trietil sililo y cloruro de benzoilo en THF a temperatura ambiente para resultar las mono benzoil piperazinas con el grupo benzoilo en el nitrógeno más obstaculizado (Wang et al, Ref. 90(b), esquema de reacción 58, eq. 09). Cuando el substituyente en la posición 2 fue un éster o amina, la monobenzoilación con cloruro de benzoilo sucedió en el nitrógeno menos obstaculizado de la piperazina con trieltilamina como base en THF (esquema de reacción 58, eq. 10).

Esquema de reacción 58



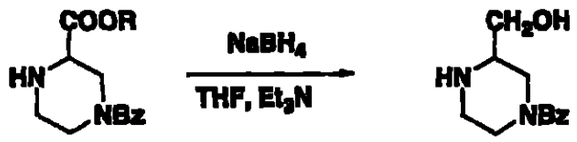
En el caso de las tetrahidropirazinas (esquema de reacción 59, eq. 11), la monobenzoilación sucedió en el nitrógeno más obstaculizado bajo las mismas condiciones como aquellas en la ecuación 10 del esquema de reacción 58 en la forma bien soportada (Rossen et al Ref.88(b)).

Esquema de reacción 59



Además, el grupo éster se puede reducir selectivamente por $NaBH_4$ en presencia de benzamida (Masuzawa et al, Ref. 91), que se muestra en el esquema de reacción 60.

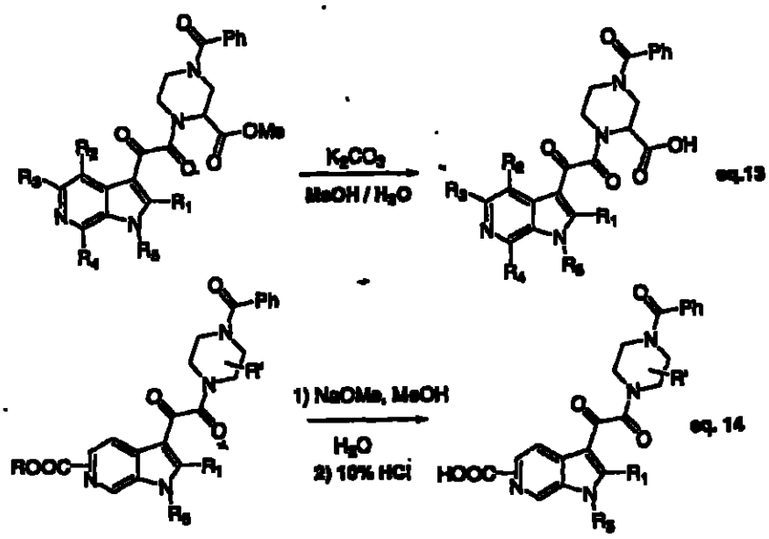
Esquema de reacción 60



eq. 12

Los grupos éster en las ligaduras de piperazina o en el núcleo de azaindol se puede hidrolizar al ácido correspondiente bajo condiciones básicas tales como K_2CO_3 (esquema de reacción 61, eq.13) o NaOMe (esquema de reacción 61, eq. 14) como bases en MeOH y agua.

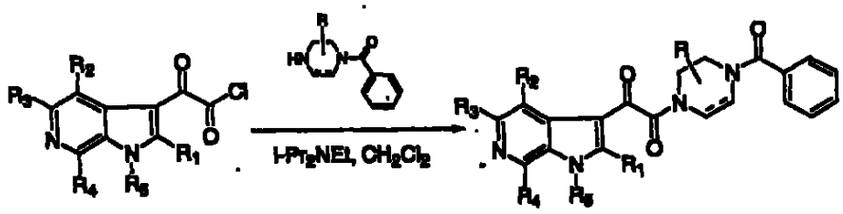
Esquema de reacción 61



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La reacción del cloruro del azaindol glioxilo con piperazinas substituidas con benzoilo o tetrahidropirazinas en CH_2Cl_2 usando I-Pr_2Net como base resulta los productos acoplados como se muestran en el esquema de reacción 62.

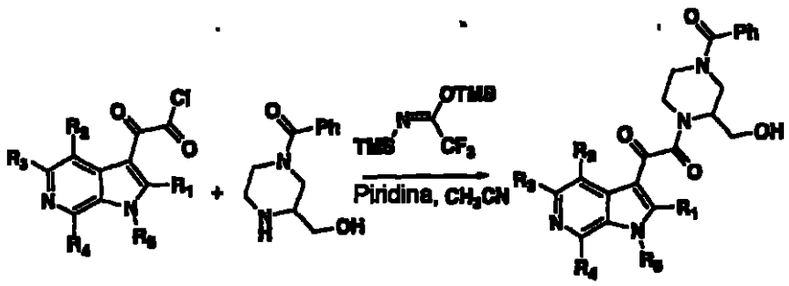
Esquema de reacción 62



En el caso de la reacciones de acoplamiento usando 3-hidroxilmetil-benzoilpiperazina, se protege temporalmente para el grupo hidroxilo como su éter TMS con BSTFA (N, O-bistrimetilsilil)trifluoroacetamida)(Furber et al. Ref 92). El átomo de nitrógeno sin protección luego puede reaccionar con cloruros de glioxilo para formar las diamidas deseadas. Durante la preparación, el grupo oculto TMS se retira para dar las diamidas de hidroximetilpiperazina libres como se muestra en el esquema de reacción 63.

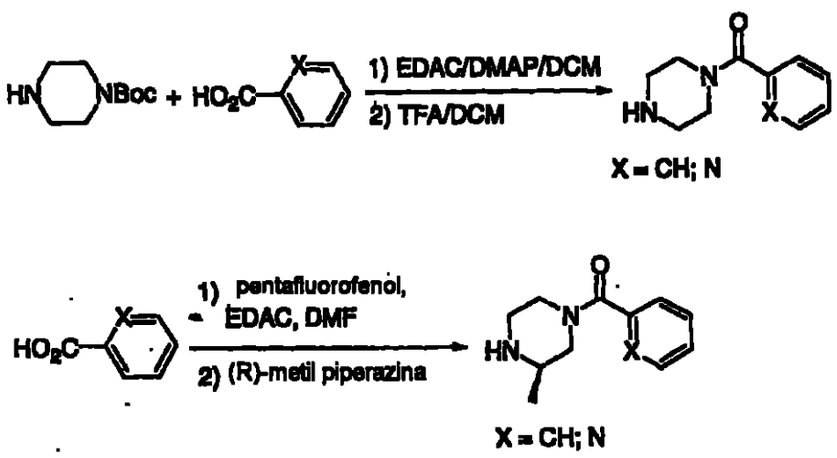
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Esquema de reacción 63



Los intermediarios de piperazina se prepararon usando la química estándar como se muestra en el esquema de reacción 64.

Esquema de reacción 64

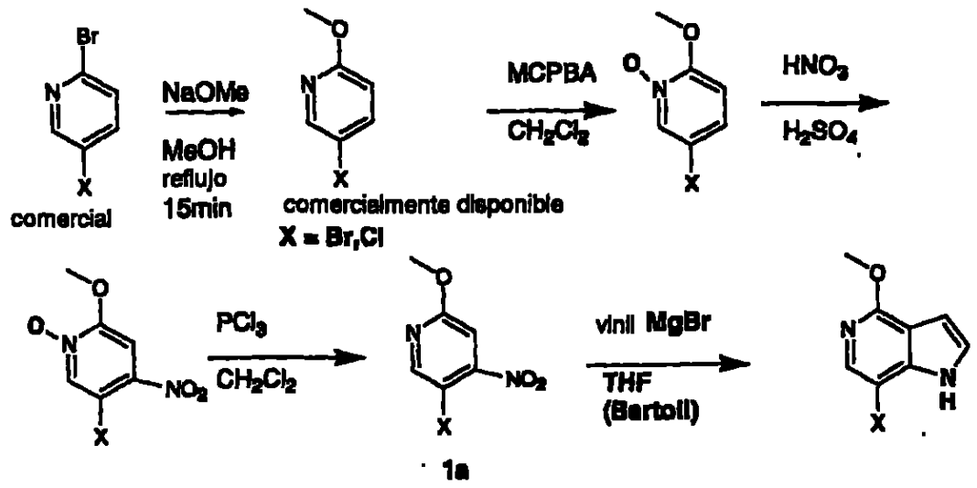


Esquema de Reacción 65

El esquema de reacción 65 detalla alguna metodología específica para la preparación de 5-azindoles para su uso en la preparación de los

compuestos reivindicados. Algunas condiciones de ciclización reductoras incluyen Fe en ácido acético, cloruro de estaño II en aq HCl o polvo de zinc en ácido acético. Las condiciones de hidrogenación u otras condiciones usadas en las secuencias de la síntesis de indol en LeimGruber-Batch también se pueden emplear.

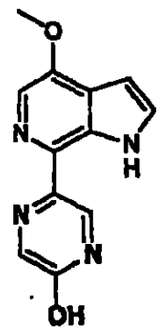
Ruta más específica para 5-azaindoles:



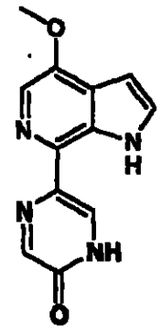
X = cloro o bromo o pueden convertirse en un substituyente y luego pueden llevarse a través de la secuencia.

Los tautómeros de nitrógeno que contienen heterociclos se cubren por esta solicitud de patente. Por ejemplo, también se conoce una hidrozipirazina para representar su tautómero correspondiente así como se muestra en el esquema de reacción 66.

Esquema de reacción 66



también representa el otro tautómero

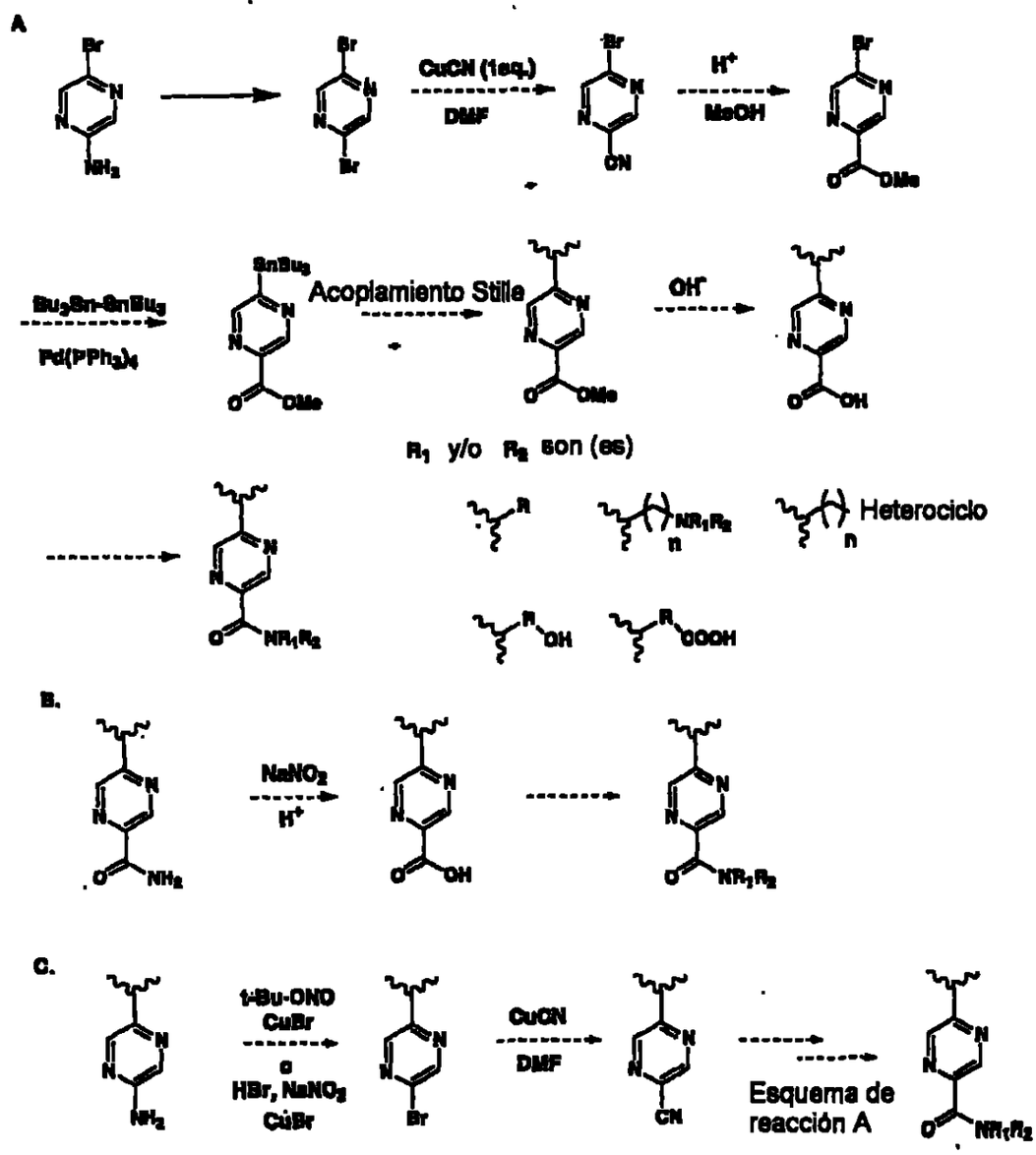


El esquema de reacción 67-74 proporciona alguna metodología no limitativa para la preparación de piperazinas substituidas que se pueden incorporar en los substituyentes de los compuestos de la reivindicación 1, particularmente como parte de R^4. Se debe observar por la nomenclatura en estos esquemas de reacción no coincide con aquella de las reivindicaciones si no más bien muestran ejemplos de métodos que se pueden usar para preparar piezas que constituyen los compuestos de las reivindicaciones. Así, R_1 y R_2 en estos esquemas no se refiere a R1 y R2 en las reivindicaciones sino por ejemplo, se refieren a grupos químicamente compatibles que pudieran vislumbrarse por los químicos expertos en la técnica y que se pueden utilizar para preparar compuestos de las reivindicaciones.

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Esquema de reacción 67

Pirazinas



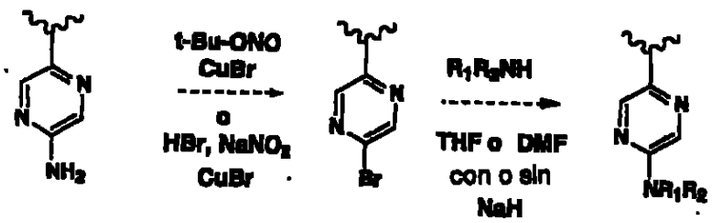
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Esquema de reacción 68

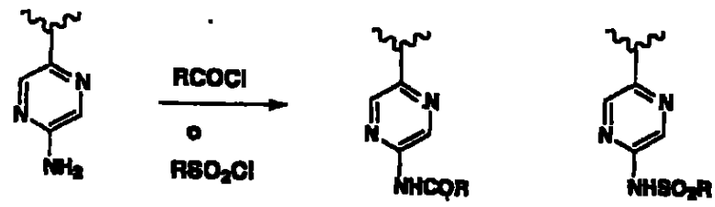
D.



E.

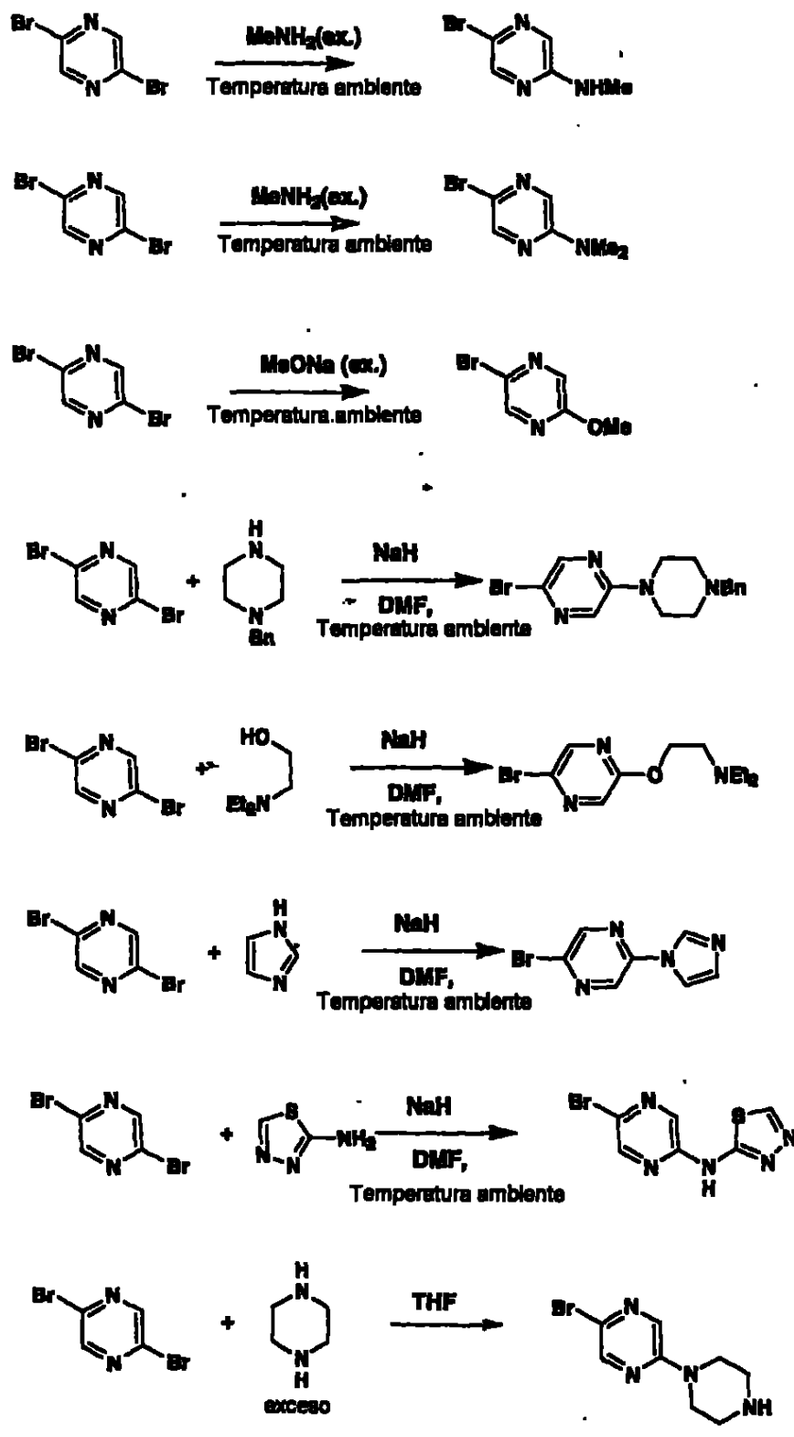


F.



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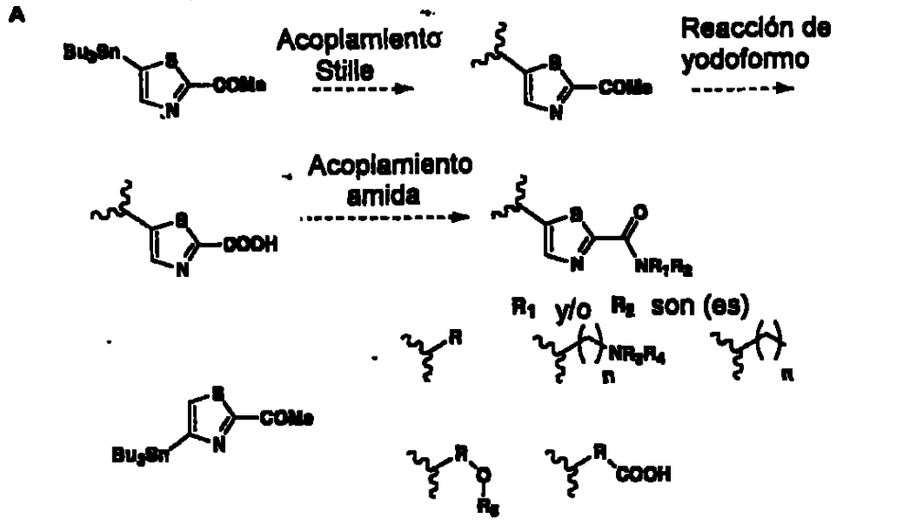
Esquema de reacción 69



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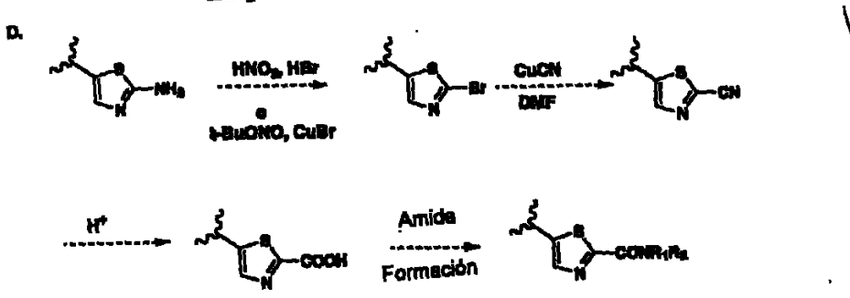
Esquema de reacción 70

Tiazol

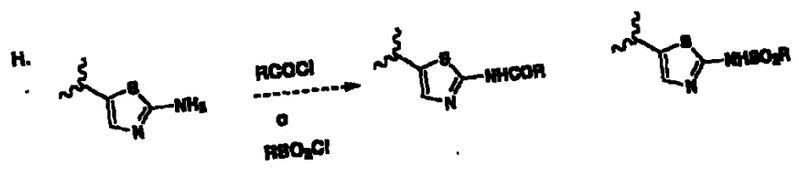


R_4, R_5, R_6 Podrá definirse igual a R_1 y R_2

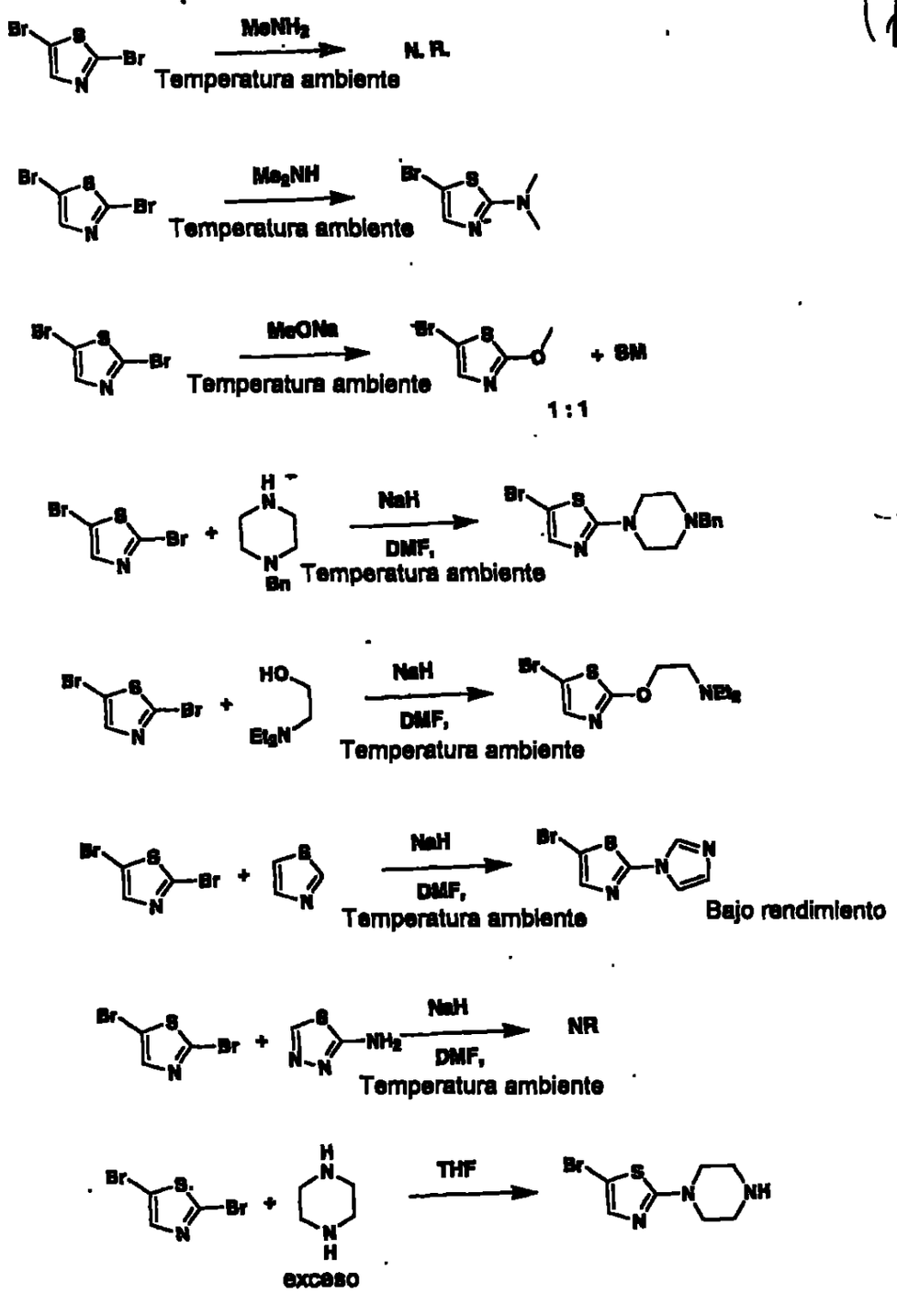
Esquema de reacción 71



Esquema de reacción 72

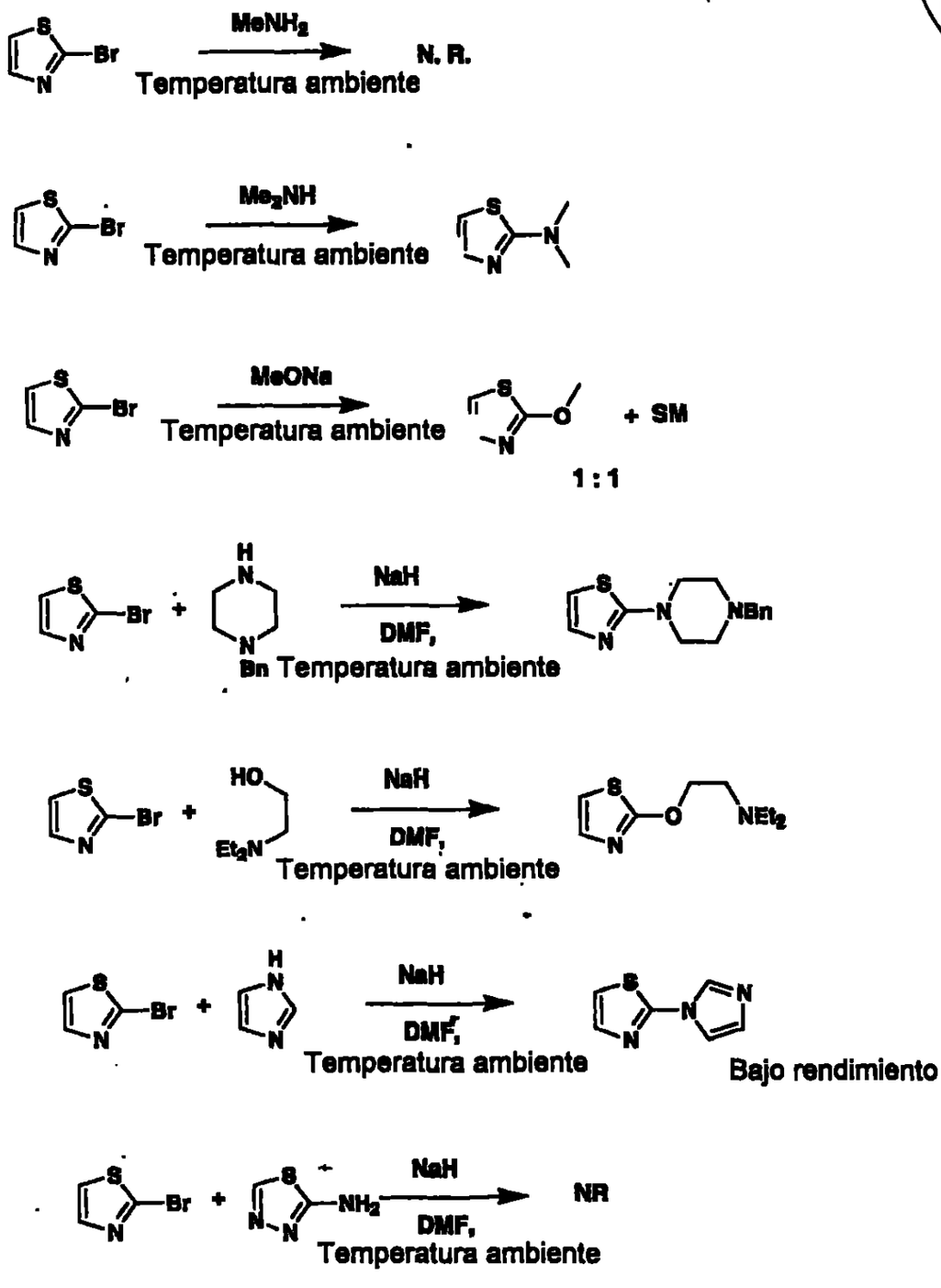


Esquema de reacción 73



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Esquema de reacción 74

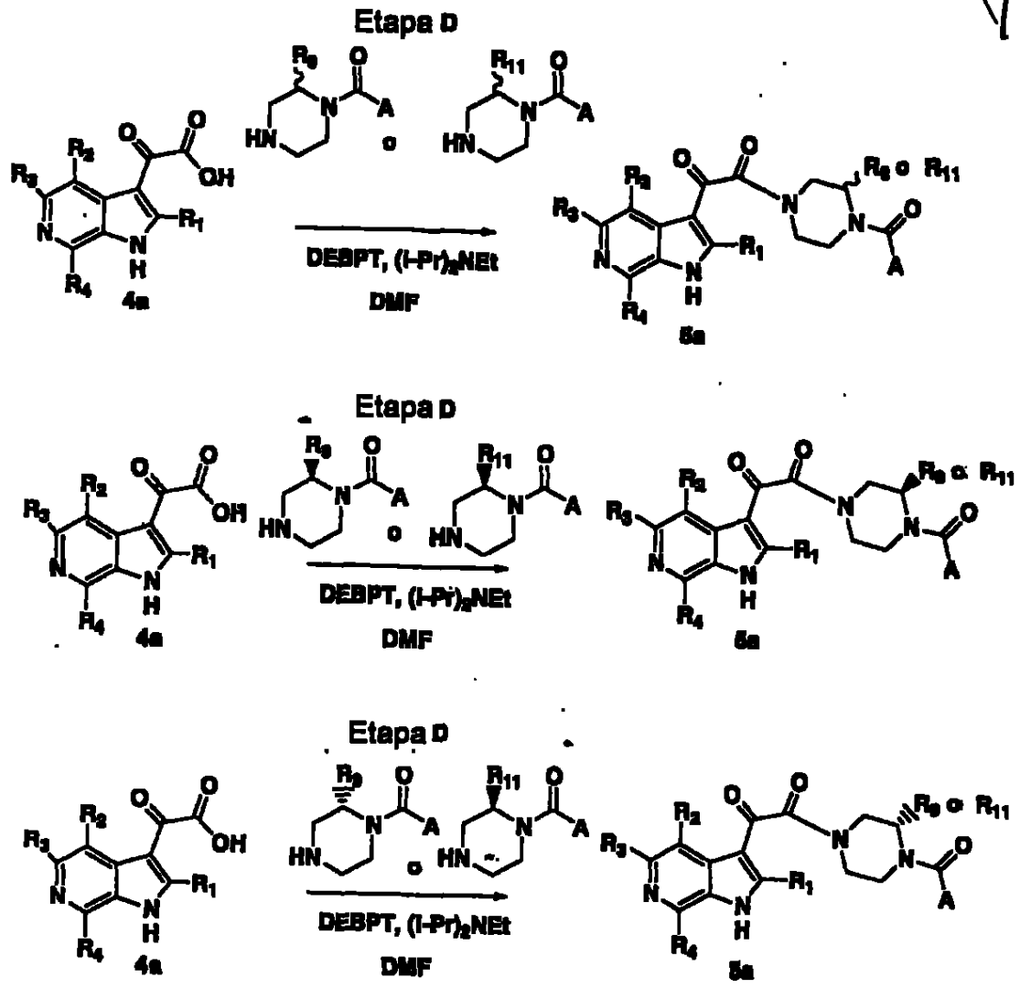


A lo largo de la discusión química, las transformaciones químicas que son bien conocidas en el arte se han discutido. El practicante promedio en el arte conoce estas transformaciones bien y está disponible una lista detallada de condiciones útiles para casi todas las transformaciones para los químicos orgánicos y esta lista está contenida en la referencia 52 del autor Larock y se incorpora en su totalidad para la síntesis de los compuestos de fórmula I.

Los esquemas de reacción 75-78 proporcionan ejemplos específicos de la síntesis general descrita en el esquema de reacción 1. Los ejemplos describen la síntesis de compuestos de la invención en los cuales la piperazina del grupo W contiene un substituyente en el anillo en una posición a continuación de nitrógeno que comprende parte de la amida colocada en el grupo A. Aunque son aspectos importantes de la invención otros patrones de substitución, se ha encontrado que los compuestos con un grupo sencillo adyacente a la amida colocada con el grupo A pueden tener ventajas de estabilidad metabólica en humanos y conservar todavía propiedades antivirales excepcionales. Las piperazinas especificas substituidas descritas en los esquemas de reacción 75-78 se pueden preparar como se describen en la referencia 90(b) o como se describe para los intermediarios 17a-d en la sección experimental. En los esquemas de reacción 75 y 76 los grupos más preferidos para

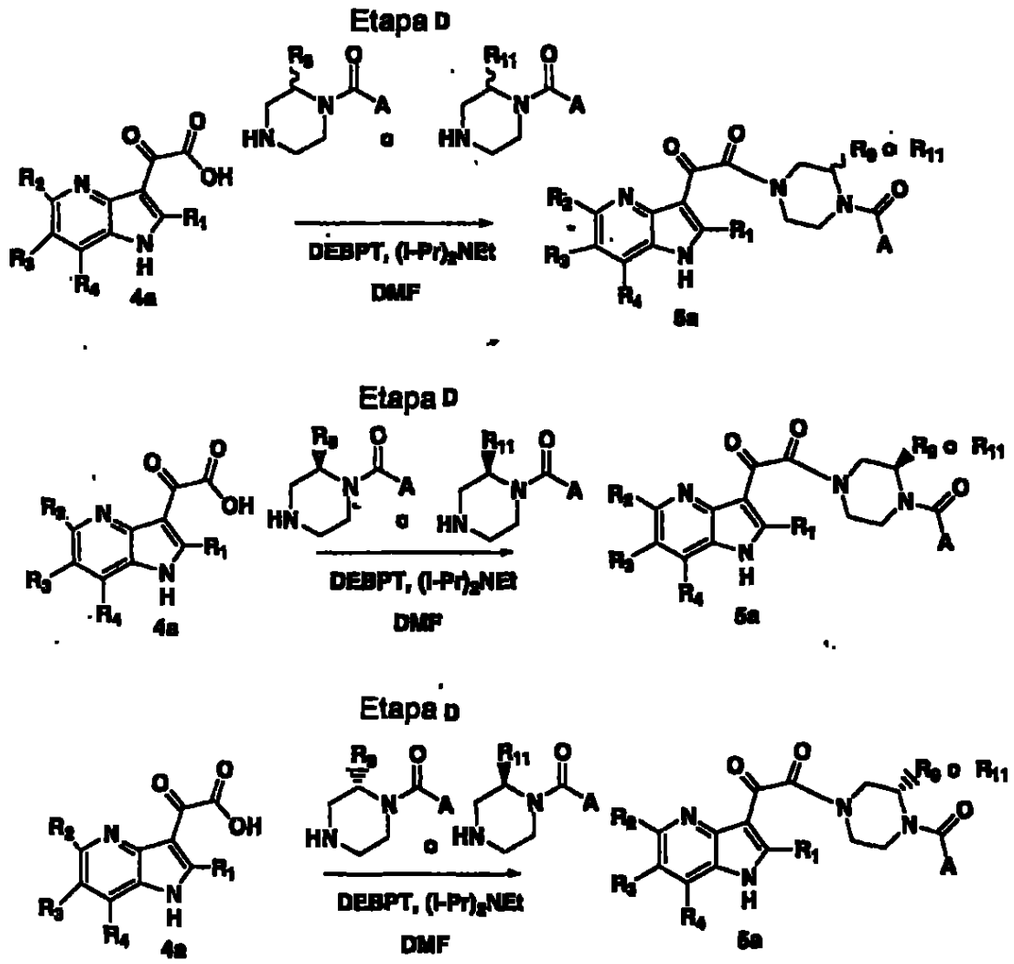
R_9 y R_{11} son los grupos C1-C6 alquilos. Como se muestra en los esquemas de reacción 77 y 78 los grupos más preferidos son metilo. Como se muestra en los esquema de reacción 75-78, los compuestos pueden ser isómeros o enantiómeros sencillos o se pueden usar como una mezcla racémica o mezcla de isómero. Los grupos A preferidos como se muestran en los esquemas de reacción 75-78 son iguales a aquellos descritos para la invención. Los grupos A más preferidos son 2-piridil o fenilo. En los esquemas de reacción 75 y 77 los grupos más preferidos para R_2 son metoxi, halógeno o hidrógeno. En los esquemas de reacción 75-76 el grupo más preferido para R1 y R3 es hidrógeno. En el esquema de reacción 76 el grupo más preferido para R2 es hidrógeno. En los esquemas de reacción 75-78 los grupos más preferidos para R4 son fenilo, fenilo substituido, heteroarilo, heteroarilo substituido, -C(O)NH2,-C(O)NHMe o C(O)heteroarilo. Los susbtituyentes más preferidos en el arilo o heteroarilo substituido son metilo, amino, halógeno, C(O)NHMe, COOH, COOMe, COOEt, o bencilo pero esta lista no se debe constituir como limitativa de la proporción ya que la posición R4 es extremadamente tolerante a una amplia substitución. Los grupos particulares en R4 de importancia definida son triazol, oxadiazol, oxazol pirazol, pirazina, pirimidina, tetrazol y fenil pero tampoco deben constituirse como limitantes.

Esquema de reacción 75



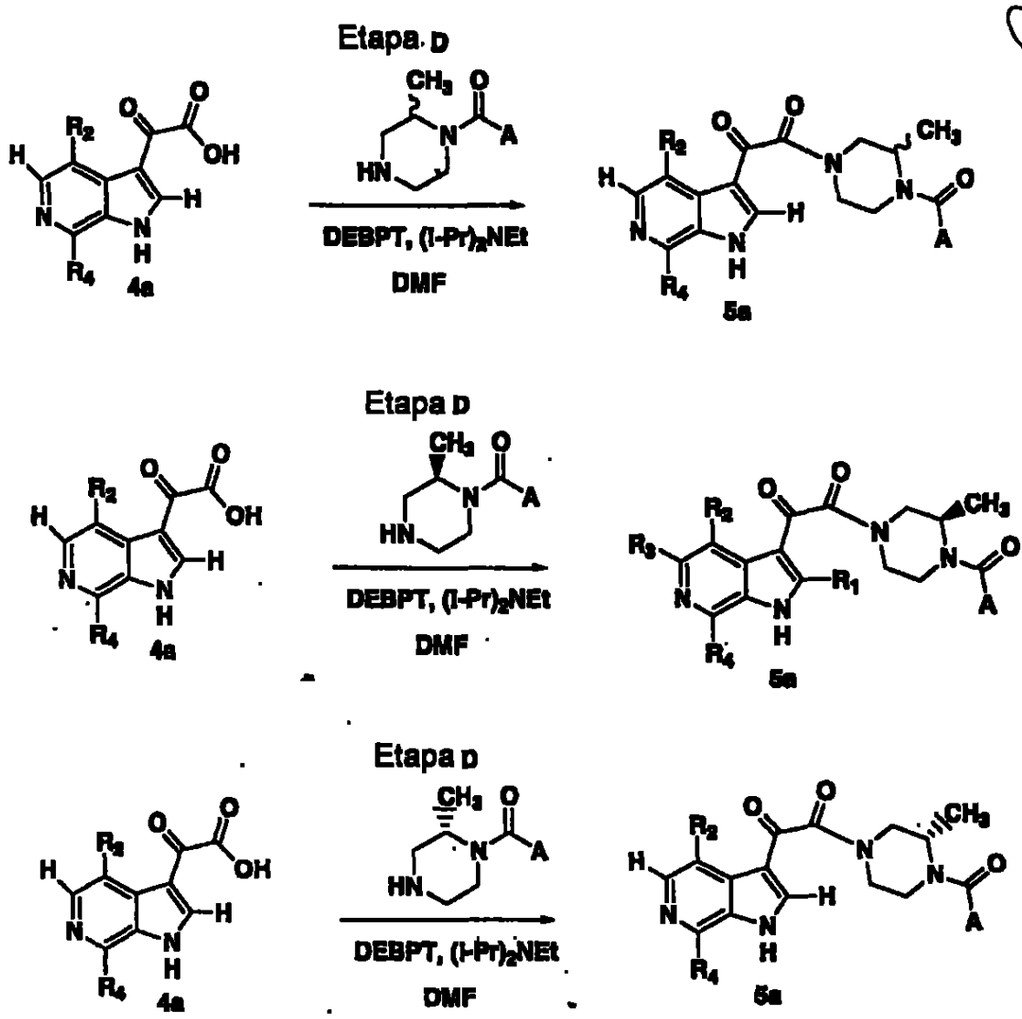
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Esquema de reacción 76

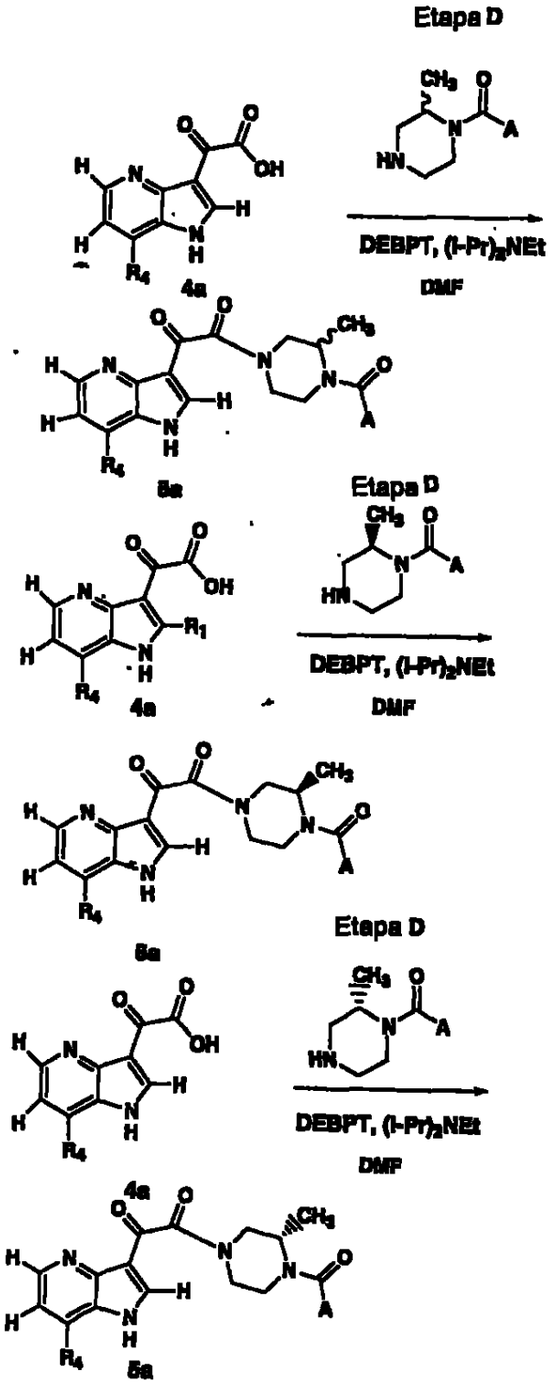


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Esquema de reacción 77

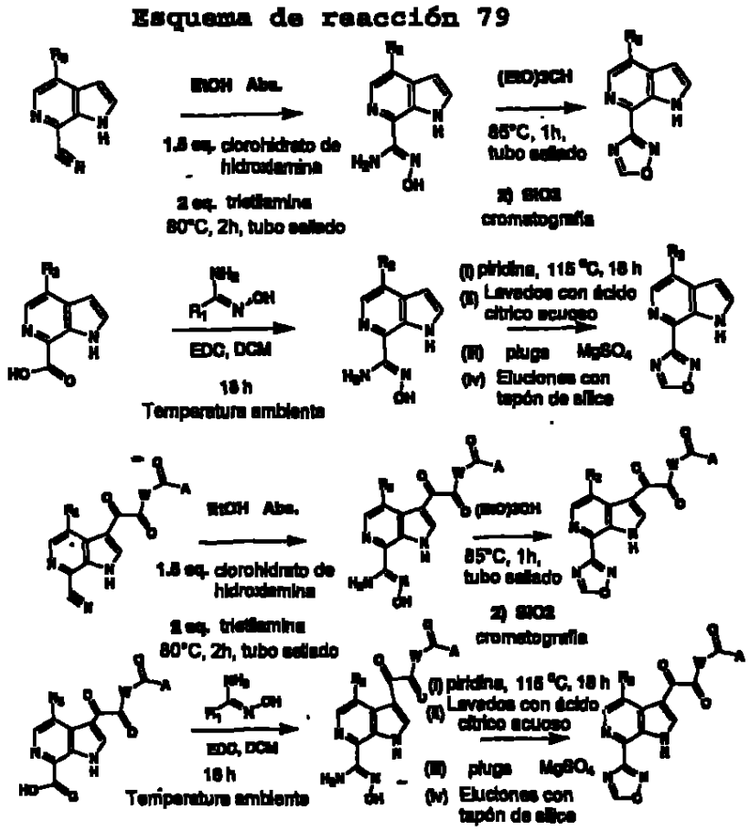


Esquema de reacción 78



Los esquemas de reacción 79 proporcionan ejemplos y condiciones típicas para la formación de intermediarios 2 que contiene un oxadiazol u oxadiazol substituido. Estos intermediarios se pueden convertir a los compuestos de la reivindicación 1 por medio de metodología estándar descrita en el esquema de reacción 1 y el resto de la solicitud. Se muestra una secuencia alternativa en el esquema de reacción 79a que utiliza intermediarios substituidos por ciano 5 para generar los oxadiazoles de la reivindicación 1. Se dan ejemplos específicos en la sección experimental. Se pueden preparar otros isómeros de oxadiazol por medio de la metodología estándar de la literatura.

Esquema de reacción 79



El esquema de reacción 80 es un método preferido para la elaboración de compuestos de fórmula I y Ia en donde R^2 es fluoro. Esto se ejemplifica específicamente en la preparación del compuesto del ejemplo 216. La síntesis de 2-hidroxi-3-nitro-5-fluoropiridina 5-80 como se muestra se efectúa generalmente por los métodos de A. Marfat and R.P. Robinson U.S. Patent 5,811,432 (columna 25, ejemplo 5) y Nesnow and Heidleberger (J. Heterocyclic Chem. 1973, 10, pg 779) excepto que un número de mejoras de procedimientos se incorporaron como se señala en la descripción de cada etapa. 2-Hidroxi-5-fluoropiridina 4-80 también está comercialmente disponible. La formación de la sal de tetrafluoroborato de diazonio 2-80 a partir de 5-amino-2-metoxi piridina 1-80 avanza con un rendimiento esencialmente cuantitativo y se aisla por medio de filtración. La reacción Schiemann proporciona pobres rendimientos de la 2-metoxi-fluoropiridina deseada usando las condiciones de literatura debido principalmente a la contaminación importante con 3-fluoro 1-(N)-metil piridina y otros subproductos. Sin embargo, la adopción de un procedimiento similar a aquel descrito en Sanchez, J.P.; Rogowski, J. W.; Heterocycl Chem 1987, 24, 215 para un compuesto relacionado proporciona rendimientos muy altos de 2-metoxi-5-fluoro piridina 3-80 esencialmente limpios pero volátiles como una solución en tolueno. En el interés de la conveniencia, se logra la desmetilación a gran escala usando HCl acuoso en botellas a presión a 140°C por 1 hora. Previo al calentamiento se agita la solución de tolueno con HCl luego se retira el tolueno por decantación. El método de la literatura para efectuar

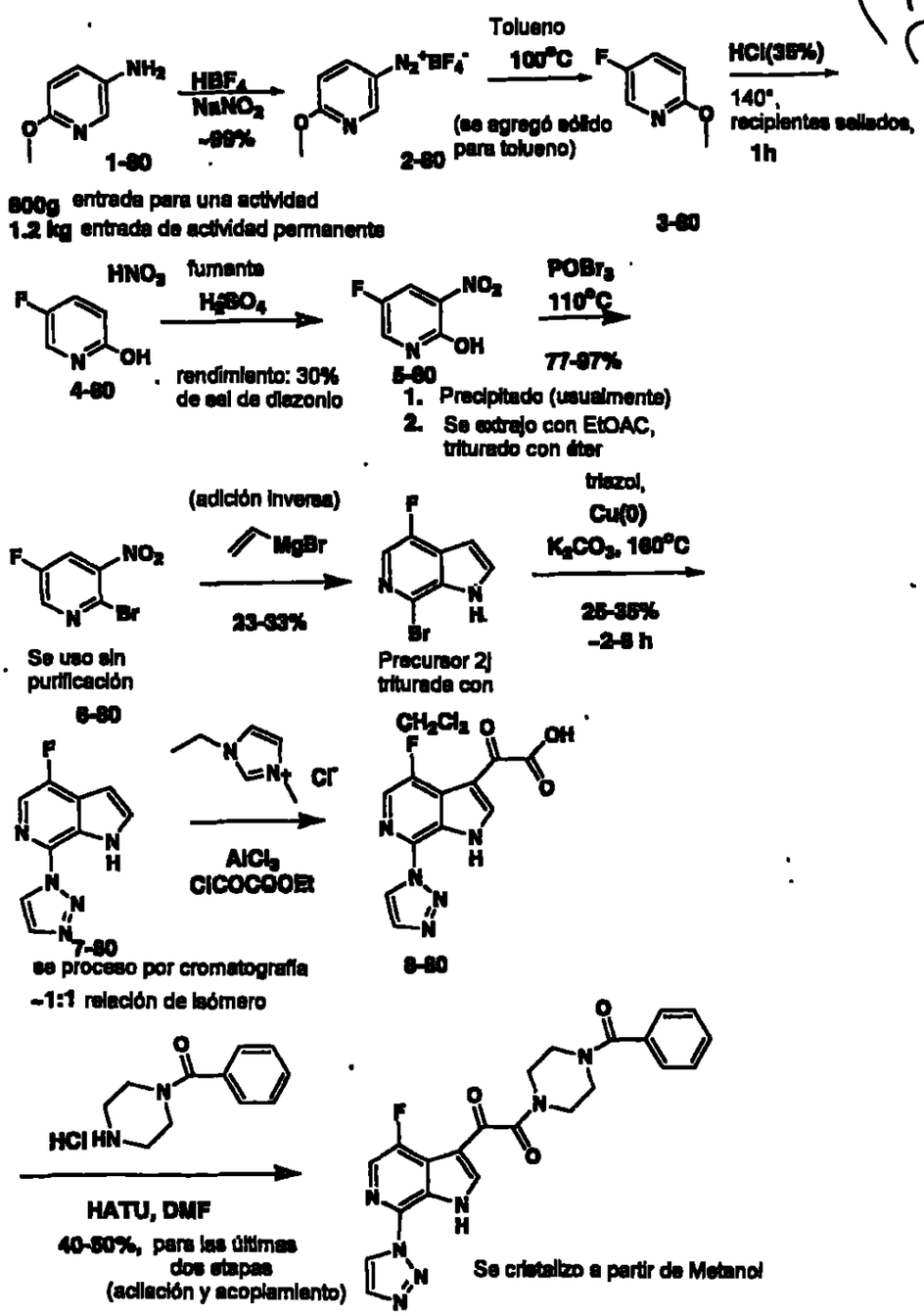
esta etapa usando HBr a 100°C también fue exitoso a escala pequeña y tuvo la ventaja de evitar el uso de botellas a presión. La nitración de 4-80 como se describe por Marfat proporcionó rendimientos menores a los esperados de manera que se modificó ligeramente un procedimiento usando la guía de A.G. Burton, P.J.Hallis, and A.R. Katritzky (Tetrahedron Letters 1971, 24, 2211-2212) en el control de la región química de la nitración de piridonas por medio de la modulación de la acidez del medio. Los rendimientos químicos de 2-hidroxi-3-nitro-5-fluoro piridina 5-80 se mejoraron significativamente utilizando el procedimiento descrito en la sección experimental. Ocasionalmente el producto falló al precipitarse durante la preparación y luego fueron necesarios esfuerzos considerables para aislar este compuesto altamente soluble en agua de la capa acuosa. Al usar un exceso puro de $POBr_3$ el compuesto 5-80 se convirtió a 2-bromo-3-nitro-5-fluoro piridina 6 que se puede usar sin purificación adicional en la reacción subsecuente de formación de azaindol. La adición de la piridina 6 al bromuro de vinil magnesio en exceso en THF a baja temperatura resultó en el 4-fluoro-7-bromo-6-azaindol (precursor 5j) deseado en rendimientos de hasta 35% después de la preparación ácida y rendimiento por medio de cristalización. Un desventaja de este método es que la preparación es difícil debido a grandes cantidades de sales formadas por coproductos en la reacción y la baja conversión al producto limpio no obstante. La reacción también es exotérmica y requeriría así cuidado a mayores escalas. A pesar de los rendimientos moderados como se mencionó arriba la reacción avanza limpiamente y

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proporciona el producto puro precursor 5j sin cromatografía de manera que se anticipa que los estudios más detallados de esta química pueden resultar en mejoras al rendimiento. Un desplazamiento mediado por carbonato de potasio/cobre selectivo del grupo 7 bromo por el 1,2,3-triazol comercialmente disponible proporciona una mezcla de aproximadamente 1:1 de triazoles a partir de los cuales se aisla el 7-80 deseado por medio de cromatografía en rendimientos de 25-35%. Se puede usar cobre y bronce más que polvo de cobre para efectuar transformaciones similares. Esta reacción no se debe permitir que se sobrecaliente ya que el desplazamiento en paralelo del flúor es posible y se ha observado. La acilación sucede más eficientemente bajo condiciones que utilizan un líquido iónico de cloro aluminato de imidazolio ácido en exceso para proporcionar un reactivo altamente activado glioxilante (K.S. Yeung et al Tetrahedron Lett. 2002, 43, 5793). La acilación de 7-80 usualmente no avanza hasta la terminación —y resulta típicamente en una conversión de alrededor del 75% cuando se mide por LC/MS. Una ventaja para estas condiciones es que la siguiente etapa típica, hidrólisis de éster, avanza in situ para proporcionar el ácido deseado 8-80 que se aísla directamente por precipitación durante la preparación. El acoplamiento de la benzamida de piperazina se encuentra que es más limpio y produjo rendimientos superiores del compuesto del Ejemplo 216 usando el acoplamiento basado en HATU detallado que con otros reactivos de acoplamiento estándar tales como EDC o DEPBT.

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Esquema de reacción 80



Ejemplo 216

Química

General:

Las preparaciones adicionales de los materiales de partida y precursores están contenidas es WANG et. al. numero de serie de E.U. 09/912,710 presentada en Julio 25, 2001 (que es una continuación parcial del numero de serie de E.U. 09/765,189, presentada Enero 18, 2001, abandonada que corresponde a PCT WO 01/62255) que se incorpora como referencia.

Química

Todos los datos de cromatografía liquida (LC) se registraron en un cromatógrafo liquido Shimadzu LC-10AS usando un detector SPD-10AV UV-Vis con los datos de espectrometría de masas (MS) determinados usando una plataforma de micromasa para LC en el modo de electrorocío.

Método LC/MS (esto es identificación del compuesto)

Columna A:	columna YMC ODS-A S7 3.0x50 mm
Columna B:	columna PHX-LUNA C18 4.6x30 mm
Columna C:	columna XTERRA ms C18 4.6x30 mm
Columna D:	columna YMC ODS-A C18 4.6x30 mm
Columna E:	columna YMC ODS-A C18 4.6x33 mm
Columna F:	columna YMC C18 S5 4.6x50 mm

Columna G: columna XTERRA C18 S7 3.0x50 mm

Columna H: columna YMC C18 S5 4.6x33 mm

Columna I: columna YMC ODS-A C18 3.0x50 mm

Columna J: columna XTERRA C18 S5 4.6x50 mm

Columna K: columna YMC ODS-A C18 4.6x33 mm

Columna L: columna Xterra MS C18 5uM 4.6x30 mm

Columna M: columna YMC ODS-A C18 4.6x33 mm

Condiciones de corrida estándar de LC (se usa a menos que se señale de otra manera)

Gradiente: 100% solvente A /0% solvente B a 0% solvente A/100% solvente B

Solvente A = 10% MeOH -90% H_2O -0.1% TFA, solvente B= 90% MeOH -10% H_2O -0.1% TFA; y R_t en min.

Tiempo de gradiente: 2 minutos

Tiempo de retención 1 minuto

Relación de flujo 5mL/min

Longitud de onda del detector: 220nm

Solvente A 10% MeOH/90% H_2O/0.1% ácido trifluoracético

Solvente B 10% MeOH/90% H_2O/0.1% ácido trifluoracético

Condiciones alternas de la corrida de LC B:

Gradiente: 100% solvente A /0% solvente B a 0% solvente A/100% solvente B

Solvente A = 10% MeOH -90% H_2O -0.1% TFA, solvente B=

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90% MeOH -10% H_2O -0.1% TFA; y R_t en min.

Tiempo de gradiente 4 minutos

Tiempo de retención 1 minuto

Relación de flujo 4mL/min

Longitud de onda del detector: 220nm

Solvente A 10% MeOH/90% H_2O/0.1% ácido trifluoracético

Solvente B 10% MeOH/90% H_2O/0.1% ácido trifluoracético

Los compuestos purificados por CLAR preparativa se diluyeron en MeOH (1.2 mL) y se purificaron usando los siguientes métodos en un sistemas CLAR preparativo automatizado Shimadzu LC-10A o un sistema CLAR preparativo automatizado Shimadzu LC-8A con una longitud de onda de detector (SPD-10AV UV-VIS) y sistemas de solventes (A y B) iguales que los anteriores.

Método CLAR preparativo (esto es purificación del compuesto)

Método de purificación: Gradiente inicial (40% B, 60% A) se lleva hasta un gradiente final (100% B, 100% A) durante 20 minutos, se mantiene por 3 minutos (100% B, 0% A)

Solvente A 10% MeOH/90% H_2O/0.1% ácido trifluoracético

Solvente B 10% H_2O/90% MeOH/0.1% ácido trifluoracético

Columna columna YMC C18 S5 20x100 mm

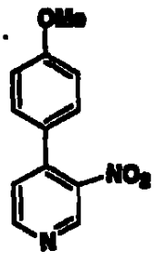
Longitud de onda del detector: 220nm

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Procedimientos típicos y caracterización de ejemplos seleccionados:

Preparación de los precursores:

Precursor 1

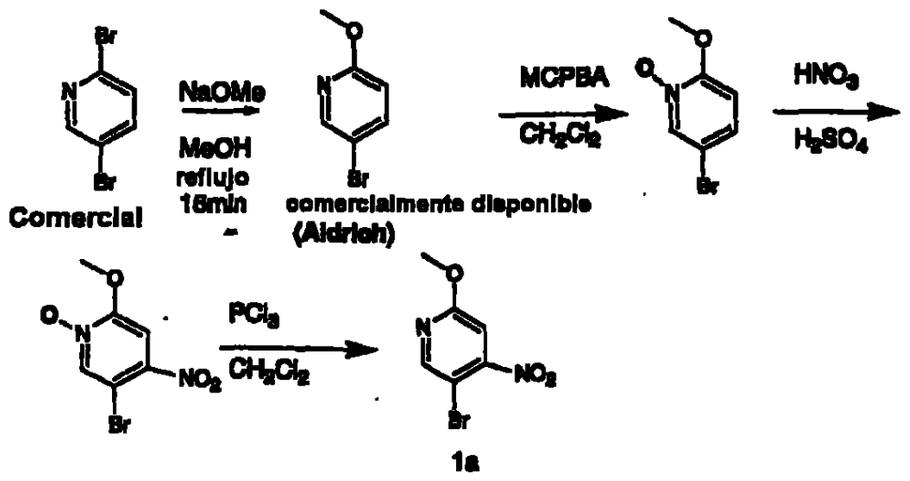


Se combinaron el ácido 4-Metoxifenilborónico (24.54 g), clorohidrato de 4-cloro-3-nitropiridina (26.24 g), $Pd(Ph_3P)_4$ (4 g) y K_2CO_3 (111 g) en DME (500 mL). La reacción se calentó a reflujo durante 10 horas. Después de que la mezcla se enfrió bajo temperatura ambiente, esta se vació en una solución de NH_4OAc acuosa saturada (500 mL). La fase acuosa se extrajo con EtOAc (3 x 200 mL). El extracto combinado se concentró para dar un residuo el cual se purificó al usar cromatografía en gel de sílice (10% hasta 30% EtOAc/PE) para proporcionar 10.6 g del precursor 1,3-Nitro-4-(4-metoxifenil)piridina. EM m/z: $(M+H)^+$ calculado para $C_{12}H_{11}N_2O_3$: 231.08; encontrado 231.02. Tiempo de retención CLAR: 1.07 minutos (columna B).

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Precursor 1a

Ruta alternativa para 5-azaindoles:

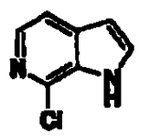


La 2-metoxi-5-bromo piridina puede adquirirse de Aldrich (u otros) o prepararse. La oxidación con 1.1 eq de MCPBA en diclorometano (20ml per 10.6 mmol bromo) en presencia de $MgSO_4$ anhidro (0.4g per mL diclorometano) con agitación desde 0° a temperatura ambiente por aproximadamente 14 h proporcionan la preparación de N-óxido y purificación cromatográfica instantánea durante gel de sílice usando un 5% de gradiente EtOAc/Hexano de EtOAc creciente. El N-óxido (1.6g) se disolvió en 10 ml, ácido sulfúrico al 98% y se enfrió a 0°. Se agregaron 10 ML de ácido nítrico al 69% y luego se permitió calentar a temperatura ambiente con agitación. La reacción luego se calentó y se agitó a 80°C durante 14h y luego se vació sobre hielo, se extrajo con

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diclorometano, se lavó con agua, y se concentró para dar un sólido amarillo el cual se purificó por cromatografía instantánea sobre gel de sílice al usar 1:1 EtOAc/hexano y luego un gradiente para proporcionar un sólido cristalino amarillo:). ^1H RMN ($CDCl_3$) δ 8.50 (s, 1H), 7.59 (s, 1H), 4.12 (3H, s). CL EM mostró el M+H deseado. El N-óxido se redujo por disolver el material de partida en diclorometano (0.147M substrato) y se enfrió a 0°. Una solución de 1.2 eq PCl_3 (0.44M) en diclorometano se agregó lentamente para mantener la reacción a 0°. Se calentó a temperatura ambiente y se agitó durante 72h. La preparación acuosa y la concentración proporcionaron un sólido amarillo el cual puede usarse en reacciones subsecuentes o purificación por cromatografía. Nota: una secuencia similar puede usarse con 2-metoxi-5-cloro-piridina como material de partida.

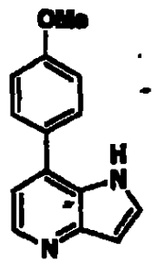
Precursor 2a



Procedimiento típico para la preparación de azaindol de nitropiridina: Preparación de 7-cloro-6-azaindol, El precursor 2a, es un ejemplo de la etapa A del esquema de reacción 1. Se disolvió 2-cloro-3-nitropiridina (5.0g, 31.5mmol) en THF seco (200 mL). Después de que la solución se enfrió hasta -78°C, se agregó

bromuró de vinil magnesio (1.0M en THF, 100 mL) gota a gota. La temperatura de reacción se mantuvo a -78°C durante 1 h, y luego a -20°C por otras 12 h antes de que se apagara por adición de una solución de NH_4Cl acuoso al 20% (150 mL). La fase acuosa se extrajo con EtOAc (3 x 150 mL). La capa orgánica combinada se secó sobre $MgSO_4$, se filtró y el filtrado se concentró in vacuo para dar un residuo el cual se purificó por cromatografía en columna de gel de sílice (EtOAc/Hexano, 1/10) para proporcionar 1.5g (31%) de 7-cloro-6-azaindol, El precursor 2a. ^1H RMN (500 MHz, CD_3OD) δ 7.84 (d, 1H, J = 10.7 Hz), 7.55 (dd, 1H, J = 10.9, 5.45 Hz), 6.62 (d, 1H, J = 5.54 Hz), 4.89 (s, 1H). EM m/z: $(M+H)^+$ calculadõ para $C_7H_6ClN_2$: 153.02; encontrado 152.93. Tiempo de retención CLAR: 0.43 minutos (columna A).

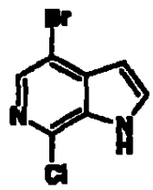
Precursor 2b



El precursor 2b, 7-(4-Metoxifenil)-4-azaindol, se preparó por el mismo método como el precursor 2a al partir del 3-Nitro-4-(4-metoxifenil)piridina, El precursor 1. EM m/z: $(M+H)^+$ calculado para $C_{14}H_{13}N_2O$: 225.10; encontrado 225.02. Tiempo de retención CLAR: 1.39 minutos (columna B).

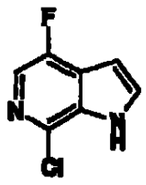
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Precursor 2c

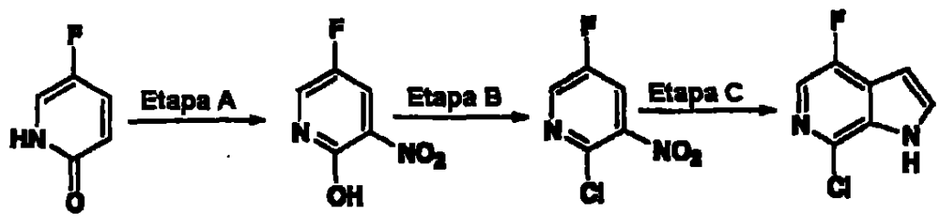


El precursor 2c, 4-bromo-7-cloro-6-azaindol, se preparó por el mismo método como el precursor 2a, al partir del 2-Cloro-3-nitro-5-bromo-piridina (disponible de Aldrich, Co.). EM m/z: $(M+H)^+$ calculado para $C_7H_5BrClN_2$: 230.93; encontrado 231.15. Tiempo de retención CLAR: 1.62 minutos (columna B).

Precursor 2d



El precursor 2d, 4-fluoro-7-cloro-6-azaindol (arriba), se preparó de conformidad a el siguiente esquema de reacción:



A) HNO_3 humeante, H_2SO_4;

B) $POCl_3$/DMF, 110°C;

C) Bromuro de vinilmagnesio, THF, -78°C ~ -20°C

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Se deberá notar que la 2-cloro-5-fluoro-3-nitro piridina, ZZ3', puede prepararse por el método en el ejemplo 5B de la referencia Marfat, A.; and Robinson, R. P.; "Azaoxindol Derivatives" U.S. Patent 5,811, 432 1998. La preparación de abajo proporcionar algunos detalles los cuales elevan los rendimientos de esta ruta.

En la etapa A, el compuesto zz1' (1.2 g, 0.01 mol) se disolvió en ácido sulfúrico (2.7 mL) a temperatura ambiente. Se agregaron ácido nítrico fumante premezclado (1 mL) y ácido sulfúrico gota a gota a 5-10°C para la solución del compuesto zz1'. La mezcla de reacción luego se calentó a 85°C durante 1 hora, luego se enfrió hasta temperatura ambiente y se vació en hielo (20 g). El sólido amarillo precipitado se recolectó por filtración, se lavó con agua y se agregó aire para proporcionar 1.01 g del compuesto zz2'.

En la etapa B, el compuesto zz2' (500 mg, 3.16 mmol) se disolvió en oxicloruro de fósforo (1.7 mL, 18.9 mmol) y dimetoxietano a temperatura ambiente. La reacción se calentó a 110°C durante 5 horas. El exceso de oxicloruro de fósforo luego se retiró por concentración de la mezcla de reacción in vacuo. El residuo se procesó por cromatografía sobre gel de sílice, se eluyó con cloroformo (100%) para proporcionar en 176 mg del producto zz3'.

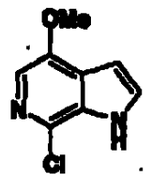
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En la etapa C, el compuesto zz3' (140 mg, 0.79 mmol) se disolvió en THF (5 mL) y se enfrió a -78°C bajo una atmósfera de nitrógeno. A esta solución se agregó gota a gota una solución de bromuro de vinil magnesio (1.2 mmol, 1.0 M en dietil éter, 1.2 mL). La mezcla de reacción luego se mantuvo a -20°C durante 15 horas. La mezcla de reacción luego se apagó con cloruro de amonio saturado, y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sulfato de magnesio, se filtraron, y el filtrado se concentró in vacuo. El residuo se procesó por cromatografía en sílice para proporcionar 130 mg del precursor 2d. ^{1}H RMN (500 MHz, CD_3OD) δ 7.78 (s, 1H), 7.60 (d, 1H, J = 3.0 Hz), 6.71 (d, 1H, J = 3.05 Hz). EM m/z: $(M+H)^+$ calculado para $C_7H_5ClFN_2$: 171.10; encontrado 171.00. Tiempo de retención CLAR: 1.22 minutos (columna A).

El precursor 2d, 4-fluoro-7-cloro-6-azaindol, se preparó por el mismo método como el precursor 2a, al partir del 2-Cloro-3-nitro-5-fluoro-piridina el cual se preparó de conformidad a el procedimiento de arriba. Los detalles experimentales para esta preparación están contenidos en Wang et. al. PCT WO 01/62255. ^{1}H RMN (500 MHz, CD_3OD) δ 7.78 (s, 1H), 7.60 (d, 1H, J = 3.0 Hz), 6.71 (d, 1H, J = 3.05 Hz). EM m/z: $(M+H)^+$ calculado para $C_7H_5ClFN_2$: 171.10; encontrado 171.00. Tiempo de retención CLAR: 1.22 minutos (columna A).

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Precursor 2e



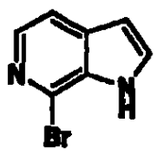
El precursor 2e se preparó por ya sea el método A o el método B, de abajo:

Método A: Una mezcla de 4-bromo-7-cloro-6-azaindol (1 g), CuI (0.65 g) y NaOMe (4 ML, 25% en metanol) en MeOH (16 mL) se calentó a 110-120°C durante 16 horas en un tubo sellado. Después de enfriarse a temperatura ambiente, la mezcla de reacción se neutralizó con HCl 1N a un pH 7. La solución acuosa se extrajo con EtOAc (3 x 30 mL). Luego la capa orgánica combinada se secó sobre $MgSO_4$, se filtró y el filtrado se concentró in vacuo para proporcionar un residuo, el cual se purificó por usar cromatografía de gel de sílice para dar 0.3 g de 4-metoxi-7-cloro-6-azaindol, El precursor 2e. EM m/z : $(M+H)^+$ calculado para $C_8H_8ClN_2O$: 183.03; encontrado 183.09. Tiempo de retención CLAR: 1.02 minutos (columna B).

Método B: Una mezcla de 4-bromo-7-cloro-6-azaindol (6 g), CuBr (3.7 g) y NaOMe (30 mL, 5% en MeOH) se calentó a 110°C durante 24 horas en un tubo sellado. Después de enfriarse a temperatura ambiente, la mezcla de reacción se agregó a NH_4Cl acuoso saturado. La solución acuosa resultante se extrajo con EtOAc (3 x 30 mL). La capa orgánica combinada

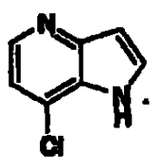
se secó sobre $MgSO_4$, se filtró y el filtrado se concentró in vacuo para proporcionar un residuo, el cual se purificó por usar cromatografía por gel de sílice para dar 1.8 g de 4-metoxi-7-cloro-6-azaindol, El precursor 2e.

Precursor 2f



El precursor 2f, 7-bromo-6-azaindol se preparó por el mismo método como el precursor 2a, al partir del 2-Bromo-3-nitro-piridina (disponible de Aldrich, Co.). EM m/z: $(M+H)^+$ calculado para $C_7H_6BrN_2$: 197.97; encontrado 197.01. Tiempo de retención CLAR: 0.50 minutos (columna A).

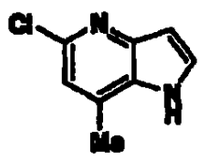
Precursor 2g



El precursor 2g, 7-cloro-4-azaindol se preparó por el mismo método como el precursor 2a, al partir del 4-Cloro-3-nitro-piridina (sal HCl, disponible de Austin Chemical Company, Inc.). EM m/z: $(M+H)^+$ calculado para $C_7H_6ClN_2$: 153.02; encontrado 152.90. Tiempo de retención CLAR: 0.45 minutos (columna A).

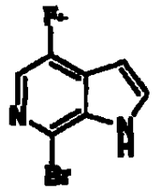
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Precursor 2h



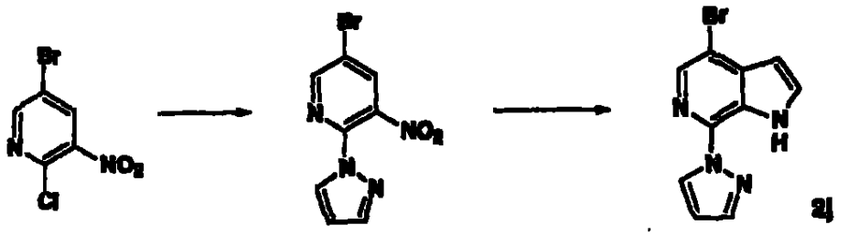
El precursor 2h, 5-cloro-7-metil-4-azaindol se preparó por el mismo método como el precursor 2a, al partir del 2-Cloro-4-metil-5-nitro-piridina (disponible de Aldrich, Co.). EM m/z: $(M+H)^+$ calculado para $C_8H_8ClN_2$: 167.04; encontrado 166.99. tiempo de retención CLAR: 1.22 minutos (columna B).

Precursor 2i



El precursor 2i, 4-fluoro-7-bromo-6-azaindol, se preparó por el mismo método como el precursor 2e, al usar $POBr_3$ en la etapa B en lugar del $POCl_3$. EM m/z: $(M+H)^+$ calculado para $C_7H_5BrFN_2$: 214.96; encontrado 214.97. Tiempo de retención CLAR: 1.28 minutos (columna G).

Precursor 2j



2j

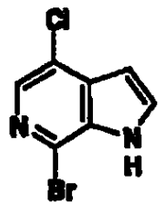
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A una mezcla de 5-bromo-2-cloro-3-nitropiridina (10 g, 42 mmol) en 1,4-dioxano (100 ml) se agregó pirazol (5.8 g, 85 mmol). La mezcla resultante se agitó a 120°C durante 26.5 h., y luego se evaporó después de enfriarse a temperatura ambiente. El material crudo se purificó por cromatografía instantánea (0 hasta 5% EtOAc/Hexanos) para dar el producto deseado 5-Bromo-3-nitro-2-pirazol-1-il-piridina. ^{1}H RMN: (CD_3OD) δ 8.77 (s, 1H), 8.56 (s, 1H), 8.45 (s, 1H), 7.73 (s, 1H), 6.57 (s, 1H); CL/EM: (ES+) m/z $(M+H)^+$ = 269, 271, CLAR R_t = 1.223.

A un matraz de fondo redondo de 250 ml se cargó 5-bromo-3-nitro-2-pirazol-1-il-piridina (1.02 g, 3.8 mmol) y THF (30 ml). La mezcla luego se enfrió a -78°C, y se agregó una solución THF de bromuro de vinil magnesio (23 mL, 18.4 mmol, 0.8 M). Después de 3 minutos, la mezcla de reacción se calentó a -45°C y se quedó agitando durante 1 h. La reacción luego se apagó con cloruro de amonio, y la mezcla resultante se extrajo con EtOAc. Los extractos combinados se evaporaron in vacuo, y el residuo se purificó por cromatografía de columna instantánea (5% EtOAc/Hexanos) para dar el compuesto 2 (el cual puede contener CLAR alrededor de 50% de un producto lateral, presumiblemente 3-vinilamino del compuesto 1); ^{1}H RMN: ($CDCl_3$) δ 10.75 (b s, 1H), 8.73 (s, 1H), 8.10 (s, 1H), 7.82 (s, 1H), 7.52 (s, 1H), 6.67 (s, 1H), 6.53 (s, 1H); CL/EM: (ES+) m/z (M+H) = 262,264; CLAR R_t = 1.670.

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Precursor 2k

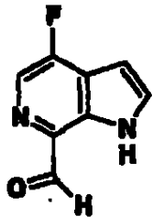


2k

A una solución de 2-bromo-5-cloro-3-nitropiridina 5 (20 g, 84 mmol, preparada en 2 etapas de la 2-amino-5-cloropiridina se describe en W09622990) en THF (300 ml) a -78°C se cargó a una solución THF de bromuro de vinil magnesio (280 ml, 252 mmol, 0.9 M). La mezcla resultante se agitó a -78°C durante 1 hora, seguido por apagarse con cloruro de amonio acuoso (500 ml, saturado) y se extrajo con EtOAc (5 x 500 ml). Los extractos orgánicos combinados se lavaron con cloruro de amonio acuoso (2 x 500 mL, sat.) y agua (3 x 500 ml), se secaron ($MgSO_4$) y se evaporaron para dar un residuo de color café. El material crudo se trituró con CH_2Cl_2, y el sólido formado se filtró para dar el compuesto 6 como un sólido amarillo (8.0 g, 41%); ^1H RMN: (DMSO-d_6) 12.30 (b s, 1H), 7.99 (s, 1H), 7.80 (d, J = 3.0, 1H), 6.71 (d, J = 3.0, 1H); CL/EM: (ES+) m/z $(M+H)^+$ = 231, 233, 235; CLAR R_t = 1.833.

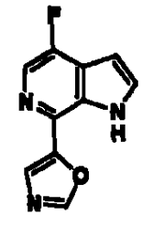
546

Precursor 2m



El 4-Fluoro-7-bromo-6-azaindol (500 mg, 1.74 mmol) se disolvió en THF (5ml) y se enfrió a -78°C y se agregó n-BuLi (2.5 M, 2.1 ml) gota a gota. La mezcla de reacción se agitó a -78°C durante 15 min., luego se agitó a 0°C durante 30 min. La reacción se enfrió hasta -78°C nuevamente, y se agregó DMF (0.7 ml, 8.7 mmol). Después de agitarse durante 30 min., se agregó agua para apagar la reacción. La mezcla de reacción se extrajo con acetato de etilo. La capa orgánica se secó sobre $MgSO_4$, se filtró, se concentró y se procesó por cromatografía para proporcionar 208 mg del precursor 2m. CL/EM: (ES^+) m/z $(M+H)^+$ = 164.98. Rt = 0.44 min.

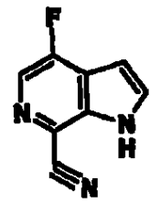
Precursor 2n



Una mezcla del precursor 2m (50 mg, 0.30 mmol), carbonato de potasio (42 mg, 0.30 mmol) y isocianuro de tosilmetilo (60 mg, 0.30 mmol) en MeOH (3ml) se calentó a

reflujo durante alrededor de 2 hr. El solvente se retiró in vacuo y el residuo se trató con agua con hielo y se extrajo con éter. La capa orgánica se lavó con una solución acuosa de HCl (2%), agua y se secó sobre sulfato de magnesio. Después de la filtración y la evaporación del solvente, el residuo se purificó en sílice para proporcionar el compuesto del título (60mg). CL/EM: (ES^+) m/z $(M+H)^+$ = 204. Rt = 0.77 min.

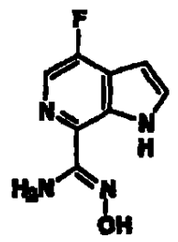
Precursor 2o



El 4-Fluoro-7-Bromo-6-azaindol (510 mg, 2.39 mmol) en DMF anhidro (5 mL) se trató con cianuro de cobre (430 mg, 4.8 mmol) a 150°C en un tubo sellado durante 1h. Una solución acuosa de NH_4OH (10 mL) se agregó y la reacción se extrajo con dietil éter (2 x 50 mL) y acetato de etilo (2 x 50 mL). Las fases orgánicas se combinaron y se secaron sobre sulfato de sodio, se filtraron, se concentraron al vacío y procesó por cromatografía sobre gel de sílice (gradiente de elución AcOEt/Hexanos 0-30%) para proporcionar el compuesto del título como un sólido color café (255 mg, 66%) CL/EM: (ES^+) m/z $(M+H)^+$ = 162.

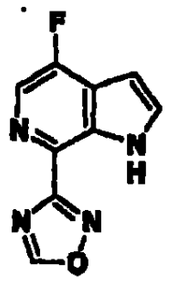
548

Precursor 2p



El precursor 2o (82 mg, 0.51 mmol) se disolvió en etanol absoluto (200% proof, 5 mL) y se trató con clorohidrato de hidroxilamina (53 mg, 0.76 mmol) y trietilamina (140 µL, 1.0 mmol) y la mezcla de reacción se calentó hasta 80°C en un tubo sellado durante 2h. El solvente se retiró in vacuo y el residuo sólido amarillo pálido se lavó con agua para proporcionar el compuesto del título. CL/EM: (ES+) m/z $(M+H)^+$ = 195. Este compuesto se tomó para la siguiente etapa sin purificación adicional.

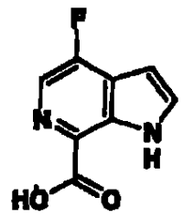
Precursor 2q



El precursor 2p se disolvió en trimetilortoformato (1 mL) y se calentó a 85°C en un tubo sellado durante 1h, luego esto se enfrió hasta temperatura ambiente, el solvente se

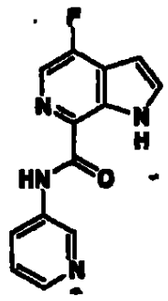
retiró in vacuo y el residuo se procesó por cromatografía sobre gel de sílice (AcOEt/Hexanos, gradiente de elución 10-60%) para proporcionar el compuesto del título (54 mg, CL/EM: (ES$^+$) m/z $(M+H)^+$ =205).

Precursor 2r



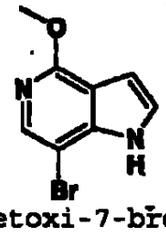
El precursor 2q (100 mg, 0.62 mmol, crudo) en etanol (5 mL) se trató con una solución acuosa de hidróxido de sodio (50%, 2 mL) y la mezcla de reacción se calentó a 110°C durante la noche en un tubo sellado. El pH se ajustó hasta 2 con HCl (6N) y un precipitado café se filtró completamente. La solución se concentró hasta secarse para proporcionar el compuesto del título como un sólido amarillo pálido CL/EM: (ES$^+$) m/z $(M+H)^+$ =181. Este compuesto se usó sin purificación adicional.

Precursor 2s



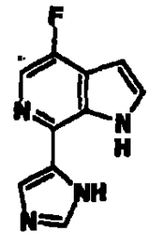
El precursor 2r (0.62 mmol) se disolvió en DMF (1 mL) y se trató con 3-aminopiridina (58.3 mg, 0.62 mmol), DEBT (185 mg, 0.62) y base Hunig (216 µL, 1.26 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18h. Se agregó agua y la reacción se extrajo con AcOEt (2 x 25 mL) y $CHCl_3$ (2 x 25 ML), se secó sobre sulfato de sodio, se concentró y se procesó por cromatografía sobre gel de sílice (AcOEt/Hexanos gradiente de elución 0-50%) para proporcionar el compuesto del título como un sólido color café CL/EM: (ES^+) m/z $(M+H)^+$ = 257.

Precursor 2s'



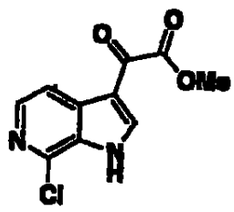
El precursor 2h; 4-metoxi-7-bromo-5-azaindol se preparó por el mismo método como el precursor 2a, al partir del 2-metoxi-5-bromo-4-nitro-piridina (el precursor 1a). ^1H RMN ($CDCl_3$) δ 8.52 (s, 1H), 7.84 (s, 1H), 7.12 (t, 1H), 6.68 (d, 1H), 3.99 (s, 3H). CL EM mostró el M+H deseado.

Precursor 2t



Una mezcla del aldehído precursor 2m (150 mg, 0.91 mmol), cianuro de sodio (44mg, 0.091 mmol) y tosilmetil isocianuro (177 mg, 0.91 mmol) en EtOH (3ml) se agitó a temperatura ambiente durante 30 min., luego se filtró y los cristales se lavaron con éter-hexano (1:1) y se secaron. Los cristales obtenidos, y una solución saturada de amoniaco en metanol seco (8ml) se calentaron entre 100-110°C durante 16HR. La mezcla se concentró y se cromatografió para proporcionar 20mg del precursor 2. CL/EM: (ES+) m/z $(M+H)^+$ = 203. Rt = 0.64 min.

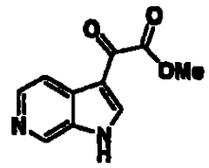
Precursor 3a



Procedimiento típico para la acilación de azaindol: Preparación de Metil (7-cloro-6-azaindol-3-il)-oxoacetato, El precursor 3a como en el ejemplo de la etapa B del esquema 1. El 7-cloro-6-azaindol, El precursor 2a (0.5 g, 3.3 mmol) se agregó a una suspensión de $AlCl_3$ (2.2 g, 16.3 mmol) en CH_2Cl_2 (100 mL). Se agitó continuamente a temperatura ambiente durante 10 minutos antes se agregó metil clorooxoacetato (2.0 g, 16.3 mmol) gota a gota. La reacción se agitó durante 8 h. La reacción se apagó con una solución NH_4OAc acuosa con hielo

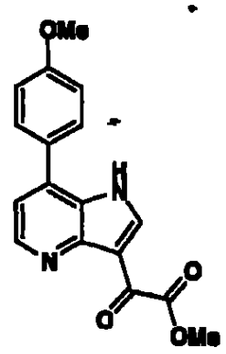
(10%, 200 mL). La fase acuosa se extrajo con CH_2Cl_2 (3 x 100 ml). La capa orgánica combinada se secó sobre $MgSO_4$, se filtró y el filtrado se concentró in vacuo para dar un residuo el cual se cargó a la siguiente etapa sin purificación adicional. El precursor 2, Metil (7-cloro-6-azaindol-3-il)-oxoacetato: EM m/z: $(M+H)^+$ calculado para $C_{10}H_8ClN_2O_3$: 239.02; encontrado 238.97. Tiempo de retención CLAR: 1.07 minutos (columna A).

Precursor 3b



El precursor 3b, Metil(6-azaindol-3-il)-oxoacetato, se preparó por el mismo método como el precursor 3a, al partir del 6-azaindol. EM m/z: $(M+H)^+$ calculado para $C_{10}H_9N_2O_3$: 205.06; encontrado 205.14. Tiempo de retención CLAR: 0.49 minutos (columna A).

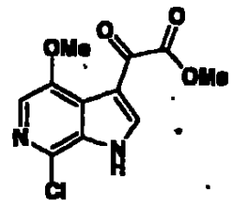
Precursor 3c



553

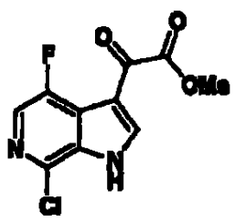
El precursor 3c, Metil (7-(4-metoxifenil)-4-azaindol-3-il)-oxoacetato, se preparó por el mismo método como el precursor 3a, al partir del 7-(4-metoxifenil)-4-azaindol (El precursor 2b). EM m/z: $(M+H)^+$ calculado para $C_{17}H_{15}N_2O_4$: 311.10; encontrado 311.04. Tiempo de retención CLAR: 1.15 minutos (columna A).

Precursor 3d



El precursor 3d, metil (7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetato se preparó por el mismo método como el precursor 3a, al partir del precursor 2e, 4-metoxi-7-cloro-6-azaindol. EM m/z: $(M+H)^+$ calculado para $C_{12}H_{12}ClN_2O_4$: 283.05; encontrado 283.22. Tiempo de retención CLAR: 1.37 minutos (columna B).

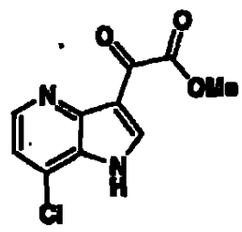
Precursor 3e



554

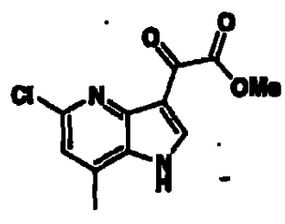
El precursor 3e, Metil (7-cloro-4-fluoro-6-azaindol-3-il)-oxoacetato se preparó por el mismo método como el precursor 3a al partir del precursor 2d, 4-fluoro-7-cloro-6-azaindol. ^{1}H RMN (500 MHz, CD_3OD) δ 8.63 (s, 1H), 8.00 (s, 1H), 3.95 (s, 3H). EM m/z: $(M+H)^+$ calculado para $C_{10}H_7ClFN_2O_3$: 257.01; encontrado 257.00. Tiempo de retención CLAR: 1.26 minutos (columna A).

Precursor 3f



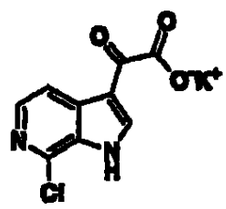
El precursor 3f, Metil (7-cloro-4-azaindol-3-il)-oxoacetato se preparó por el mismo método como el precursor 3a, al partir del precursor 2g, 7-cloro-4-azaindol. EM m/z: $(M+H)^+$ calculado para $C_{10}H_8ClN_2O_3$: 239.02; encontrado 238.97. Tiempo de retención CLAR: 0.60 minutos (columna A).

Precursor 3g



El precursor 3g, Metil (5-cloro-7-metil-4-azaindol-3-il)-oxoacetato se preparó por el mismo método como el precursor 3a, al partir del precursor 2h, 5-cloro-7-metil-4-azaindol. EM m/z: $(M+H)^+$ calculado para $C_{11}H_{10}ClN_2O_3$: 253.04; encontrado 252.97. Tiempo de retención CLAR: 1.48 minutos (columna B).

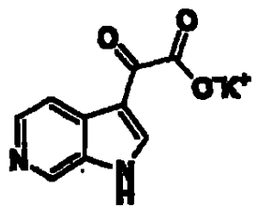
Precursor 4a



Procedimiento típico de hidrólisis del éster: Preparación de (7-cloro-6-azaindol-3-il)-oxoacetato de potasio, El precursor 4a, como un ejemplo de la etapa C del esquema 1. El metil (7-cloro-6-azaindol-3-il)-oxoacetato crudo, El precursor 3a, y un exceso de K_2CO_3 (2 g) se disolvieron en MeOH (20 mL) y H_2O (20 mL). Después de 8 h, la solución se concentró y el residuo se purificó por cromatografía en columna de gel de sílice para proporcionar 200 mg de Potasio (7-cloro-6-azaindol-3-il)-oxoacetato. EM m/z: $(M+H)^+$ del ácido correspondiente se observo. Calculado para $C_9H_6ClN_2O_3$: 225.01; encontrado 225.05. Tiempo de retención CLAR: 0.83 minutos (columna A).

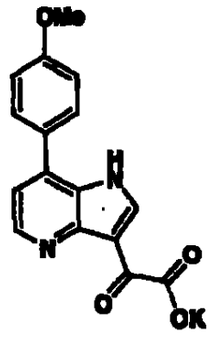
556

Precursor 4b



El (6-azaindol-3-il)oxoacetato de potasio, El precursor 4b, se preparó por el mismo método como el precursor 4a, al partir del Metil (6-azaindol-3-il)oxoacetato, El precursor 3b. EM m/z: $(M+H)^+$ del ácido correspondiente se observó. Calculado para $C_9H_7N_2O_3$: 191.05; encontrado 190.99. Tiempo de retención CLAR: 0.12 minutos (columna A).

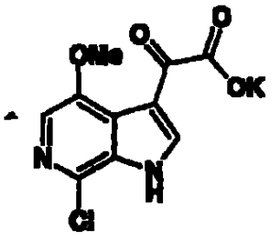
Precursor 4c



El precursor 4c, (7-(4-metoxifenil)-4-azaindol-3-il)-oxoacetato de potasio, se preparó por el mismo método como el precursor 4a, al partir del Metil (7-(4-metoxifenil)-4-azaindol-3-il)-oxoacetato, El precursor 3c. EM m/z: $(M-K+H)^+$ calculado para $C_{16}H_{13}N_2O_4$: 297.07; encontrado 297.04. Tiempo de retención CLAR: 1.00 minutos (columna A).

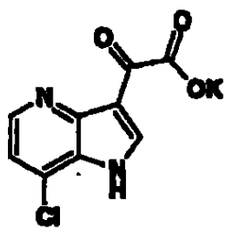
557

Precursor 4d



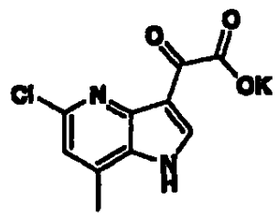
El precursor 4d, (7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetato de potasio se preparó por el mismo método como el precursor 4a al partir del Metil (7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetato, El precursor 3d. EM m/z: $(M+H)^+$ del ácido correspondiente del compuesto 4d $(M-K+H)^+$ calculado para $C_{10}H_8ClN_2O_4$: 255.02; encontrado 255.07. Tiempo de retención CLAR: 0.74 minutos (columna A).

Precursor 4e



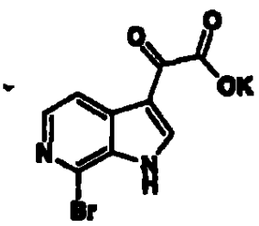
El precursor 4e, (7-cloro-4-azaindol-3-il)-oxoacetato de potasio se preparó por el mismo método como el precursor 4a, al partir del Metil (7-cloro-4-azaindol-3-il)-oxoacetato, El precursor 3f. EM m/z: $(M+H)^+$ del ácido correspondiente del compuesto 4e $(M-K+H)^+$ calculado para $C_9H_6ClN_2O_3$: 225.01; encontrado 225.27. Tiempo de retención CLAR: 0.33 minutos (columna A).

Precursor 4f



El precursor 4f, (5-cloro-7-metil-4-azaindol-3-il)-oxoacetato de potasio se preparó por el mismo método como el precursor 4a, al partir del Metil (5-cloro-7-metil-4-azaindol-3-il)-oxoacetato, El precursor 3g. EM m/z: $(M+H)^+$ del ácido correspondiente del compuesto 4f $(M-K+H)^+$ calculado para $C_{10}H_8ClN_2O_3$: 239.02; encontrado 238.94. Tiempo de retención CLAR: 1.24 minutos (columna B).

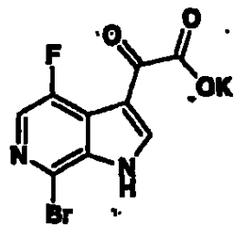
Precursor 4g



El precursor 4g, (7-bromo-6-azaindol-3-il)-oxoacetato de potasio se preparó por el mismo método como el precursor 4a, al partir del Metil (7-bromo-6-azaindol-3-il)-oxoacetato (preparado según el método del precursor 3a del 7-Bromo-6-azaindol, El precursor 2F). ^1H RMN (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.16 (d, 1H, J = 5.3 Hz), 8.08 (d, 1H, J = 5.45 Hz); ^{13}C RMN (125 MHz, DMSO-D_6). δ 180.5, 164.0, 141.6, 140.4, 132.4, 125.3, 115.5, 113.0.

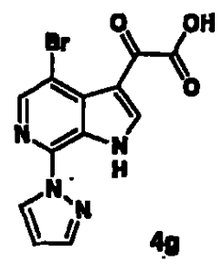
559

Precursor 4h



El precursor 4h, (7-bromo-4-fluoro-6-azaindol-3-il)-oxoacetato de potasio se preparó por el mismo método como el precursor 4a, al partir del Metil (7-bromo-4-fluoro-6-azaindol-3-il)-oxoacetato (preparado según el método del precursor 3a del 7-Bromo-4-fluoro-6-azaindol, El precursor 2i). EM m/z: $(M+H)^+$ del ácido correspondiente del compuesto 4g $(M-K+H)^+$ calculado para $C_9H_5BrFN_2O_3$: 286.95; encontrado 286.94. Tiempo de retención CLAR: 0.94 minutos (columna A).

Precursor 4i

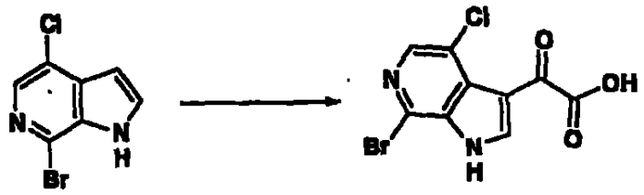


4g

Cloruro de 1-etil-3-metilimidazolio (0.172 g, 1.1 mmol) se agregó un cloruro de aluminio (0.560 g, 4.2 mmol), y la mezcla se agitó vigorosamente. Durante la formación de un líquido, se agregó el precursor 2j, seguido por clorooxoacetato de etilo (0.12 ml, 1.1 mmol). La mezcla se

permitió agitar a temperatura ambiente durante 16 h, después del cual se agregó clorooxoacetato adicional (0.12 ml, 1.1 mmol). Siguiendo esta adición, la reacción se permitió agitar a temperatura ambiente durante otras 24 h. El matraz se enfrió hasta 0°C y se agregó agua, durante el cual se formo el precipitado. El material sólido se filtró, se lavó con agua y metanol, y se secó sobre alto vacío para dar el compuesto 3; CL/EM: (ES+) m/z (M+H) = 334, 336; CLAR R_t = 1.390.

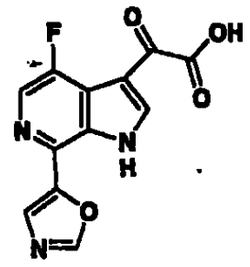
Precursor 4j



Al cloruro de 1-etil-3-metilimidazolio (2.54 g, 17.3 mmol) se agregó cloruro de aluminio (6.91 g, 51.8 mmol). La mezcla se agitó vigorosamente a temperatura ambiente durante 10 minutos. Al líquido amarillo resultante se agregó el precursor 2k (2.0 g, 8.64 mmol) y clorooxoacetato de etilo (2.0 ml, 17.3 mmol), y se agitó a temperatura ambiente durante 16 h. La mezcla de reacción luego se agregó hielo/agua (300 ml) para dar los precipitados, los cuales se filtraron y se lavaron con agua para dar el compuesto del título como un sólido

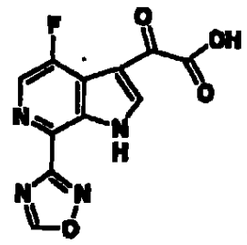
amarillo (1.98 g). La solución acuosa se extrajo con EtOAc (3 x 300 ml), y los extractos se evaporaron in vacuo para dar un segundo lote del compuesto 8 como un sólido amarillo (439 mg, rendimiento total 92%); ^{1}H RMN: (DMSO-D_6) 14.25 (b s, 1H), 13.37 (s,. 1H), 8.56 (s, 1H), 8.18 (s, 1H); CL/EM: (ES+) m/z $(M+H)^+$ = 303, 305, 307; CLAR R_t = 1.360.

Precursor 4k



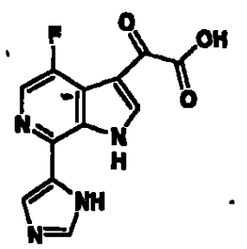
Se agregó cloruro de 1-etil-3-metilimidazolio (82mg, 0.56 mmol) a un matraz el cual contiene el precursor 2n (56 mg, 0.28 mmol) y la mezcla se enfrió hasta 0°C. Se agregó cloruro de aluminio (336 mg, 2.52 mmol) en una porción seguida por ClCOCOOEt (58 µL, 0.56 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 días. Se agregó agua con hielo para apagar la reacción. La mezcla de reacción se filtró. El sólido se lavó con agua y dietil éter y se secó en al aire para proporcionar el compuesto del título (58mg). CL/EM: (ES+) m/z $(M+H)^+$ = 276. Rt = 0.85 min.

Precursor 4m



El cloruro de 1-etil-3-metilimidazolio (73mg, 0.52 mmol) y cloruro de aluminio (198 mg, 1.56 mmol) se agitaron juntos bajo nitrógeno durante 1h. A esta solución se agregó intermediario 2q (54 mg, 0.26 mmol) y cloruro de etiloxalilo (58 µL, 0.52 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18h. La reacción se apagó con agua y la mezcla se agitó durante 15 min. El sólido se recolectó por filtración y se lavó con agua y dietil éter. CL/EM (ES+) m/z $(M+H)^+$ =276. Este compuesto se usó sin purificación adicional.

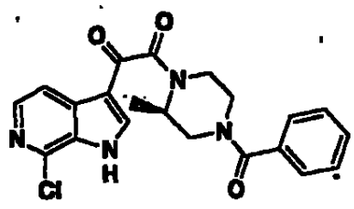
Precursor 4n



Se agregó cloruro de 1-etil-3-metilimidazolio (26mg, 0.18 mmol) a un matraz el cual contiene el precursor 2t (18 mg, 0.09 mmol) y la mezcla se enfrió hasta 0°C. Se agregó cloruro de aluminio (92 mg, 0.54 mmol) en una porción seguida

por ClCOCOOEt (20 µL, 0.18 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 días. Se agregó agua con hielo para apagar la reacción. La mezcla de reacción se filtró. El sólido se lavó con agua y dietil éter y se secó al aire para proporcionar el compuesto D (18mg). CL/EM: (ES$^+$) m/z $(M+H)^+$ = 275. R_t = 0.49 min.

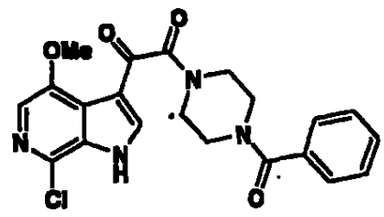
Precursor 5a



Procedimiento típico para acoplar el derivado de piperazina y el ácido: Preparación de 1-benzoil-3-(R)-metil-4-[(7-cloro-6-azaindol-3-il)-oxoacetil]piperazina, El precursor 5, es un ejemplo de la etapa D del esquema 1. Se combinaron 7-cloro-6-azaindol 3-glioxilato de potasio, El precursor 4a, (100 mg, 0.44 mmol), 3-(R)-metil-1-benzoilpiperazina (107 mg, 0.44 mol), 3-(dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona (DEPBT) (101 mg, 0.44 mol) y base Hunig (diisopropiletilamina, 0.5 mL) en 5 mL de DMF. La mezcla se agitó a temperatura ambiente durante 8 h. El DMF se removió por medio de evaporación a presión reducida y el residuo se purificó al usar un sistema CLAR preparativo

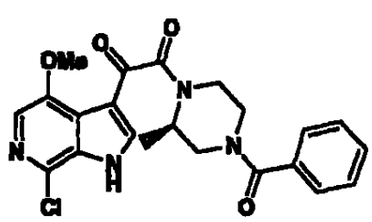
automatizado Shimadzu para dar 1-(benzoil)-3-(R)-metil-4-[(7-cloro-6-azaindol-3-il)-oxoacetil]-piperazina (70 mg, 39%). EM m/z: $(M+H)^+$ Calculado para $C_{21}H_{20}ClN_4O_3$: 411.12; encontrado 411.06. Tiempo de retención CLAR: 1.32 minutos (columna A).

Precursor 5b



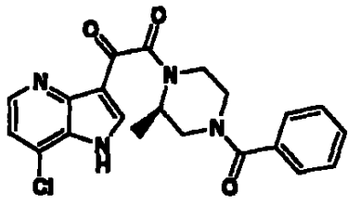
El precursor 5b, 1-benzoil-4-[(7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a al partir del (7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetato de potasio, El precursor 4d, y 1-benzoilpiperazina. EM m/z: $(M+H)^+$ calculado para $C_{21}H_{20}ClN_4O_4$: 427.12; encontrado 427.12. Tiempo de retención CLAR: 1.28 minutos (columna A).

Precursor 5c



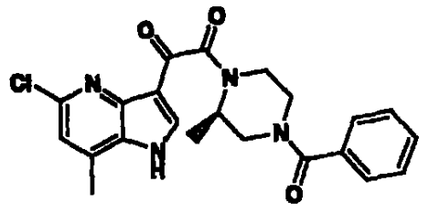
El precursor 5c, 1-benzoil-3-(R)-metil-4-[(7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a al partir del (7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetato de potasio, El precursor 4d, y 1-benzoilpiperazina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.72 (s, 1H), 7.40 (s, 5H), 3.89 (s, 3H), 3.71-3.40 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{22}H_{22}ClN_4O_4$: 441.13; encontrado 441.17. Tiempo de retención CLAR: 1.33 minutos (columna A).

Precursor 5d



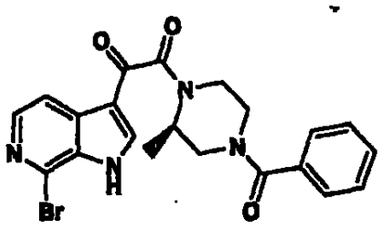
El precursor 5d, 1-benzoil-3-(R)-metil-4-[(7-cloro-4-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a, al partir del (7-cloro-4-azaindol-3-il)-oxoacetato de potasio, El precursor 4e, y 1-benzoil-3-(R)-metil piperazina. EM m/z: $(M+H)^+$ calculado para $C_{21}H_{20}ClN_4O_3$ 411.12, encontrado 411.04. Tiempo de retención CLAR: 1.10 minutos (columna A).

Precursor 5e



El precursor 5e, 1-benzoil-3-(R)-metil-4-[(5-cloro-7-metil-4-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a, al partir del (5-cloro-7-metil-4-azaindol-3-il)-oxoacetato de potasio, el precursor 4f, y 1-benzoil-3-(R)-metil piperazina. EM m/z: $(M+H)^+$ calculado para $C_{22}H_{22}ClN_4O_3$ 425.24, encontrado 425.04. Tiempo de retención CLAR: 1.72 minutos (columna B).

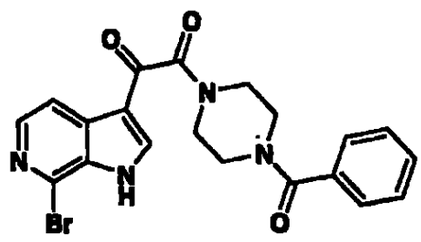
Precursor 5f



El precursor 5f, 1-benzoil-3-(R)-metil-4-[(7-bromo-6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a, a partir de la sal de potasio del ácido (7-bromo-6-azaindol-3-il)-oxoacético, El precursor 4g, y 1-benzoil-3-(R)-metilpiperazina. EM m/z: $(M+H)^+$

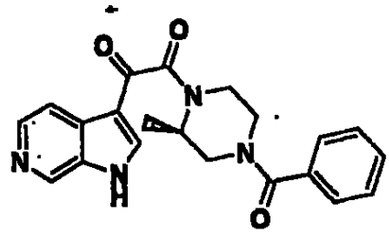
calculado para $C_{21}H_{20}BrN_4O_3$: 455.07; encontrado 455.14. Tiempo de retención CLAR: 1.45 minutos (columna B).

Precursor 5g



El precursor 5g, 1-benzoil-4-[(7-bromo-6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a, al partir de la sal de potasio del ácido (7-bromo-6-azaindol-3-il)-oxoacético, El precursor 4g, y 1-benzoilpiperazina. EM m/z: $(M+H)^+$ calculado para $C_{20}H_{18}BrN_4O_3$: 441.06; encontrado 441.07. Tiempo de retención CLAR: 1.43 minutos (columna B).

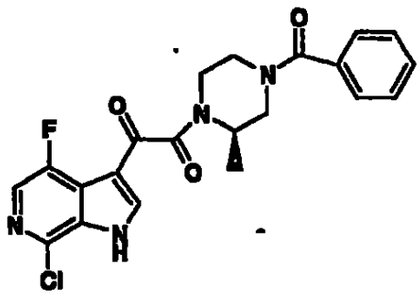
Precursor 5h



El precursor 5h, 1-benzoil-3-(R)-metil-4-[(6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a al partir del (6-azaindol-3-il)oxoacetato de

(m, 8H); CL/EM (ES+) m/z $(M+H)^+$ 415 se observó; tiempo de retensión 1.247 minutos; CL/EM método: YMC ODS-A C18 S7 3.0 x 50 mm columna; Inicio % B = 0, Final % B = 100, Tiempo de gradiente = 2 minutos; Relación de flujo = 5 mL/min.; detector de longitud de onda = 220 nm.

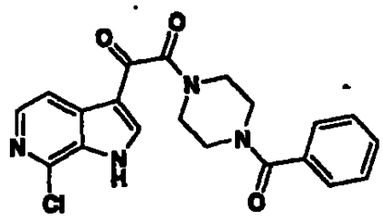
Precursor 5j



1-benzoil-3-(R)-metil-4-[(4-fluoro-7-cloro-6-azaindol-3-il)-oxoacetil]-piperazina se preparó por acoplamiento de (7-cloro-4-fluoro-6-azaindol-3-il)oxoacetato de potasio, se preparó como se describe arriba por el precursor 5i, con 1-benzoil-3-(R)-metilpiperazina en presencia de DEPBT bajo las condiciones estándar (como se describe por el precursor 5a) para proporcionar 1-benzoil-3-(R)-metil-4-[(4-fluoro-7-cloro-6-azaindol-3-il)-oxoacetil]piperazina, el precursor 5j. ^1H RMN (500 MHz, CD_3OD) δ 8.42, 8.37 (s, s, 1H), 8.03 (s, 1H), 7.71-7.45 (m, 5H), 4.72-3.05 (m, 7H), 1.45-1.28 (m, 3H); CL/EM (ES+) m/z $(M+H)^+$ 429 se observaron; tiempo de retensión 1.297 minutos; CL/EM método: YMC ODS-A C18 S7

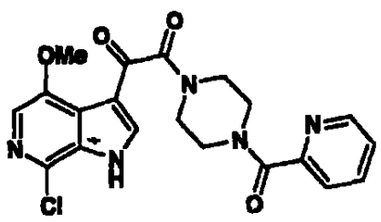
3.0 x 50 mm columna; Inicio % B = 0, Final % B = 100, Tiempo de gradiente = 2 minutos; Relación de flujo = 5 mL/min.; detector de longitud de onda = 220 nm.

Precursor 5k

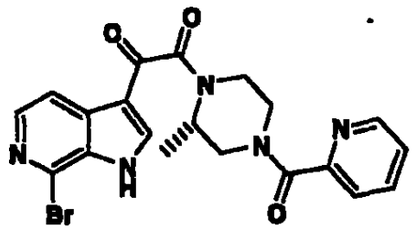


El precursor 5K, 1-benzoil-4-[(7-cloro-6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a, al partir de la sal de potasio del ácido (7-cloro-6-azaindol-3-il)-oxoacético, El precursor 4a, y 1-benzoilpiperazina. EM m/z: $(M+H)^+$ calculado para $C_{20}H_{18}ClN_4O_3$: 397.11; encontrado 396.97. Tiempo de retención CLAR: 2.37 minutos (columna F, tiempo de gradiente = 3 min., relación de flujo = 4 ml/min.).

Precursor 51

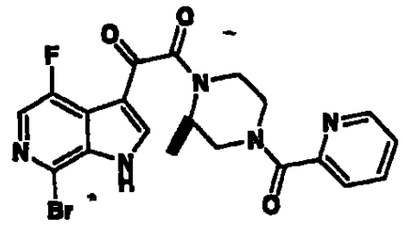


Precursor 5n



El precursor 5n, (S)-1-picolinoil-3-metil-4-[(7-bromo-6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a al partir del (7-bromo-6-azaindol-3-il)oxoacetato de potasio, El precursor 4g, y (S)-3-metil-1-picolinoil-piperazina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.63-7.36 (m, 7H), 5.02-3.06 (m, 7H), 1.42-1.26 (m, 3H).

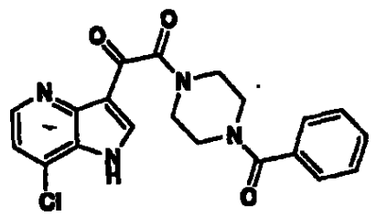
Precursor 5o



El precursor 5o, (R)-1-picolinoil-3-metil-4-[(7-bromo-4-fluoro-6-azaindol-3-il)-oxoacetil]piperazina se preparó por el mismo método como el precursor 5a al partir del (7-bromo-4-fluoro-6-azaindol-3-il)oxoacetato de potasio, El precursor 4h, y (R)-3-metil-1-picolinoil-piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.68-7.52 (m, 6H), 4.94-2.69 (m, 7H), 1.48-1.24 (m, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{20}H_{18}BrFN_5O_3$: 474.06;

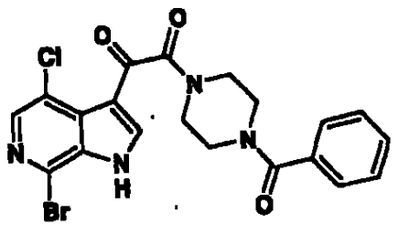
encontrado 474.23. Tiempo de retención CLAR: 1.20 minutos (columna A).

Precursor 5p



El precursor 5p, 1-benzoil-4-[(7-cloro-4-azaindol-3-il)-oxoacetil]piperazina se prepàró por el mismo método como el precursor 5a al partir del (7-cloro-4-fluoro-4-azaindol-3-il)oxoacetato de potasio, El precursor 4e, y 1-benzoil-piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.83 (s, 1H), 8.63 (d, 1H, J = 5.35 Hz), 7.91 (d, 1H, J = 5.75 Hz), 7.47 (m, 5H), 3.80-3.30 (m, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{20}H_{18}ClN_4O_3$: 397.11; encontrado 397.02. Tiempo de retención CLAR: 1.20 minutos (columna A).

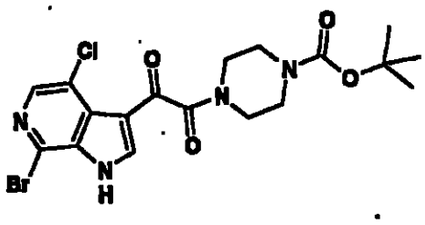
Precursor 5q



El precursor 5q, 1-(4-Benzoil-piperazin-1-il)-2-(7-bromo-1H-pirrolo[2,3-c]piridin-3-il)-etano-1,2-diona. A una solución del ácido precursor 4j (2.4 g, 7.9 mmol) en DMF (40

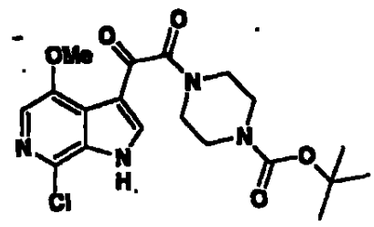
ml) se agregó 3-(dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona (DEPBT, 5.96 g, 19.9 mmol), clorohidrato de benzoilpiperazina (2.71 g, 11.9 mmol), y N,N diisopropiletilamina (14 ml, 80.4 mmol). La mezcla se agitó a temperatura ambiente durante 16 h. La mezcla de reacción luego se agregó agua (400 ml) y se extrajo con EtOAc (4 x 300 ml). Los extractos combinados se evaporaron in vacuo para dar un residuo color café, el cual se trituró con MeOH para proporcionar el compuesto del título como un sólido blanco (2.8 g, 74%); ^{1}H RMN: (DMSO-d_6) 13.41 (s, 1H), 8.48 (s, 1H), 8.19 (s, 1H), 7.45 (b s, 5H), 3.80-3.35 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 475, 477, 479; CLAR (condiciones alternas B, columna G) R_t = 1.953.

Precursor 5r



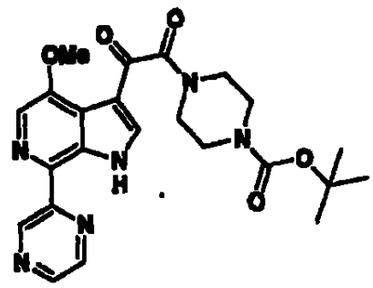
El precursor 5r se preparó por el procedimiento usado para 5q al usar mono N-Boc piperazina. ^{1}H RMN: ($CDCl_3$) δ 8.26 (s, 1H), 8.19 (s, 1H), 3.71 (b s, 2H), 3.53 (b m, 6H), 1.48 (s, 9H); CL/EM: (ES+) m/z $(M+H)^+$ = 471, 473, 475; CLAR (condiciones alternas B, columna G) R_t = 1.543.

Precursor 5s



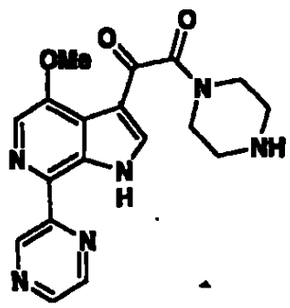
El precursor 5s se preparó por el procedimiento usado para 5b al usar mono N-Boc piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{19}H_{24}ClN_4O_5$: 423.14; encontrado 423.07 Tiempo de retención CLAR: 1.44 minutos (columna L).

Precursor 5t



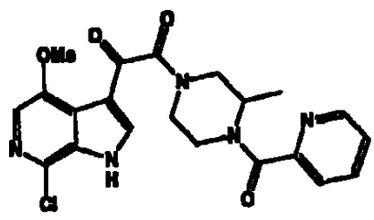
El precursor 5t, se preparó del precursor 5s y la pirazin-2-il estanano, por medio del procedimiento descrito en la sección posterior de preparación de los compuestos de la fórmula 1. EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{27}N_6O_5$: 467.20; encontrado 467.47. Tiempo de retención CLAR: 1.57 minutos (columna C).

Precursor 5u



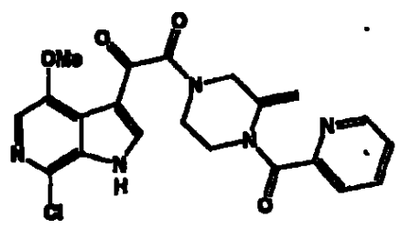
Preparación del precursor 5u: El precursor 5t (30 mg) se disolvió en TFA (0.5 g). Después de que la reacción se agitó durante 30 minutos, la mezcla se concentró in vacuo para dar el intermediario 5u deseado el cual se usó en las reacciones adicionales sin ninguna purificación. EM m/z: $(M+H)^+$ Calculado para $C_{18}H_{19}N_6O_5$: 367.15; encontrado 367.06. Tiempo de retención CLAR: 0.91 minutos (columna M).

Precursor 5v



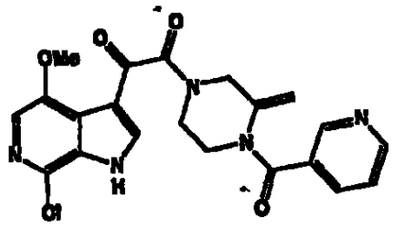
El precursor 5v se preparó por el procedimiento usado para 5b al usar 2-metil-1-picolinoilpiperazina. EM m/z: $(M+H)^+$ Calculado para $C_{21}H_{21}ClN_5O_4$: 442.13; encontrado 442.11. Tiempo de retención CLAR: 1.01 minutos (columna G).

Precursor 5xa



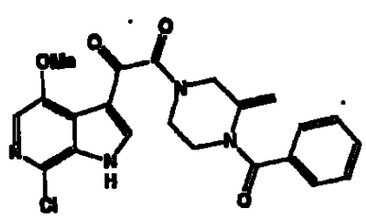
El precursor 5xa se preparó por el procedimiento usado para 5b al usar (R)-2-metil-1- picolinoilpiperazina. EM m/z: $(M+H)^+$ Calculado para $C_{21}H_{21}ClN_5O_4$: 442.13; encontrado 442.23. Tiempo de retención CLAR: 1.12 minutos (columna L).

Precursor 5y



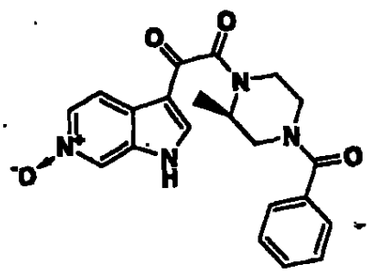
El precursor 5y se preparó por el procedimiento usado por el 5b al usar (R)-2-metil-1-nicotinoilpiperazina. EM m/z: $(M+H)^+$ Calculado para $C_{21}H_{21}ClN_5O_4$: 442.13; encontrado 442.15. Tiempo de retención CLAR: 0.87 minutos (columna C).

Precursor 5z



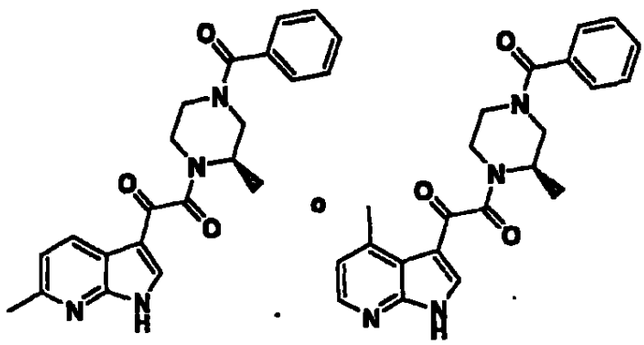
El precursor 5z se preparó por el procedimiento usado por el 5b al usar (R)-2-metil-1-benzoilpiperazina. EM m/z: $(M+H)^+$ Calculado para $C_{22}H_{22}ClN_4O_4$: 441.13; encontrado 441.46. Tiempo de retención CLAR: 1.27 minutos (columna C).

Precursor 6



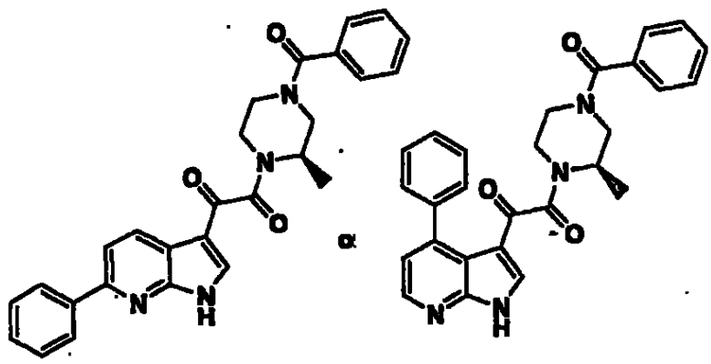
Procedimiento típico para la formación de N-óxido: Preparación de 1-benzoil-3-(R)-metil-4-[(6-óxido-6-azaindol-3-il)-oxoacetil]piperazina, El precursor 6.20 mg de 1-benzoil-3-(R)-metil-4-[(6-azaindol-3-il)-oxoacetil]piperazina, El precursor 5H, (0.053 mmol) se disolvió en CH_2Cl_2 (2 mL). 18 mg de mCPBA (0.11 mmol) luego se agregó en la solución y la reacción se agitó durante 12 h a temperatura ambiente. El CH_2Cl_2 se removió por medio de evaporación a presión reducida y el residuo se purificó al usar un sistema CLAR preparativo automatizado Shimadzu para dar el compuesto mostrado arriba (5.4 mg, 26%). EM m/z: $(M+H)^+$ Calculado para $C_{21}H_{21}N_4O_4$: 393.16; encontrado 393.11. Tiempo de retención CLAR: 0.90 minutos (columna A).

Precursor 7



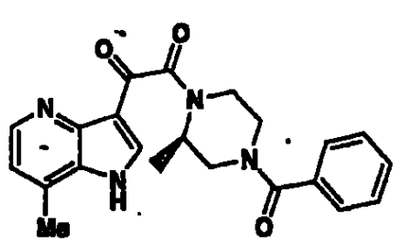
Preparación de 1-benzoil-3-(R)-metil-4-[(6-metil-7-azaindol-3-il)-oxoacetil]-piperazina o 1-benzoil-3-(R)-metil-4-[(4-metil-7-azaindol-3-il)-oxoacetil]-piperazina. Un exceso de MeMgI (3M en THF, 0.21 ml, 0.63 mmol) se agregó dentro de una solución de 1-benzoil-3-(R)-metil-4-[(6-óxido-6-azaindol-3-il)-oxoacetil]piperazina, El precursor 6, (25 mg, 0.064 mmol). La mezcla de reacción se agitó a temperatura ambiente y luego se apagó con MeOH. Los solventes se removieron bajo vacío, el residuo se diluyó con MeOH y se purificó al usar un sistema CLAR preparativo automatizado Shimadzu para dar un compuesto mostrado arriba el cual es un isómero simple pero la regioquímica no se asigna definitivamente. (6.7 mg, 27%). EM m/z: $(M+H)^+$ Calculado para $C_{22}H_{23}N_4O_3$: 391.18; encontrado 391.17. Tiempo de retención CLAR: 1.35 minutos (columna B).

Precursor 8



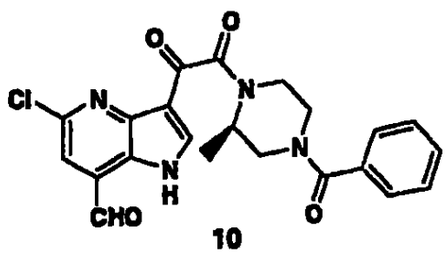
La 1-benzoil-3-(R)-metil-4-[(6-fenil-7-azaindol-3-il)-oxoacetil]piperazina o la 1-benzoil-3-(R)-metil-4-[(4-fenil-7-azaindol-3-il)-oxoacetil]piperazina (la regioquímica no se asigna definitivamente) se prepararon por el método descrito por el ejemplo 7 al partir con 1-benzoil-3-(R)-metil-4-[(6-óxido-6-azaindol-3-il)-oxoacetil] piperazina, El precursor 6, y bromuro de fenil magnesio (Reactivo de fenil Grignard). EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{25}N_4O_3$: 453.19; encontrado 454.20. Tiempo de retención CLAR: 1.46 minutos (columna B).

Precursor 9

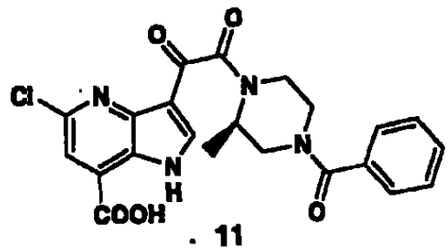


Una mezcla de Pd(10% en carbono, 100 mg), ácido trifluoroacético (1 mL) y 1-benzoil-3-(R)-metil-4-[(5-cloro-7-metil-4-azaindol-3-il)-oxoacetil]piperazina, El precursor 5E (1.5 g) en MeOH (50 mL) y EtOAc (50 ML) se agitaron en un reactor Parr bajo una atmósfera de hidrógeno (45 psi) durante 48 horas. Después de que los sólidos se removieron por filtración, el filtrado se concentró in vacuo para proporcionar el precursor 9 (1 g) el cual se usó sin purificación adicional. EM m/z: $(M+H)^+$ calculado para $C_{21}H_{21}N_4O_3$ 391.18, encontrado 391.15. Tiempo de retención CLAR: 1.15 minutos (columna A).

Precursores 10 y 11



10

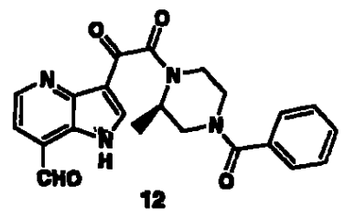


11

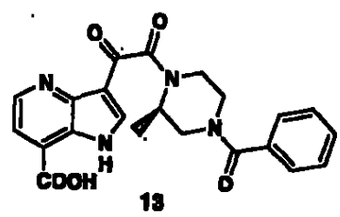
Preparación del precursor 10; 1-benzoil-3-(R)-metil-4-[(5-cloro-7-carbonil-4-azaindol-3-il)-oxoacetil]-piperazina y El precursor 11, 1-benzoil-3-(R)-metil-4-[(5-cloro-7-hidroxicarbonil-4-azaindol-3-il)-oxoacetil]-piperazina: Una mezcla de 1-benzoil-3-(R)-metil-4-[(5-cloro-7-metil-4-azaindol-3-il)-oxoacetil]piperazina (1.78 g) y SeO_2 (4.7 g) en dioxano/agua (100:1) se puso a reflujo durante 10 horas. Después de enfriarse a temperatura ambiente, la mezcla se concentró in vacuo para proporcionar un residuo. El residuo se purificó al usar cromatografía en gel de sílice con EtOAc y MeOH como solventes eluyentes para proporcionar el precursor 10 (350 mg) y el precursor 11 (410 mg).

El precursor 10, 1-benzoil-3-(R)-metil-4-[(5-cloro-7-carbonil-4-azaindol-3-il)-oxoacetil]-piperazina: EM m/z: $(M+H)^+$ Calculado para $C_{22}H_{20}ClN_4O_4$: 439.12, encontrado 439.01. Tiempo de retención CLAR: 1.37 minutos (columna A); El precursor 11, 1-benzoil-3-(R)-metil-4-[(5-cloro-7-hidroxicarbonil-4-azaindol-3-il)-oxoacetil]-piperazina: EM m/z: $(M+H)^+$ calculado para $C_{22}H_{20}ClN_4O_5$: 455.11, encontrado 455.10. Tiempo de retención CLAR: 1.44 minutos (columna A).

Precursores 12 y 13



12



13

El precursor 12, 1-benzoil-3-(R)-metil-4-[(7-carbonil-4-azaindol-3-il)-oxoacetil]-piperazina y el precursor 13, 1-benzoil-3-(R)-metil-4-[(7-hidroxicarbonil-4-azaindol-3-il)-oxoacetil]-piperazina se hicieron de conformidad a el mismo procedimiento de preparación de los precursores 10 y 11, por usar el precursor 9 como material de partida. El precursor 12, 1-benzoil-3-(R)-metil-4-[(7-carbonil-4-azaindol-3-il)-oxoacetil]-piperazina: EM m/z: $(M+H)^+$ calculado para $C_{22}H_{21}N_4O_4$: 405.16, encontrado 405.14. Tiempo de retención CLAR: 0.91 minutos (columna A); El precursor 13, 1-benzoil-3-(R)-metil-4-[(7-hidroxicarbonil-4-azaindol-3-il)-oxoacetil]-piperazina: EM m/z: $(M+H)^+$ calculado para $C_{22}H21N_4O_5$: 421.15, encontrado 421.09. Tiempo de retención CLAR: 1.02 minutos (columna A).

Precursores 14a-1-14a-21

Los siguientes agentes de estaño y agentes de boro puede obtenerse de fuentes comerciales y usarse sin cualquier tratamiento adicional (Tabla I-1).

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Tabla I-1

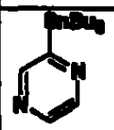
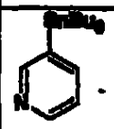
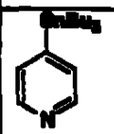
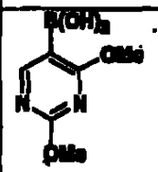
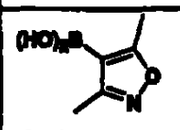
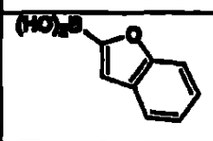
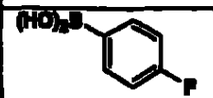
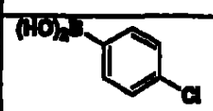
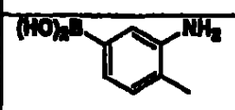
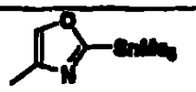
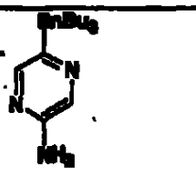
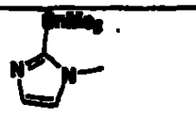
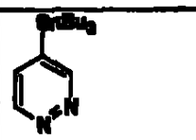
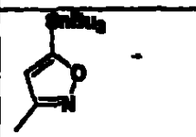
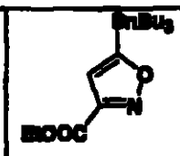
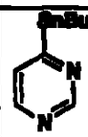
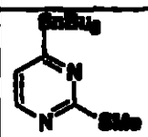
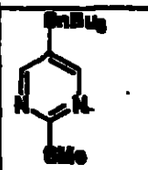
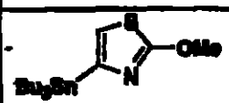
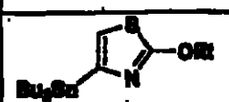
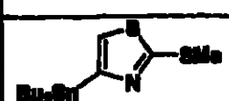
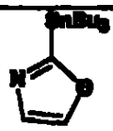
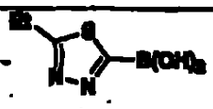
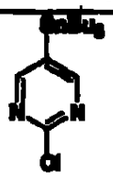
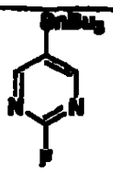
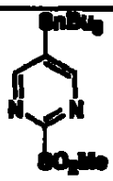
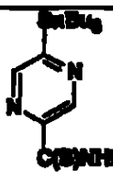
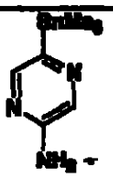
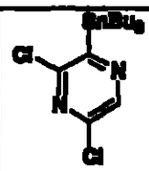
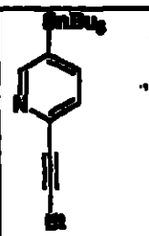
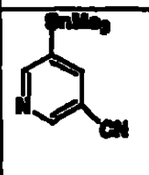
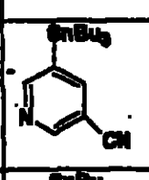
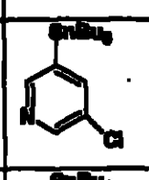
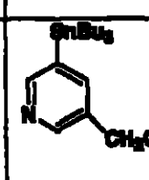
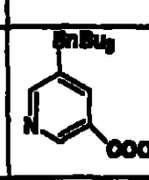
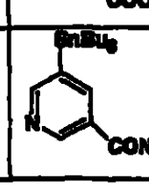
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14a-3		Frontier Scientific, Inc.
14a-4		Matrix Scientific
14a-5		Matrix Scientific
14a-6		Aldrich, Co.
14a-7		Aldrich, Co.
14a-8		Aldrich, Co.
14a-9		Aldrich, Co.
14a-10		Aldrich, Co.
14a-11		Lancaster

Tabla I-2

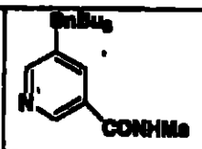
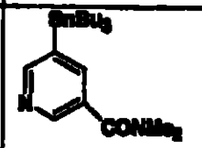
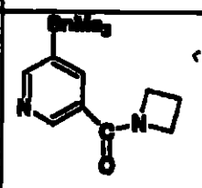
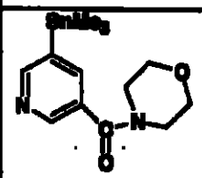
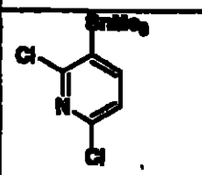
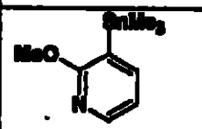
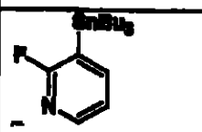
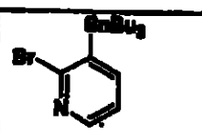
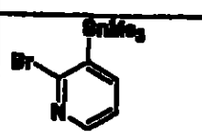
Número de precursor	Estructura	Referencias
14-1		Dondoni, A., et al Synthesis, 1987, 693
14-2		Aldous, D. J., et al US – 5,453,433
14-3		Sandosham, J., et al Tetrahedron 1994, 50, 275.
14-4		Lehn, L. M., et al. Chem. Eur. J. 2000, 6, 4133.
14-5		Jutzi, P., et al J. Organometallic Chem. 1983, 246, 163.
14-6		Jutzi, P., et al J. Organometallic Chem. 1983, 246, 163.
14-7		Graybill, T. L., et al Bioorg. Med. Chem. Lett. 1995, 5 (4), 387.
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14-11		Kondo, Y., et al Tetrahedron Lett. 1989,30, 4249
14-12		Or, Y. S., et al US-6,054,435
14-13		Or, Y. S., et al US-6,054,435
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14-15		Okada, T., et al WO-0123383
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14-17		Sandosham, J., et al Acta Chem. Scand. 1989, 43, 684.
14-18		Nicolaou, K. C., et al WO-9967252
14-19		Nicolaou, K. C., et al WO-9967252
14-20		Nicolaou, K. C., et al WO-9967252
14-21		Benhada, R., et al Tetrahedron Lett. 1999, 40, 5701.

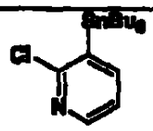
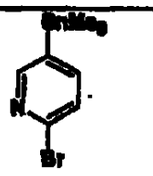
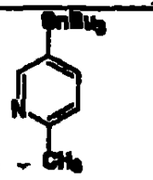
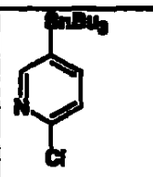
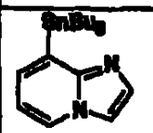
14-22		Collins, I, et al Tetrahedron Lett. 1999, 40, 4069.
14-23		Pusa, R. W., et al DE-19502178
14-24		Bunnage, M.E.et.al PCT Int. Appl. WO 0024745 A1 (2000); and Sandosham, J. et. Al. Tetrahedron (1994), 50(1), 275-84.
14-25		De 5-iodo-cloro-1,3 pirimidina. Fluoropirimidinas son obtenidas por fluorinación de cloropirimidinas con CsF en N-metil-2-pirrolidininona o DMF 2.5-63 h a 80-150 °C. El yodo luego se convirtió al reactivo de litio con tBuLi y se atrapó con Bu_3SnCl. Ver Sandosham arriba
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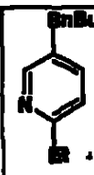
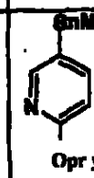
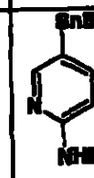
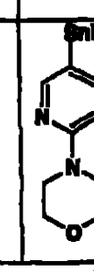
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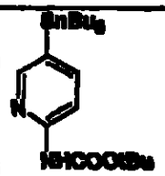
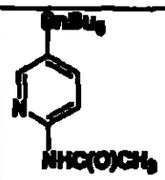
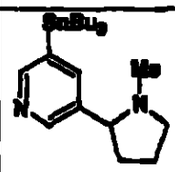
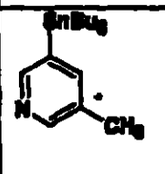
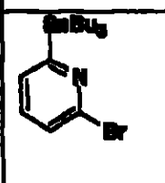
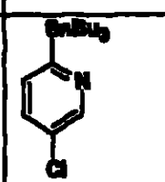
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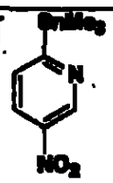
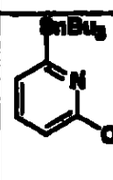
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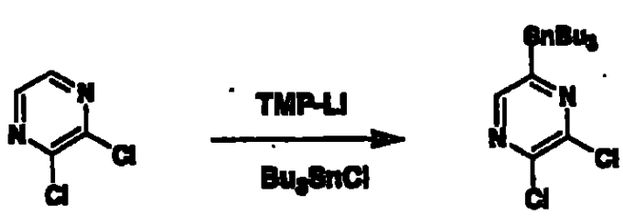
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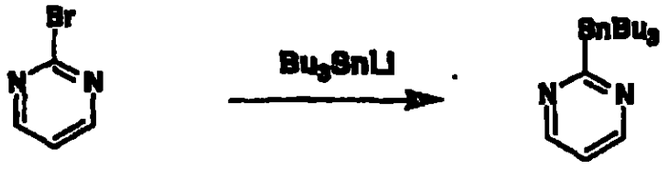
Precursor 14-66



Preparación de 2,3-dicloro-5-(tri-n-butilestanil)pirazina (Un ejemplo del procedimiento general Tin-01, a continuación): TMP-Li (2,2,6,6-tetrametilpiperidinil litio) se preparó por la adición de n-butil litio (1.6 M, 6.25 mL) a una solución de 2,2,4,4-tetrametilpiperidina (1.4 g) en THF seco (180 ml) a -78°C. La solución luego se permitió calentar a 0°C, se agitó a 0°C durante 15 minutos, luegó se enfrió hasta -78°C. A la

solución se agregó 2,3-dicloropirazina (1.35 g), y seguido por una adición de cloruro de tri-n-butilestaño (3.25 g) en otras 2 horas. La reacción se apagó con solución acuosa de cloruro de amonio. La capa orgánica se separó, y capa acuosa se extrajo con acetato de etilo (3 x 100 mL). El extracto orgánico combinado se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para proporcionar 2,3-dicloro-5-(tri-n-butilestanil)pirazina (1 g).

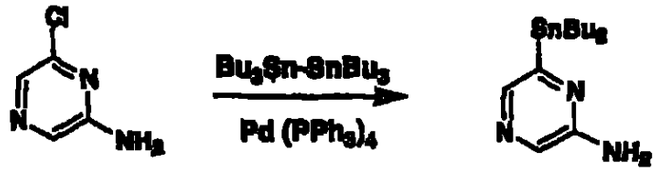
Precursor 14-67



Preparación de 2-(tri-n-butilestanil)-pirimidina: (Ejemplo del procedimiento general Tin-03, a continuación) Tri-n-butilestanil litio se preparó a 0°C en THF seco (20 mL) de hidruro de tri-butilestaño (2.2 mL) y LDA (diisopropilamida de litio, 2M, 4.09 mL). La solución de tri-n-butilestanil litio luego se enfrió a -78°C y a esto se agregó 2-bromopirimidina (1 g). La mezcla de reacción luego se permitió calentar a temperatura ambiente durante 8 horas. La reacción luego se apagó con solución acuosa de cloruro de amonio. La

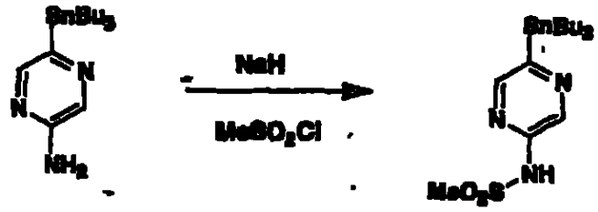
capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo (3 x 20 mL). La capa orgánica combinada se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para proporcionar 2-(tri-n-butilestanil)-pirimidina (190 mg).

Precursor 14-68



Preparación de 2-amino-6-(tri-n-butilestanil)pirazina (ejemplo del procedimiento general Tin-04, a continuación): A un tubo sellado, 2-amino-6-cloro-pirazina (1 g), bis (tri-butilestaño) (3.92 mL) y tetrakis-trifenilfosfina paladio, $Pd(Ph_3P)_4$ (100 mg) se combinaron en dioxano (10 mL). La reacción se calentó a 110-120°C durante 10 h. Después de que la mezcla se enfrió bajo temperatura ambiente, esta se vació en 20 mL de agua. La solución se extrajo con EtOAc (4 x 20 mL). El extracto combinado se concentró in vacuo para dar un residuo el cual se purificó por cromatografía en gel de sílice para proporcionar 2-amino-6-(tri-n-butilestanil)pirazina (0.5 g).

Precursor 14-69

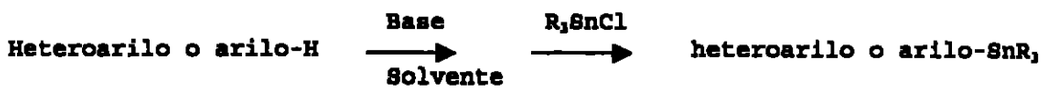


Preparación de la 2-metilsulfonilamino-5-(tri-n-butilestanil)pirazina (ejemplo del procedimiento general Tin-05, a continuación): Se agregó NaH (60%, 20 mg) dentro de una solución de 2-amino-5-(tri-n-butilestanil) pirazina (0.2 g) en THF (30 mL) a temperatura ambiente. Después de que la mezcla se agitó a temperatura ambiente durante 30 minutos, a esto se agregó cloruro de metilsulfonilo (63 mg). La mezcla de reacción se agitó a temperatura ambiente durante 8 horas. La reacción se apagó con una solución acuosa de cloruro de amonio. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo (3 x 100 mL). El extracto orgánico combinado se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para proporcionar 2-metilsulfonilamino-5-(tri-n-butilestanil)pirazina (20 mg).

Precursores 14-70-14-129

Los precursores 14-70-14-129 se prepararon de conformidad a los siguientes procedimientos generales designados Estaño-01 hasta Estaño-05 (Tabla I-3).

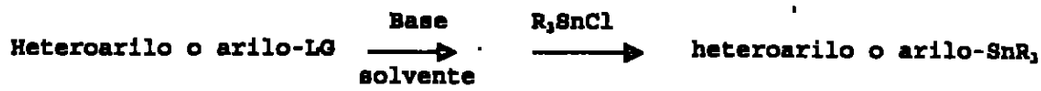
Procedimiento general Estaño-01:



Base = LDA, TMP-Li, n-Buli, S-BuLi o t-BuLi;
Solvente = THF, dietil éter o DME;
R = metilo o butilo

A una solución de una base (1.1 equivalentes) seleccionados de diisopropilamida de litio, 2,2,6,6-tetrametilpiperidinil litio, n-butil litio, sec-butil litio o tert-butil litio en un solvente seleccionado de tetrahidrofurano, dietil éter o dimetoxietano (concentración de aproximadamente 0.05 mmol base/ml del solvente) a -78°C se agregó un arilo apropiado o un substrato de heteroarilo (1.0 equivalentes) seguido por una adición de cloruro de tri-n-butilestaño o cloruruo de trimetilestaño (1.1 equivalentes) en otras 2 horas. La reacción se apagó con solución acuosa de cloruro de amonio. La capa orgánica se separó, y capa acuosa se extrajo con acetato de etilo. El extracto orgánico combinado se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para proporcionar el estanano deseado.

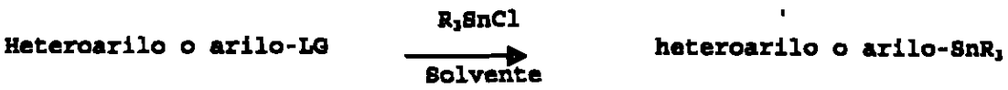
Procedimiento general Estaño-02:



LG = Br o I; Base = n-BuLi, o t-BuLi;
Solvente = THF, éter o DME;
R = metilo o butilo

A una solución de una base (1.1 equivalentes) seleccionada de n-butil litio, sec-butil litio o tert-butil litio en un solvente seleccionado de tetrahidrofurano, dietil éter o dimetoxietano (concentración de aproximadamente 0.05 mmol base/ml del solvente) a -78°C se agregó un arilo apropiado o bromuro de heteroarilo o arilo o substrato de yoduro de heteroarilo (1.0 equivalentes). La mezcla de reacción se agitó a -78°C durante un periodo adecuado para generar el anión por medio de un intercambio de metal-halógeno luego esto se agregó cloruro de tri-n-butilestaño o cloruro de trimetilestaño (1.1 equivalentes). La reacción se apagó con una solución acuosa de cloruro de amonio. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo. El extracto orgánico combinado se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para proporcionar el estanano deseado.

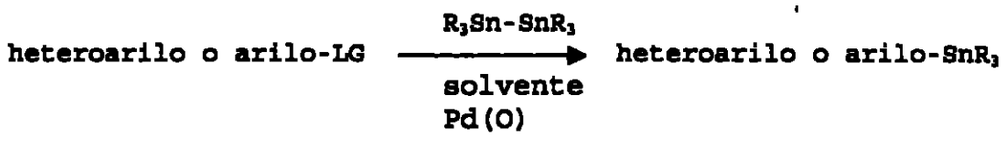
Procedimiento general Estaño-03:



LG = F, Cl, Br, I, Solvente = THF, dietil éter o DME;
R = metilo o butilo

El Tri-n-butilestanil litio o trimetilestanil litio (1.3 equivalentes) se preparó a 0°C en un solvente seco seleccionado de THF, dietil éter ó dimetoxietano (20 mL) de hidruro de tri-n-butilestaño o hidruro de trimetilestaño, respectivamente (1.3 equivalentes) y LDA (diisopropilamida de litio, 1.3 equivalentes) a un concentración de aproximadamente 0.4 mmol de alquilestanil de litio/mL del solvente. La solución de tri-n-butilestanil de litio o el trimetilstannil de litio luego se enfrió a -78°C y a esto se agregó un haloarilo apropiado o substrato de haloheteroarilo (1.0 equivalente). La mezcla de reacción luego se permitió calentar a temperatura ambiente durante 8 horas. La reacción luego se apagó con solución acuosa de cloruro de amonio. La capa orgánica se separó, y capa acuosa se extrajo con acetato de etilo (3 x 20 mL). La capa orgánica combinada se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para proporcionar el precursor deseado de estanano.

Procedimiento general Estaño-04:



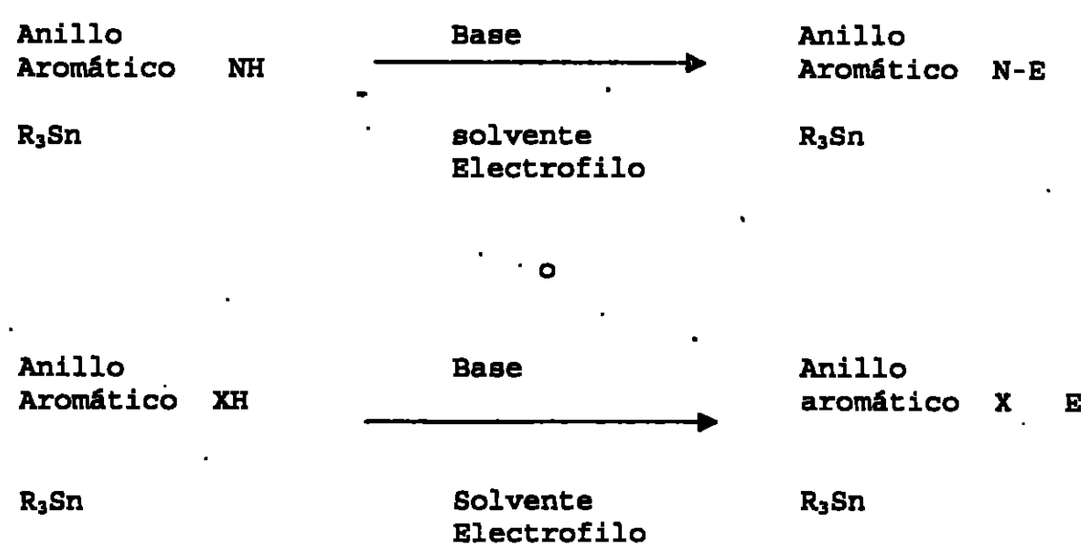
LG = Cl, Br, I o OTf; Solvente = Dioxano o Tolueno; R = metilo o butilo

A un tubo sellado, un substrato de arilo o heteroarilo apropiado (1.0 equivalente), bis(tri-butilestaño) o hexametildiestaño (1.0 equivalente) y tetraquis-trifenilfosfino paladio, $Pd(Ph_3P)_4$ (1.0 mol%) se combinaron en dioxano o tolueno (10 mL). La reacción se calentó a 110-120°C durante 10 h. Después de que la mezcla se enfrió bajando a temperatura ambiente, esto se vació dentro de agua. La solución se extrajo con acetato de etilo y los extractos combinados se concentraron in vacuo para dar un residuo el cual se purificó por cromatografía en gel de sílice para resultar el producto de estanano deseado.

Procedimiento general Estaño-05:

El siguiente esquema de reacción describe la derivación de precursores de estanano en los cuales el estanano tiene un grupo NH de anillo reactivo o grupo amino hidroxi o tiol exocíclico reactivo. El estanano de partida se trata con base en un solvente apropiado luego se reactivan con electrófilos adecuados tales como haluros de alquilo, cloruros ácidos,

cloruros sulfonilo, isocianatos y similares.



Electrófilo = R'-haluro, R'C(O)Cl, R'OC(O)Cl, R'R'NCOCl, $R'SO_2Cl$, R'NCO, R'NSO, R'NCNR''

E = R'-, R'C(O)-, R'OC(O)-, R'R''NC(O)-, $R'SO_2$-, R'NC(O)-, R'NS(O)-, R'NCNR''

Solvente = CH_2Cl_2, THF, dietil éter, DMF

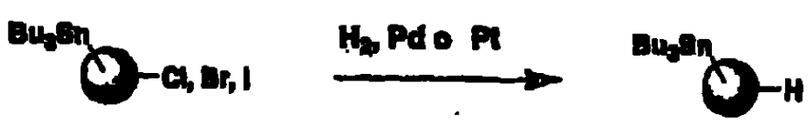
R = metilo o butilo; X = NH, O o S

Base = NaH, BuLi, LAD, K_2CO_3, Et_3N, DBU, DMAP, NaHMDS

Una base apropiada seleccionada del hidruro de sodio, n-butil litio, diisopropilamida de litio, carbonato de potasio, trietilamina, DBU, DMAP o hexametildisilazida de sodio (1.0 equivalente) se agregó dentro de una solución de un substrato

de estaño apropiado (como se describe arriba, 1.0 equivalente) en un solvente apropiado seleccionado de diclorometano, THF, éter dietílico o N,N-dimetilformamida a una temperatura entre -78°C y temperatura ambiente. Después la mezcla se agitó durante un periodo suficiente para permitir desprotonación, típicamente durante 5 a 30 minutos, luego a esto se agregó un electrófilo adecuado tal como un haluro alquilo, cloruro ácido, sulfonilo (1.0 equivalente). La mezcla de reacción se agitó, típicamente a temperatura ambiente, durante un periodo de 2 a 8 horas. La reacción se apagó con solución acuosa de cloruro de amonio. La capa orgánica se separó, y la capa acuosa se extrajo con acetato de etilo (3 x 100 mL). El extracto orgánico combinado se secó sobre sulfato de magnesio, se filtró y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía en gel de sílice para resultar el precursor deseado de estanano.

Procedimiento general Estaño-06

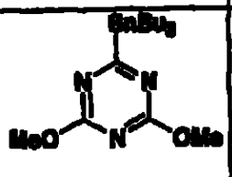
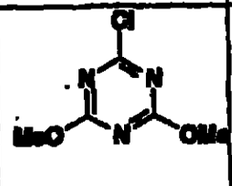
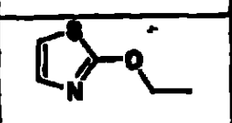
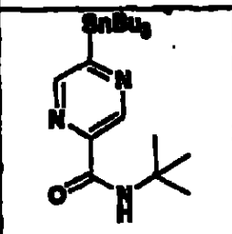
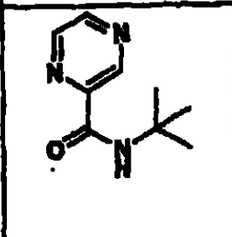


Un agente de estanano de haluro arilo se disolvió en alcohol apropiado, ya sea metanol o etanol. Después de

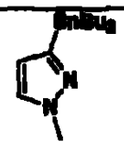
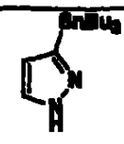
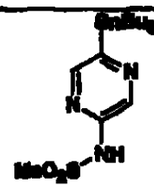
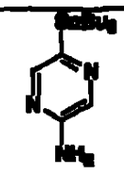
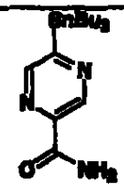
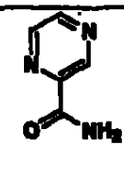
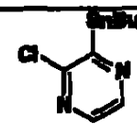
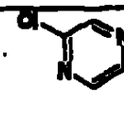
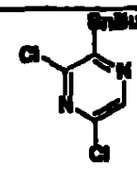
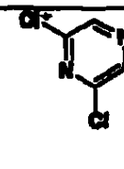
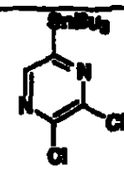
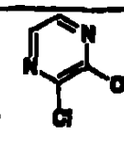
que un catalizador (pt o pd) se agregó al solvente, la mezcla de reacción se colocó en un ambiente de hidrógeno bajo presión normal o elevada. Después de terminar la reacción, el catalizador se filtra, y, la concentración de la solución madre proporciona un residuo el cual se usa en las reacciones adicionales sin ninguna purificación.

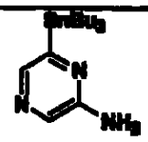
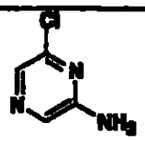
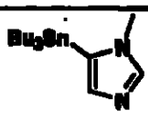
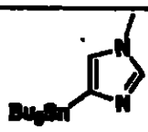
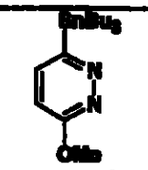
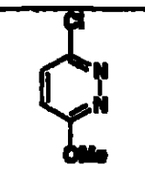
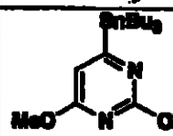
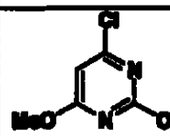
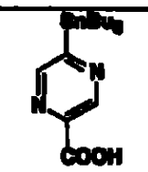
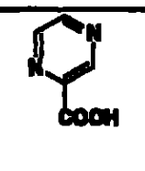
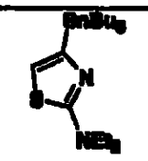
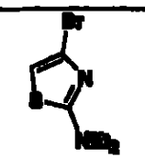
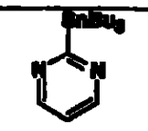
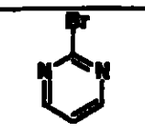
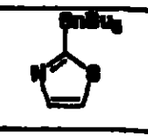
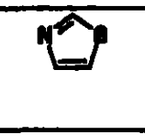
Tabla I-3

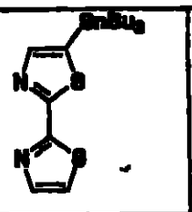
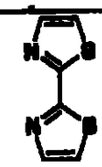
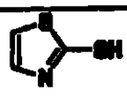
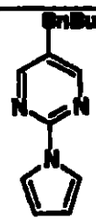
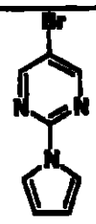
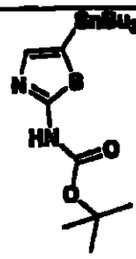
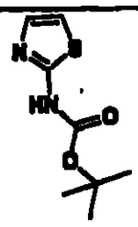
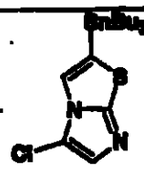
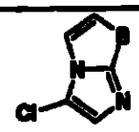
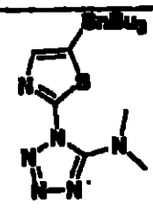
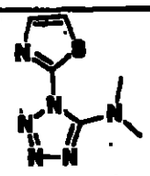
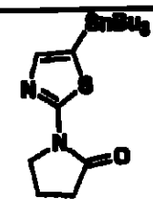
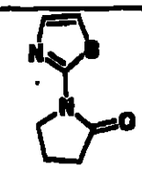
Rf = tiempo de retención

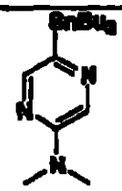
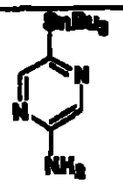
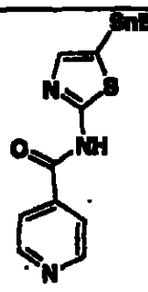
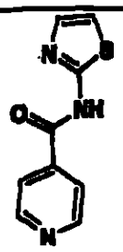
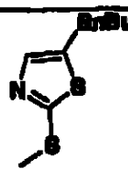
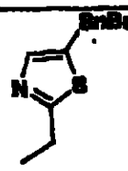
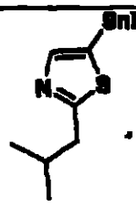
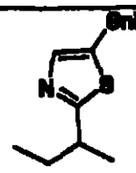
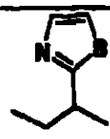
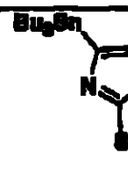
Número de Intermediario	Estructura	Material de Partida	Método aplicado	Identificación
14-70			Estaño-04	R_t = 2.33 min (Columna A) ^{1}H NMR (500 MHz, CDCl3) δ 4.00 (s, 6H), 1.63 – 0.85 (m, 27H)
14-71			Estaño-01	R_t = 2.52 min (Columna A) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 4.44 (q, 2H, *J* = 7.02 Hz), 1.63 – 0.85 (m, 30H)
14-72			Estaño-01	R_t = 2.84 min (Columna B) ^{1}H NMR (500 MHz, CDCl3) δ 9.48 (s, 1H), 8.45 (s, 1H), 2.03 – 0.88 (m, 36H)

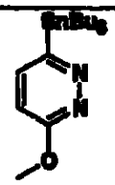
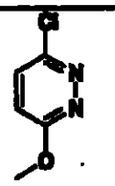
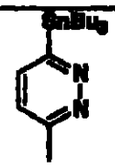
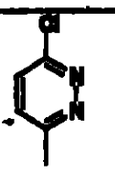
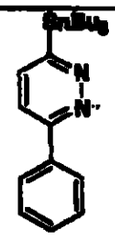
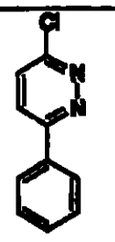
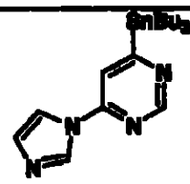
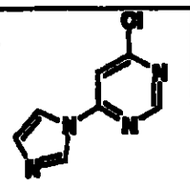
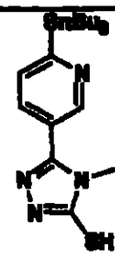
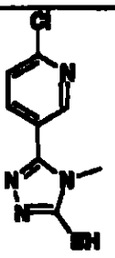
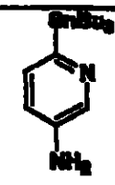
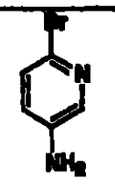
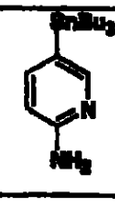
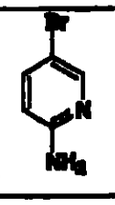
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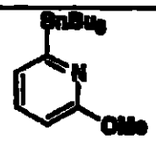
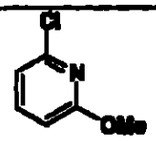
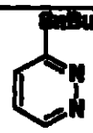
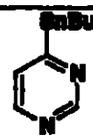
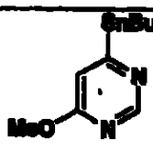
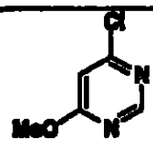
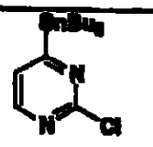
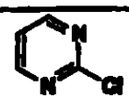
14-73			Estaño-08	R_t = 2.27 min (Columna A) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 1H), 6.29 (m, 1H), 3.94 (s, 3H), 1.56 – 0.87 (m, 27H)
14-74			Estaño-08	R_t = 2.22 min (Columna A)
14-75			Estaño-01	R_t = 2.44 min (Columna B) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.34 (s, 1H), 1.61 – 0.85 (m, 27H)
14-76			Estaño-01	R_t = 3.41 min (Columna A), relación de flujo = 4 ml/min) ^{1}H NMR (300 MHz, CDCl3) δ 8.58 (d, 1H, *J* = 2.52 Hz), 8.13 (d, 1H, *J* = 2.52 Hz), 1.63 – 0.85 (m, 27H)
14-77			Estaño-01	R_t = 3.89 min (Columna A), relación de flujo = 4 ml/min) ^{1}H NMR (300 MHz, CDCl3) δ 8.63 (s, 1H), 1.61 – 0.85 (m, 27H)
14-78			Estaño-01	R_t = 3.86 min (Columna A), relación de flujo = 4 ml/min) ^{1}H NMR (300 MHz, CDCl3) δ 8.24 (s, 1H), 1.61 – 0.85 (m,

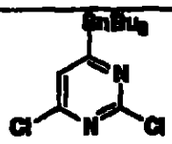
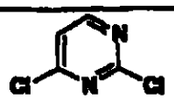
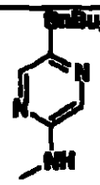
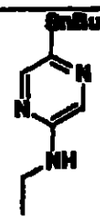
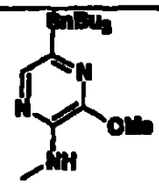
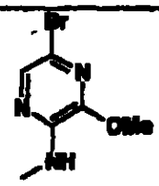
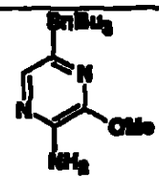
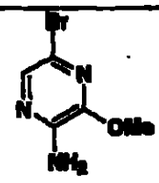
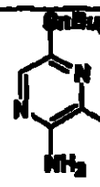
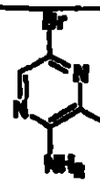
				27H)
14-79			Estaño-04	R_t= 2.10 min (Columna B) ^{1}H RMN (500 MHz, CDCl3) δ 7.90 (s, 1H), 7.26 (s, 1H), 1.58 – 0.87 (m, 27H)
14-80			Estaño-04	R_t= 1.83 min (Columna A)
14-81			Estaño-04	R_t= 1.84 min (Columna A)
14-82			Estaño-04	R_t= 1.84 min (Columna A)
14-83			Estaño-04	R_t= 1.90 min (Columna A)
14-84			Estaño-01	R_t= 2.23 min (Columna A)
14-85			Estaño-04	R_t= 1.92 min (Columna A)
14-86			Estaño-03	R_t= 2.01 min (Columna A)
14-87			Estaño-01	R_t= 2.45 min (Columna A)

14-88			Estaño-01	R_t = 2.67 min (Columna C)
14-89			Estaño-01	R_t = 2.31 min (Columna C)
14-90			Estaño-04	R_t = 2.71 min (Columna D)
14-91			Estaño-01	R_t = 2.49 min (Columna C)
14-92			EStaño-01	R_t = 2.42 min (Columna C)
14-93			Estaño-01	R_t = 3.49 min (Columna C) Relación de flujo = 4 ml/min
14-94			Estaño-01	R_t = 2.46 min (Columna C)

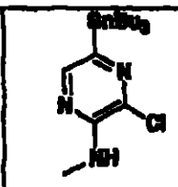
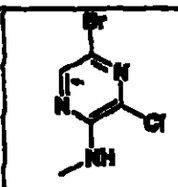
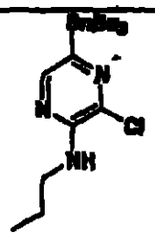
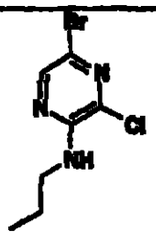
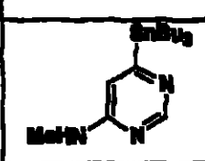
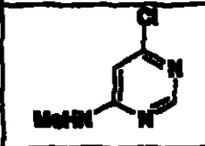
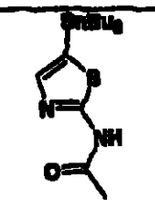
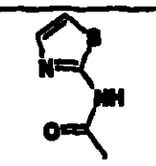
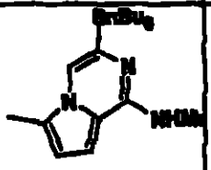
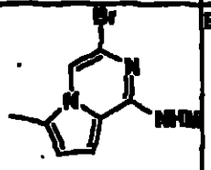
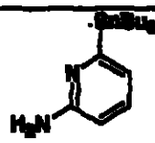
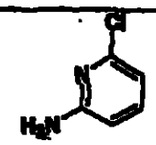
14-95			Estaño-05	Rf = 2.15 min (Columna A)
14-96			Estaño-01	R_t = 2.28 min (Columna C)
14-97			Estaño-01	R_t = 2.60 min (Columna C)
14-98			Estaño-01	R_t = 2.37 min (Columna A)
14-99			Estaño-01	R_t = 2.59 min (Columna A)
14-100			Estaño-01	R_t = 2.49 min (Columna C)
14-101			Estaño-04	R_t = 2.41 min (Columna A)

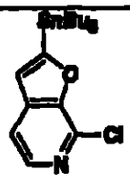
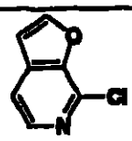
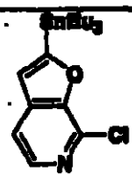
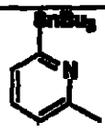
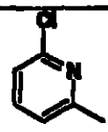
14-102			Estaño-04	R_t= 1.88 min (Columna E)
14-103			Estaño-04	R_t= 1.92 min (Columna E)
14-104			Estaño-04	R_t= 2.01 min (Columna E)
14-105			Estaño-04	R_t= 2.15 min (Columna E)
14-106			Estaño-04	R_t= 1.91 min (Columna E)
14-107			Estaño-04	Rf = 1.95 min (Columna A)
14-108			Estaño-04	Rf = 1.93 min (Columna A)

12-109			Estaño-01	Rf = 1.95 min (Columna A)
14-110			Estaño-01	Rf = 1.83 min (Columna A) ^{1}H RMN (500 MHz, CDCl3) δ 9.03 (d, 1H, J = 5.15 Hz), 7.49 (d, 1H, J = 7.95 Hz), 7.26 (m, 1H), 1.61 – 0.86 (m, 27H); ^{13}C NMR (125 MHz, CDCl3) δ 175.3, 149.8, 133.2, 123.7, 29.0, 27.3, 13.6, 10.1.
14-111			Estaño-01	Rf = 2.18 min (Columna E) ^{1}H NMR (500 MHz, CDCl3) δ 9.22 (s, 1H), 8.46 (d, 1H, J = 4.80 Hz), 7.42 (d, 1H, J = 4.75 Hz), 1.56 – 0.86 (m, 27H); ^{13}C NMR (125 MHz, CDCl3) δ 185.4, 158.0, 153.2, 130.6, 28.9, 27.2, 13.5, 9.9.
14-112			Estaño-04	Rf = 1,96 min (Columna A)
14-113			Estaño-01	Rf = 2.61 min (Columna A)

14-114			Estaño-01	Rf = 2.85 min (Columna A)
14-115			Estaño-06	Rf = 2.09 min (Columna A) ^{1}H RMN (500 MHz, CDCl3) δ 8.12 (s, 1H), 7.95 (s, 1H), 4.11 (s, 1H), 2.95 (s, 3H), 2.03 – 0.85 (m, 27H)
14-116			Estaño-06	Rf = 2.16 min (Columna A) ^{1}H RMN (500 MHz, CDCl3) δ 8.08 (s, 1H), 7.92 (s, 1H), 4.49 (s, 1H), 3.35 (m, 2H), 1.63 – 0.85 (m, 30H)
14-117			Estaño-04	Rf = 2.19 min (Columna A)
14-118			Estaño-04	Rf = 2.18 min (Columna A)
14-119			Estaño-04	Rf = 2.47 min (Columna A) ^{1}H RMN (500 MHz, CDCl3) δ 7.85 (s, 1H), 4.91 (s, 2H), 2.16 – 0.87 (m, 27H)

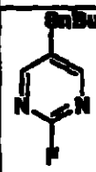
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14-120			Estaño-04	Rf = 2.61 min (Columna A)
14-121			Estaño-04	Rf = 2.92 min (Columna A)
14-122			Estaño-04	Rf = 1.93 min (Columna A)
14-123			Estaño-01	Rf = 2.20 min (Columna A)
14-124			Estaño-01	Rf = 2.50 min (Columna A) ^{1}H RMN (500 MHz, CDCl3) δ 9.07 (s, 1H), 7.87 (s, 1H), 1.59 – 0.85 (m, 27H)
12-125			Estaño-04	Rf = 1.97 min (Columna A)
14-126			Estaño-04	Rf = 1.97 min (Columna A)

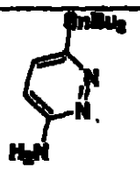
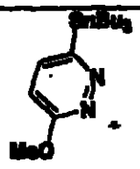
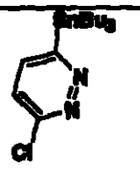
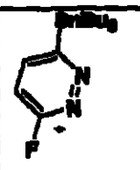
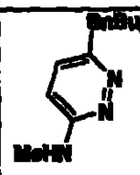
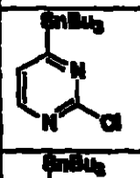
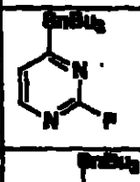
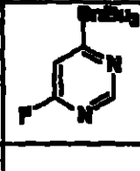
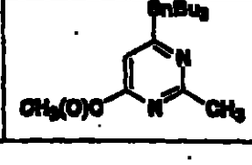
14-127			Estaño-01	Rf = 2.70 min (Columna E) ^{1}H RMN (500 MHz, CDCl3) δ 8.11 (d, 1H, J = 5.2 Hz), 7.41 (d, 1H, J = 5.2 Hz), 6.94 (s, 1H), 1.62 – 0.89 (m, 27H)
14-128			Estaño-08	^{1}H RMN (500 MHz, CDCl3) δ 8.12 (d, 1H, J = 5.2 Hz), 7.78 (s, 1H), 7.46 (d, 1H, J = 5.2 Hz), 6.84 (s, 1H), 1.98 – 0.85 (m, 27H)
14-129			Estaño-01	Rf = 1.86 min (Columna A)

La siguiente Tabla I-4 contiene reactivos de estanano novedosos los cuales se pueden preparar por la metodología descrita arriba y luego podrán usarse para preparar compuestos de la fórmula I.

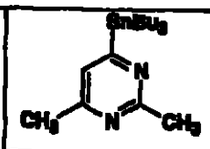
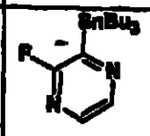
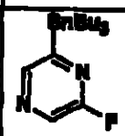
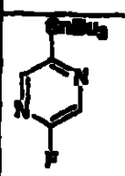
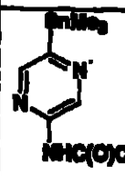
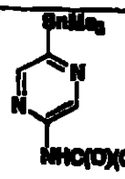
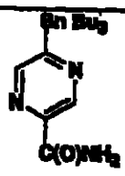
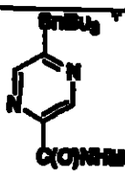
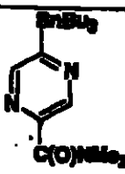
Tabla I-4

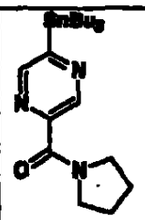
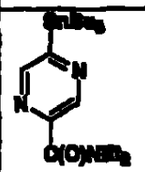
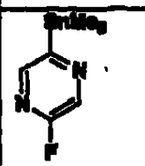
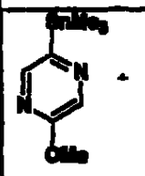
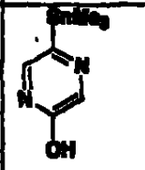
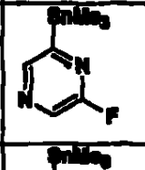
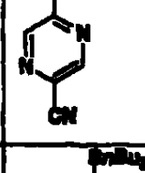
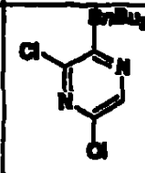
Número de Precursor	Estructura	Referencia
		De 5-yodo-2-cloro-1,3 pirimidina. Fluoropirimidinas son obtenidas por fluorinación de cloropirimidinas con CsF en N-metil-2-pirrolidinona o DMF 2.5-63 h a 80-150°C. El yodo luego se convirtió al reactivo de litio con tBuli y se atrapó con

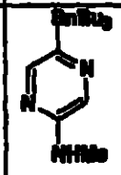
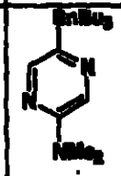
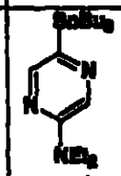
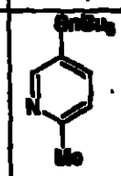
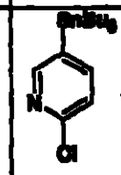
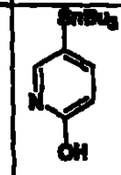
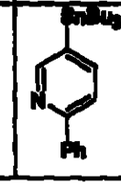
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		Bu3SnCL Ver Sandosham arriba
		
		
		
		
		
		
		
		
		

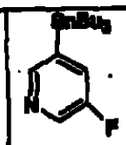
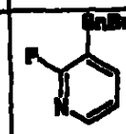
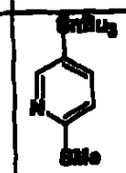
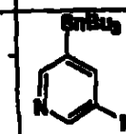
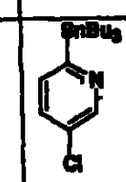
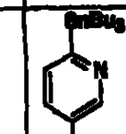
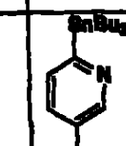
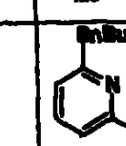
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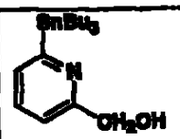
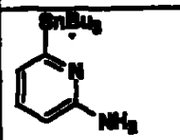
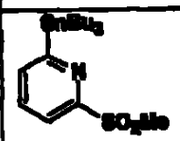
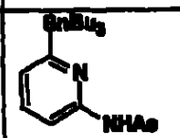
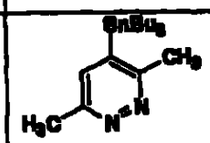
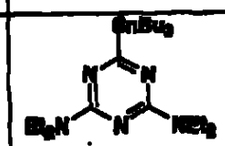
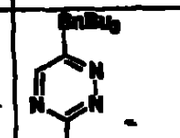
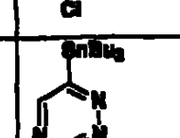
		
		
		
		
		
		
		
		Turck, A.; et.al Lab..; J. Organomet. Chem. (1991), 412(3), 301-10. Metalación de 2,6-dicloropirazina y se apagó con Bu3SnCl

		Análogo para Lehn, L. M., et al. Chem. Eur. J. 2000, 6, 4133.
		
		
		
		
		
		
		

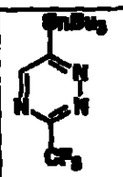
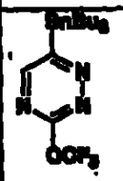
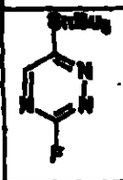
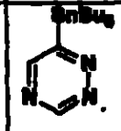
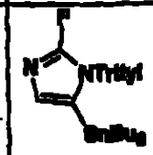
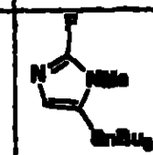
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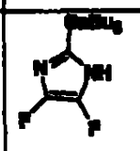
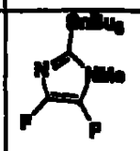
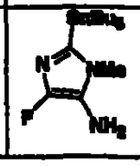
		
		
		
		
		
		
		
		
		

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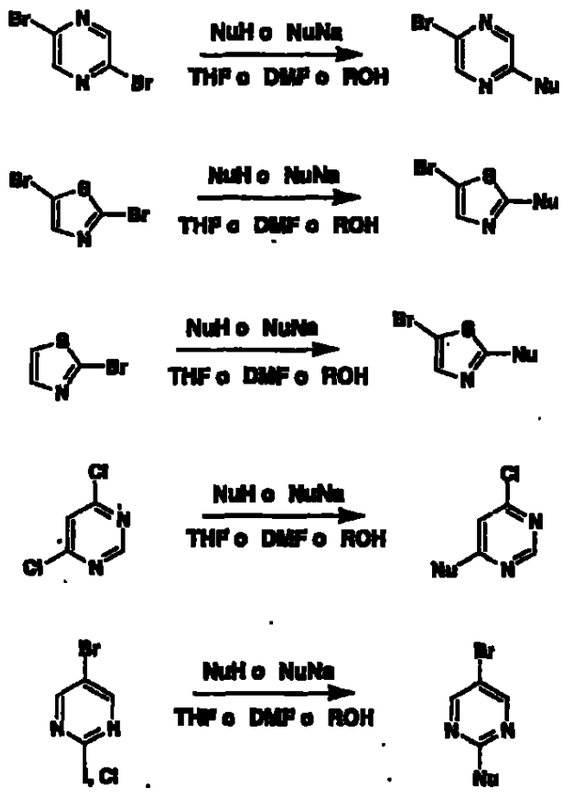
		
		
		
		
		Metalación de 1-tritil-4-yodo imidazol (preparado en Takahashi, Kazuyuki; Kirk, Kenneth L.; Cohen, Louis A. Lab. Chem., Natl. Inst. Arthritis Diabetes Dig. Kidney Dis., Bethesda, MD, USA. J. Labelled Compd. Radiopharm. (1986), 23(1), 1-8) usando tBuli en THF a -78 y se apago con Bu_3SnCl. Destritilado con TFA o HCL aq después de acoplar al núcleo de azaindol.
		Metalación de 1-metil-4-yodo imidazol (preparado en Takahashi, Kazuyuki; Kirk, Kenneth L.; Cohen, Louis A. Lab. Chem., Natl. Inst. Arthritis Diabetes Dig. Kidney Dis., Bethesda,

		MD, USA. J. Labelled Compd. Radiopharm. (1986), 23(1), 1-8) usando tBuLi en THF a -78 y se apagó con Bu_3SnCl. El Borai, M.; Moustafa, A. H.; Anwar, M.; Abdel Hay, F. I. El derivado de bromo es descrito en Pol. J. Chem. (1981), 55(7-8), 1659-65 y se puede usar para generar el reactivo de estaño por medio de transmetalación.
		
		4,5-difluoroimidazol preparado como en Dolensky, Bohumil;et.al, USA. J. Fluorine Chem. (2001), 107(1), 147-148.
		Dolensky, Bohumil;et.al, USA. J. Fluorine Chem. (2001), 107(1), 147-148.
		

Procedimientos generales seleccionados, por medio de reacciones S_NAr, para la preparación de materiales de partida para agentes de estaño.

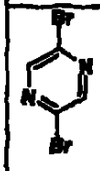
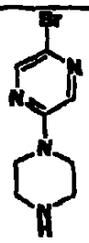
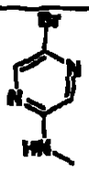
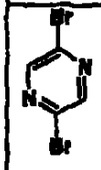
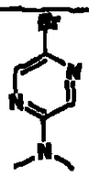
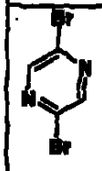
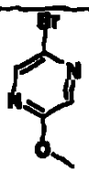
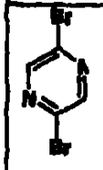
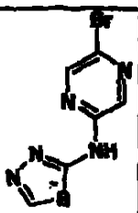
a. Preparación de 2-bromo-5-substituido-pirazina, 5-bromo-2-substituido-tiazol, 2-substituido-tiazaol, 4-cloro-6-

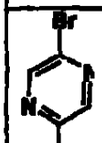
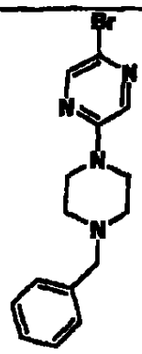
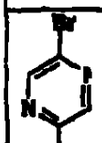
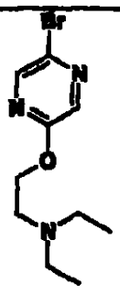
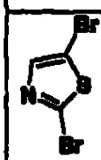
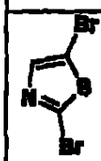
substituido-pirimidina y 5-bromo-2-substituido-pirimidina



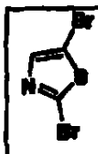
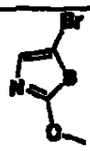
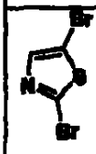
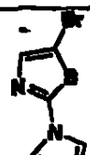
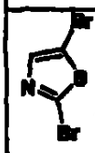
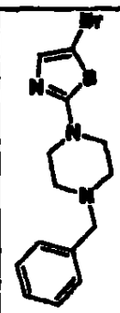
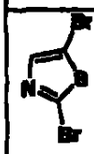
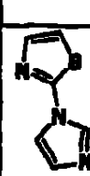
En un matraz se combinaron en un solvente tal como THF, DMF o alcohol, con o sin una adición de NaH, una pirazina, pirimidina o tiazol apropiados (1.0 equivalente) y un nucleófilo (Nu), tal como derivados de amina, alcohol o tio en un equivalente o una cantidad de exceso. La reacción se agitó ya sea a temperatura ambiente o bajo calentamiento durante uno a tres días. Después de que se retiraron todos los solventes, el residuo se dividió entre $NaHCO_3$ saturado y EtOAc. La capa acuosa se extrajo con acetato de etilo y los extractos combinados se concentraron in vacuo para dar un residuo, el cual se purificó por cromatografía en gel de

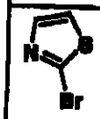
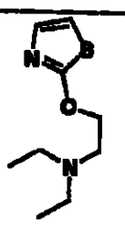
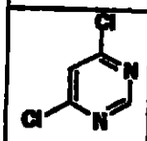
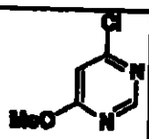
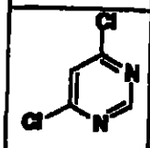
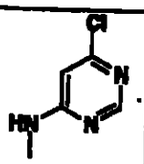
sílice para resultar el producto deseado.

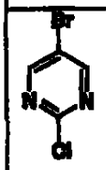
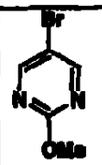
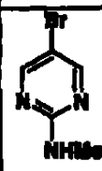
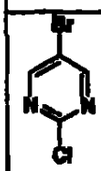
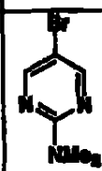
Material de Partida	Producto	Condición de Reacción	Rf (minutos)	EM (M+H)+ Calc.	EM (M+H)+ Obsv.
 SM-01		SM-01 (2g) Piperazina (10 g), THF (50 ml), t.a.	0.56 (columna G)	243.02	243.03
 SM-01		SM-01 (1 g), $MeNH_2$ (2M en THF, 100 ml), t.a.	0.89 (columna E)	187.93	187.98
 SM-01		SM-01 (1g), Me_2NH (2M en THF, 100 ml), t.a.	1.19 (columna E)	201.92	202.00
 SM-01		SM-01 (1 g), MeONa (0.5M en MeOH, 100 ml), t.a.	1.05 (columna E)	188.91	188.97
 SM-01		SM-01 (50 mg), NaH (17 mg), 2-amino-1,3,4-tiadiazol (25 mg),	1.21 (columna E)	257.94	257.89

		DMF 5 ml) t.a.			
 SM-01		SM-01 (50 mg), NaH (17 mg), N-bencilpiperazina (25 mg), DMF 5 ml) t.a.	1.04 (columna E)	333.07	332.99
 SM-01		SM-01 (50 mg), NaH (17 mg), N,N-dimetilamino-etanol (0.033 ml), DMF 5 ml) t.a.	0.72 (columna E)	274.06	273.97
 SM-02		SM-02 (2 g) Piperazina (10 g), THF (50 ml), t.a.	0.89 (columna E)	247.99	247.97
 SM-02		SM-05 (1 g), Me_2NH (2M en THF, 100 ml), t.a.	0.65 (columna E)	206.89	206.96

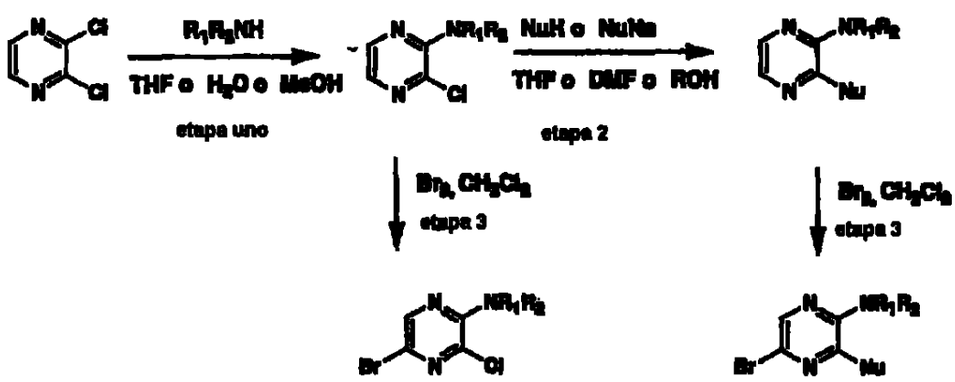
625

 SM-02		SM-02 (1 g), MeONa (0.5M in MeOH, 100 ml), t.a.	1.35 (column E)	193.93	193.84
 SM-02		SM-03 (50 mg), NaH (16 mg), Imidazol (77 mg), DMF 5 ml) t.a.	0.89 (columna E)	229.94	229.83
 SM-02		SM-02 (50 mg), NaH (16 mg), N-benclipiperazina (30 mg), DMF 5 ml) t.a.	1.02 (columna E)	338.03	337.98
 SM-02		SM-02 (50 mg), NaH (16 mg), N,N-dietilamino-etanol (0.033 ml), DMF 5 ml) t.a.	0.83 (columna E)	279.02	278.95
 SM-03		SM-09 (50 mg), NaH (25 mg),	0.31 (columna E)	151.91	152.03

		imidazol (25 mg), DMF 5 ml) t.a.			
 SM-03		SM-03 (50 mg), NaH (25 mg), N-benclipipe-razina (37 mg), DMF 5 ml) ta.	0.66 (columna E)	260.07	260.12
 SM-03		SM-03 (50 mg), NaH (25 mg), N,N-dimetilamino-etanol (0.05 ml), DMF 5 ml) t.a.	0.46 (columna E)	201.11	201.02
 SM-04		SM-04 (1g), MeONa (0.5M en MeOH, 13.52 ml), t.a.	0.86 (columna E)	145.02	144.99
 SM-04		SM-04 (1g), $MeNH_2$ (2M en THF,	0.46 (columna E)	144.03	143.96

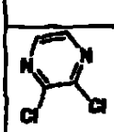
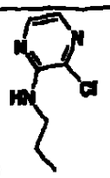
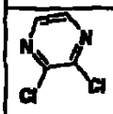
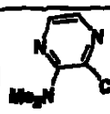
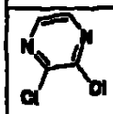
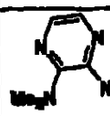
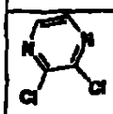
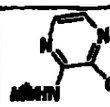
		100ml), t.a.			
 SM-05		SM-05 (1g), MeONa (0.5M en MeOH, 100ml), 1 día, t.a.	0.91 (columna E)	188.97	188.91
 SM-05		SM-05 (1g), $MeNH_2$ (2M en THF, 100 ml), t.a.	0.84 (columna E)	187.99	187.94
 SM-05		SM-05 (1g), Me_2NH (2M en THF, 100 ml), t.a.	1.24 (columna E)	202.00	201.98

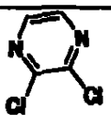
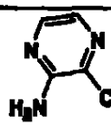
b. Preparación de 2-bromo-5,6-disubstituido-pirazina



Etapa uno

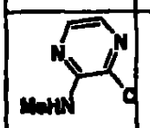
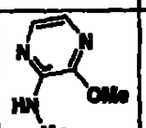
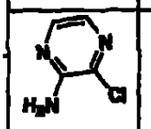
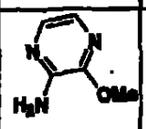
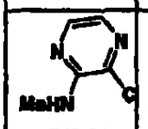
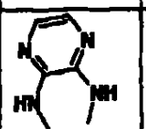
En un matraz, se combinaron en un solvente tal como agua o THF o sin solvente una pirazina (1.0 equivalente) y un nucleofilo apropiados, tales como amina o alcóxido de sodio en una cantidad de exceso. La reacción se agitó ya sea a temperatura ambiente o bajo calentamiento durante uno a tres días. Después de que se retiraron todos los solventes, se recolectó un residuo y se usó en las etapas adicionales sin ninguna purificación.

Material de partida	Producto	Condición de Reacción	Rt (minutos)	EM (M+H) + Calc.	EM (M+H)+ Obsv.
 SM-06		SM-06 (100 mg), propilamina (2 ml), t.a.	1.28 (Columna C)	172.06	172.09
 SM-06		SM-06 (100 mg), Me_2NH (2M en THF, 10 ml) o Me_2NH (40% en agua, 10 ml), t.a.	1.21 (Columna C)	158.05	158.07
 SM-06		SM-06 (100 mg), Me2NH (40% en agua, 10 ml), 100°C	0.49 (Columna C)	167.13	167.19
 SM-06		SM-06 (100 mg), $MeNH_2$ (2M en THF, 10 ml), t.a.	0.72 (Columna C)	144.03	144.07

 SM-06		SM-06 (100 mg), NH_4OH (10 ml), 100°C	0.41 (Columna C)	162.04 (M+MeOH+H)+	162.06 $(M+MeOH+H)^+$

Etapa dos

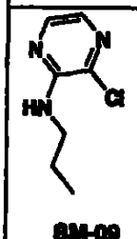
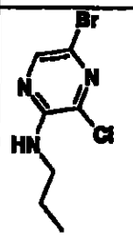
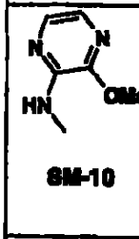
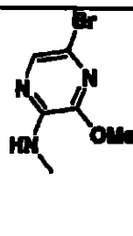
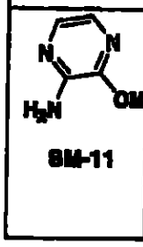
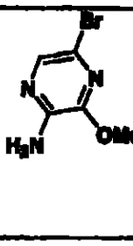
En un matraz, el derivado de pirazina crudo obtenido de la etapa uno (1.0 equivalente) y un nucleofilo, tal como amina o alcóxido de sodio en una cantidad de exceso se combinaron en un solvente tal como agua o THF o sin solvente. La reacción se agitó ya sea a temperatura ambiente o bajo calentamiento durante uno a tres días. Después de que se retiraron todos los solventes, se recolectó un residuo y se usó en las etapas adicionales sin ninguna purificación.

Material de Partida	Producto	Condición de Reacción	Rf (minutos)	EM (M+H)+ Calc.	EM (M+H)+ Obsv.
 SM-07		SM-07 (2 g), MeONa (12.5 %p, 100ml, 100°C	0.28 (columna C)	140.08	140.14
 SM-08		SM-08 (2 g), MeONa (12.5 %p, 20ml), 100°C	0.28 (columna C)	158.13	158.09
 SM-07		SM-07 (2 g), $MeNH_2$ (40% en agua, 100 ml), 110°C	0.34 (Columna C)	139.10	139.13

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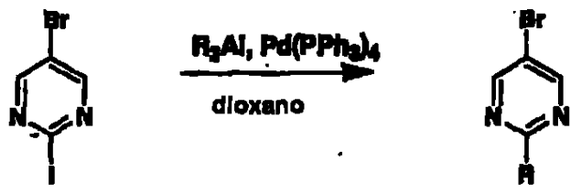
Etapa tres

En un matraz, el derivado de pirazina crudo obtenido de la etapa dos (1.0 equivalente) se disolvió en cloruro de metileno. Un exceso de bromuro se agregó ligeramente luego dentro de la solución mezclada. La reacción se agitó a temperatura ambiente durante diez horas. Después de que se retiraron todos los solventes, se recolectó un residuo y se purificó por cromatografía en gel de sílice para resultar el producto deseado.

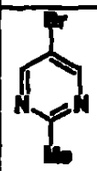
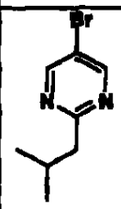
Material de Partida	Producto	Condición de Reacción	Rf (minutos)	EM (M+H)+ Calc.	EM (M+H)+ Obsv.
 SM-09		SM-09 (5 g), bromo (1.34 ml), CH_2Cl_2 (100 ml)	1.77 (columna C)	249.97	250.02
 SM-10		SM-10 (2 g), bromo (0.72 ml), CH_2Cl_2 (20 ml)	1.13 (columna C)	217.99	217.98
 SM-11		SM-11 (2 g), bromo (0.72 ml), CH_2Cl_2 (20 ml)	0.98 (columna C)	203.98	203.99

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Procedimiento general de la preparación de 2-alquil-5-bromo-pirimida:

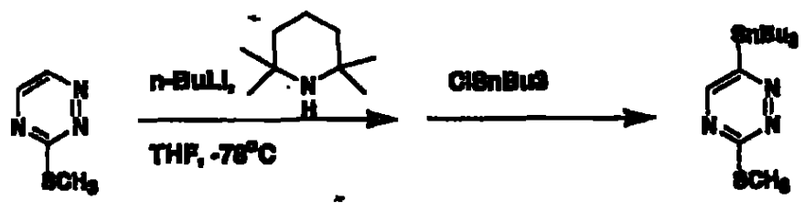


En un tubo sellado, 5-bromo-2-yodopirimidina (1.0 equivalente), tri-alquilaluminio (1.5 equivalente) y tetraquis-trifenilfosfino paladio, $Pd(Ph_3P)_4$ (1.0 mol%) se combinaron en dioxano (10 mL). La reacción se calentó a 110-120°C durante 10 h. Después la mezcla se enfrió bajo temperatura ambiente, esto se vació dentro de agua. La solución se extrajo con acetato de etilo y los extractos combinados se concentraron in vacuo para dar un residuo el cual se purificó por cromatografía en gel de sílice para resultar el producto 2-alquil-5-bromopirimidina deseado.

R3Al	Producto	Rf (minutos)	EM (M+H)+ Calc.	EM (M+H)+ Obsv.
Me_3Al		0.90 (columna E)	172.94	172.97
$(i\text{-}Bu)_3Al$		1.45 (columna E)	215.02	214.99

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Preparación de estanano de triazina por acoplamiento Stille para preparar ejemplos de la reivindicación 1. (el azufre luego pudo ser removido con níquel Raney para dar triazinas desulfuradas adicionales).

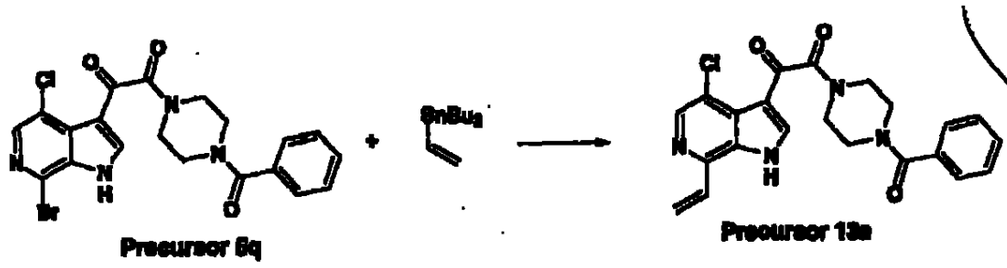


2,2,6,6-tetrametilpiperidina (2.0 mL, 11.81 mmol) en 30 ml de THF se enfrió a -78°C y se trató con n-butillitio (4.7 ml, 11.81 mmol, 2.5 M en hexano). Después de agitar 30 min a 0°C, la reacción se enfrió a -78°C nuevamente y 3-metiltio-1,2,4-triazina (1.0 g, 7.87 mmol) se agregó. La solución resultante se agitó a -78°C durante 30 min después se agregó cloruro de tributilestaño (2.1 ml, 7.87 mmol). La reacción se mantuvo a -78°C durante 1 hr, luego se apagó con agua. El solvente THF se removió en evaporador rotatorio y la solución restante se extrajo con acetato de etilo. La capa orgánica se secó sobre $MgSO_4$, se filtró y el filtrado se concentró. El residuo se procesó por cromatografía para resultar 96 mg de 3-metiltio-6-tributilestaño-1,2,4-triazina.

1H RMN (300 Hz, $CHCl_3$): 8.83 (s, 1H); 2.62 (s, 3H); 2.04-0.79 (m, 27H). CL/EM: (ES+) M/Z (M+H)+ = 418, TR = 2.29 min.

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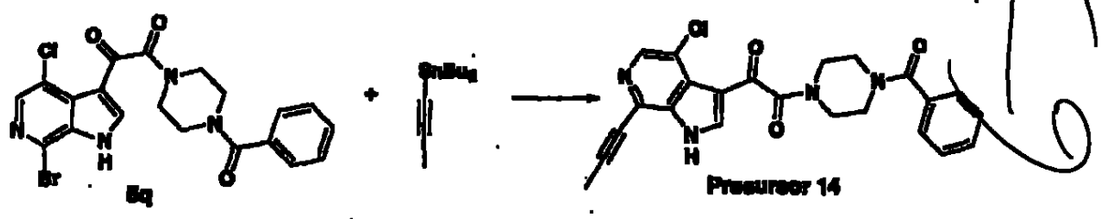
Precursor 13a



A una mezcla de **5q** (50 mg, 105 µmol) y $Pd(PPh_3)_4$ (25 mg, 21 µmol) se agregó 1,4-dioxano (1 ml) y tributilestanano de vinilo (50 mg, 158 µmol). La mezcla de reacción se calentó en un tubo sellado a 145°C durante 3 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se agregó MeOH (4 ml) y luego se filtró. El filtrado se purificó por CLAR de fase inversa preparativa para dar la sal TFA del **Precursor 13a** al usar el método: Inicio % B = 30, Final % B = 75, Tiempo de gradiente = 20 min, Relación de flujo = 25 ml/min, Columna: YMC C18 5um 20 x 100 mm, Fracción colectada: 7.92-8.58 min. **^{1}H RMN:** (CD_3OD) δ 8.61 (s, 1H), 8.37 (s, 1H), 7.47 (b s, 5H), 7.31 (dd, J = 17.3, 11.3, 1H), 6.50 (d, J = 17.3, 1H), 5.97 (d, J = 11.3, 1H), 3.97-3.38 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 423, 425; CLAR Tiempo de retención = 1.887.

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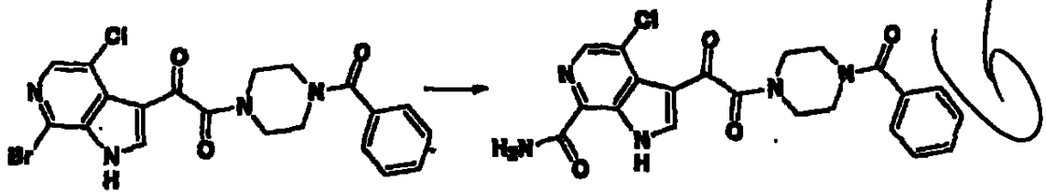
Precursor 14



A una mezcla del Precursor 5q (30 mg, 63 µmol) y $Pd(PPh_3)_4$ (20 mg, 17 µmol) se agregó 1,4-dioxano (1 ml) y 1-tributilestanil propino (40 mg, 122 µmol). La mezcla de reacción se calentó en un tubo sellado a 145°C durante 2 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se agregó MeOH (4 ml) y luego se filtró. El filtrado se purificó por CLAR de fase inversa preparativa para dar la sal TFA del **precursor 14** (1-(4-benzoil-piperazin-1-il)-2-(4-cloro-7-prop-1-inil-1H-pirrolo[2,3-c]piridin-3-il)-etan-1,2-diona) al usar el método: Inicio % B = 20, Final % B = 80, Tiempo de gradiente = 20 min, Relación de flujo = 25 ml/min, Columna: YMC C18 5um 20 x 100 mm, Fracción colectada: 8.74-9.00 min. **^{1}H RMN:** (CD_3OD) δ 8.47 (s, 1H), 8.27 (s, 1H), 7.46 (b s, 5H), 3.82-3.34 (b m, 8H), 2.26 (s, 3H); CL/EM: (ES+) m/z $(M+H)^+$ = 435, 437; CLAR (condiciones alternas B, columna G) T_r = 2.123.

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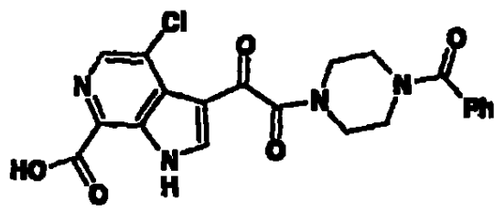
Precursor 15



A una solución del precursor 5q (50 mg, 0.11 mmol) en DMF (1 ml) se agregó CuCN (30 mg, 0.335 mmol). La mezcla de reacción se calentó a 170°C durante 30 min. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluyó con MeOH (15 ml), se filtró bajo gravedad, y el filtrado se evaporó in vacuo para resultar un residuo tono café. Al residuo en EtOH (3 ml) a temperatura ambiente se burbujeó gas de cloruro de hidrogeno durante 10 minutos para dar una solución amarilla, la cual se purificó por CLAR de fase inversa preparativa al usar el método: Inicio % B = 15, Final % B = 85, Tiempo de gradiente = 15 min, Relación de flujo = 40 ml/min, Columna: XTERRA C18 5 um 30 x 100 mm, Fracción colectada: 10.40-10.85 min; **^{1}H RMN**: (CD_3OD) 8.35 (s, 1H), 8.33 (s, 1H), 7.42 (b s, 5H), 3.95-3.41 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 440, 442; CLAR (condiciones alternas B, column G) T_r = 1.820.

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Precursor 16



Preparación del **precursor 16**:

A una suspensión del **precursor 15** (6 mg, 13 µmol) en una mezcla de AcOH (0.5 ml) y Ac_2O (1.0 ml) a 0°C se cargó con nitrato de sodio (17 mg, 246 µmol). La mezcla de reacción se agitó a 0°C durante 30 min. y luego a temperatura ambiente durante 1 hora. Después de la adición de MeOH (4 ml), la mezcla de reacción se purificó por CLAR de fase inversa preparativa para dar el solvato TFA del compuesto del título al usar el método: Inicio % B = 15, Final % B = 80, Tiempo de gradiente = 15 min, Relación de flujo = 25 ml/min, Columna: YMC C 18 5um 20 x 100 mm, Fracción colectada: 9.48-10.03 min. ^{1}H **RMN**: (DMSO-d_6) δ 12.76 (s, 1H), 8.48 (s, 1H), 8.32 (d, J = 3.0, 1H), 7.44 (b s, 5H), 3.97-3.47 (b m, traslapado con pico de agua, 8H); **CL/EM**: (ES+) m/z $(M+H)^+$ = 441, 443; CLAR (condiciones alternas B, columna G) T_r = 1.530. Ref: Amida hidrólisis: Evans, D.A.; Carter, P.H.; Dinsmore, C.J.; Barrow, J.C.; Katz, J.L.; Kung, D.W. Tetrahedron Lett. 1997, 38, 4535 y referencias citadas en la presente.

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Precursores de Piperazina adicionales

N-(benzoil)-2-metilpiperazina, Precursor 17a, se preparó de acuerdo con el procedimiento descrito en Ref. 90(b). ^{1}H RMN (300 MHz, CD_3OD) δ 7.47 (m, 5H), 3.30-2.70 (m, 7H), 1.36 (d, 3H, J = 6.90 Hz); ^{13}C RMN (75 MHz, CD_3OD) δ 171.0, 135.4, 129.7, 128.5, 126.3, ~48.5, 44.3, 14.5; [2]HRMS m/z: $(M+H)^+$ calculado para $C_{12}H_{17}N_2O$ 205.1341, encontrado 205.1341.

(R)-N-(benzoil)-2-metilpiperazina, Precursor 17b, se preparó de acuerdo con el procedimiento descrito en Ref. 90(b). ^{1}H RMN (300 MHz, CD_3OD) δ 7.41 (m, 5H), 3.31-2.70 (m, 7H), 1.35 (d, 3H, J = 6.90 Hz). EM m/z: $(M+H)^+$ Calculado para $C_{12}H_{17}N_2O$: 205.13; encontrado 205.16. Tiempo de retención CLAR: 0.51 minutos (columna L).

(S)-N-(benzoil)-2-metilpiperazina, Precursor 17c, se preparó de acuerdo con el procedimiento descrito en Ref. 90(b). ^{1}H RMN (300 MHz, CD_3OD) δ 7.41 (m, 5H), 3.31-2.72 (m, 7H), 1.35 (d, 3H, J = 6.90 Hz). EM m/z: $(M+H)^+$ Calculado para $C_{12}H_{17}N_2O$: 205.13; encontrado 205.16. Tiempo de retención CLAR: 0.50 minutos (columna L).

[2]Algunos picos de carbono se pierden debido al traslape de señales.

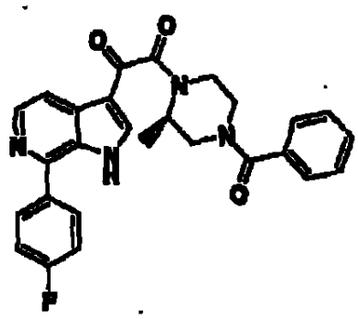
N-(benzoil)-2-etilpiperazina, Precursor 17d, se preparó de acuerdo con el procedimiento descrito en Ref. 90(b). ^{1}H RMN (300 MHz, CD_3OD) δ 7.49 (m, 5H), 3.34-2.80 (m, 7H), 2.10-1.70 (m, 2H), 0.85 (b, 3H); ^{13}C RMN (75 MHz, CD_3OD) δ 171.5,

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135.1, 129.8, 128.5, 126.5, 48.5, 46.0, 43.9, 21.8, 9.6; ^{2}HRMS m/z: $(M+H)^+$ calculado para $C_{13}H_{19}N_2O$ 219.1497, encontrado 219.1501.

Preparación de Compuestos de la Fórmula I

EJEMPLO 1



Procedimiento típico para el acoplamiento de azaindol con reactivo de boro aromático (Un ejemplo del procedimiento general descrito abajo para los ejemplos 2-14): Preparación de 1-benzoil-3-(R)-metil-4-[(7-(4-fluorofenil)-6-azaindol-3-il)-oxoacetil]-piperazina es un ejemplo de la Etapa E como se describió en el Esquema de reacción 15. A un tubo sellado, 1-(benzoil)-3-(R)-metil-4-[(7-cloro-6-azaindol-3-il)-oxoacetil]piperazina, Precursor 5a, (20 mg, 0.049 mmol), ácido 4-fluorofenilborónico, Precursor 14a-9, (8.2 mg, 0.059 mmol), $Pd(Ph_3P)_4$ (5 mg) y K_2CO_3 (20 mg, 0.14 mmol) se combinaron en 1.5 mL de DMF y 1.5 mL de agua. La reacción se calentó a 110-120°C durante 10 h. Después la mezcla se enfrió bajo temperatura ambiente, esto se vació dentro de 20 mL de

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agua. La solución se extrajo con EtOAc (4 x 20 mL). El extracto combinado se concentró para dar un residuo el cual se purificó al usar un sistema CLAR preparativo automatizado Shimadzu para dar compuesto 1-benzoil-3-(R)-metil-4-[(7-(4-fluorofenil)-6-azaindol-3-il)-oxoacetil]piperazina (1.8 mg, 7.9%). EM m/z: $(M+H)^+$ calculado para $C_{27}H_{24}FN_4O_3$: 471.18; encontrado 471.08. Tiempo de retención CLAR: 1.12 minutos (columna A).

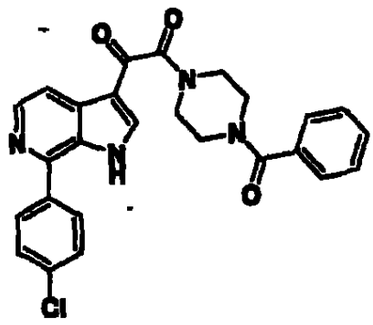
EJEMPLOS 2-14

Los Ejemplos 2-14 se prepararon de conformidad con el siguiente método general en una forma análoga a la preparación del Ejemplo 1.

Procedimiento típico para el acoplamiento de azaindol con reactivo de boro aromático: A un tubo sellado, un precursor de azaindol substituido apropiadamente (0.049 mmol), un derivado de ácido borónico apropiado (0.059 mmol), $Pd(Ph_3P)_4$ (5 mg) y K_2CO_3 (20 mg, 0.14 mmol) se combinaron en 1.5 mL de DMF y 1.5 mL de agua. La reacción se calentó a 110-120°C durante 10 h. Después la mezcla se enfrió bajo temperatura ambiente, esto se vació dentro de 20 mL de agua. La solución se extrajo con EtOAc (4 x 20 mL). El extracto combinado se concentró in vacuo para dar un residuo el cual se purificó usando un sistema CLAR preparativo automatizado Shimadzu para suministrar el compuesto deseado.

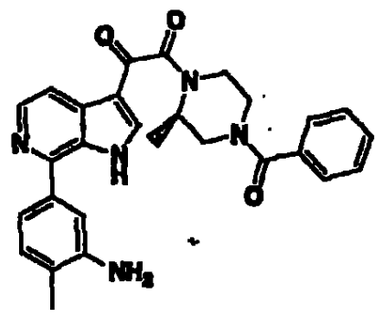
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EJEMPLO 2



El Ejemplo 2, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y ácido 4-clorofenilo borónico, Precursor 14a-10, para suministrar 1-benzoil-4-[(7-(4-clorofenil)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{24}FN_4O_3$: 473.14; encontrado 473.13. Tiempo de retención CLAR: 1.43 minutos (columna B).

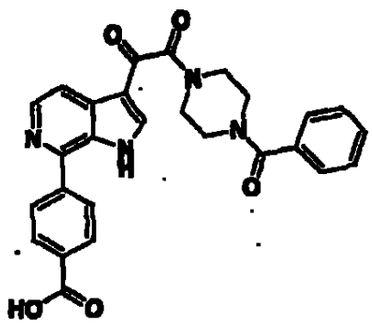
EJEMPLO 3



El Ejemplo 3, se preparó de acuerdo con el método general antes descrito partiendo del Precursor 5a y ácido 3-amino-4-metilfenilo borónico, Precursor 14a-11, para

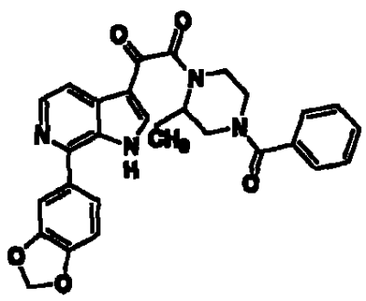
suministrar 1-benzoil-3-●-metil-4-[(7-(3-amino-4-metilfenil)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{24}ClN_4O_3$: 482.22; encontrado 482.25. Tiempo de retención CLAR: 1.35 minutos (columna B).

EJEMPLO 4



El Ejemplo 4, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y ácido 4-hidroxicarbonilfenilo borónico, Precursor 14a-12, para suministrar 1-benzoil-4-[(7-(4-carboxi-fenil)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{24}ClN_4O_3$: 483.17; encontrado 483.10. Tiempo de retención CLAR: 1.00 minutos (columna A).

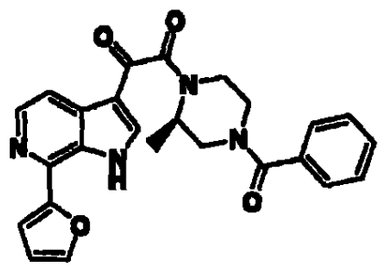
EJEMPLO 5



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El Ejemplo 5, se preparó de acuerdo con el método general antes descrito de la 1-benzoil-3-metil-4-[(7-cloro-6-azaindol-3-il)-oxoacetil]piperazina y ácido 3,4-metilendioxifenilo borónico, Precursor 14a-13, para suministrar 1-benzoil-3-metil-4-[(7-(3,4-metilendioxifenil)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{25}N_4O_5$: 497.18; encontrado 497.03. Tiempo de retención CLAR: 1.41 minutos (columna B).

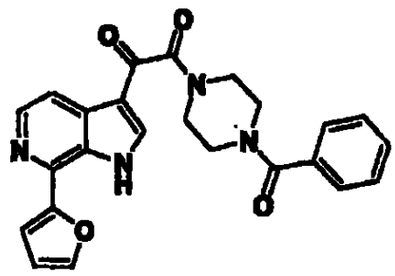
EJEMPLO 6



El Ejemplo 6, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y ácido furan-2-il borónico para suministrar 1-benzoil-3-®-metil-4-[(7-(furan-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_4$: 443.17; encontrado 443.12. Tiempo de retención CLAR: 1.20 minutos (columna A).

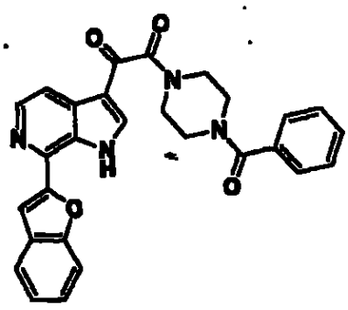
643

EJEMPLO 7



El Ejemplo 7, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y ácido furan-2-il borónico para suministrar 1-benzoil-4-[(7-(furan-2-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{21}N_4O_4$: 429.16; encontrado 428.98. Tiempo de retención CLAR: 1.36 minutos (columna A).

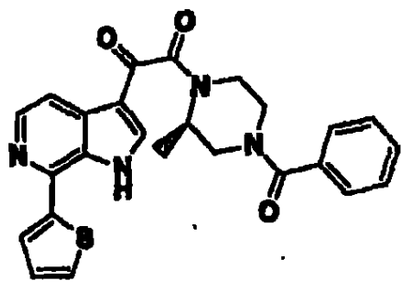
EJEMPLO 8



El Ejemplo 8, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y ácido benzofuran-2-il borónico para suministrar 1-benzoil-4-[(7-(benzofuran-2-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{23}N_4O_4$: 479.17; encontrado 479.09. Tiempo de retención CLAR: 1.67 minutos (columna B).

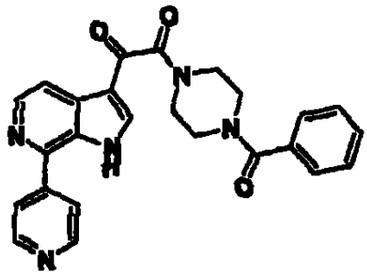
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EJEMPLO 9



El Ejemplo 9, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y ácido tien-2-il borónico para suministrar 1-(benzoil)-3-®-metil-4-[(7-(tien-2-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_3S$: 459.15; encontrado 459.10. Tiempo de retención CLAR: 1.20 minutos (columna A).

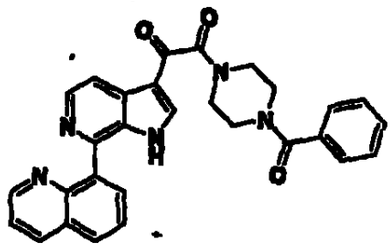
EJEMPLO 10



El Ejemplo 10, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y ácido piridin-4-il borónico para suministrar 1-(benzoil)-4-[(7-(piridin-4-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{22}N_5O_3$: 440.17; encontrado 440.10. Tiempo de retención CLAR: 0.97 minutos (columna A).

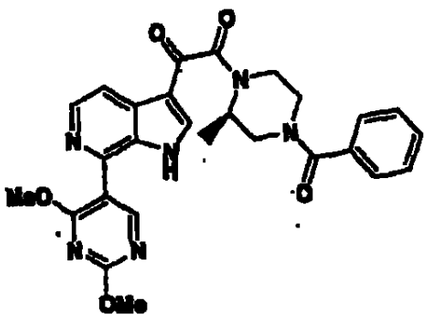
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EJEMPLO 11



El Ejemplo 11, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y ácido quinolin-8-il borónico, Precursor 14a-14, para suministrar 1-benzoil-4-[(7-(quinolin-8-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{22}N_5O_3$: 490.19; encontrado 490.09. Tiempo de retención CLAR: 1.34 minutos (columna B).

EJEMPLO 12

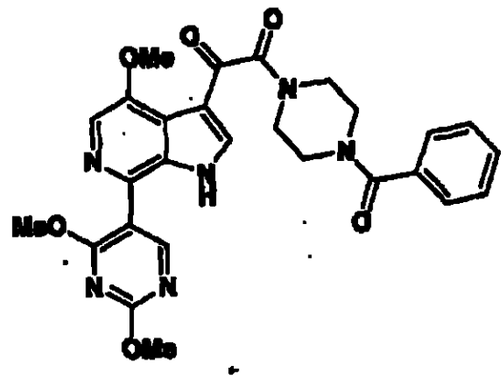


El Ejemplo 12, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y ácido 2,4-dimetoxipirimidin-5-il borónico, Precursor 14a-4, para suministrar 1-benzoil-3-®-metil-4-[(7-(2,4-dimetoxi-

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pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{27}N_6O_5$: 515.20; encontrado 515.28. Tiempo de retención CLAR: 1.17 minutos (columna B).

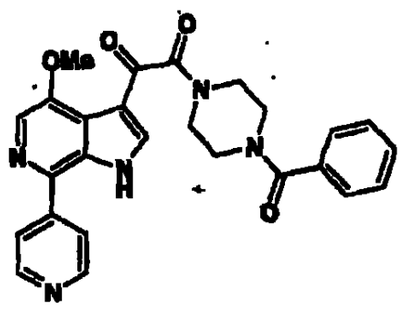
EJEMPLO 13



El Ejemplo 13, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y ácido 2,4-dimetoxipirimidin-5-il borónico, Precursor 14a-4, para suministrar 1-benzoil-4-[(4-metoxi-7-(2,4-dimetoxi-pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina ^1H RMN (500 MHz, CD_3OD) δ 8.71 (s, 1H), 8.64 (s, 1H), 8.21 (s, 1H), 7.48 (s, 5H), 4.15 (s, 3H), 4.13 (s, 3H), 3.84 (s, 3H), 3.64-3.34 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{35}N_6O_6$: 531.20; encontrado 531.26. Tiempo de retención CLAR: 1.09 minutos (columna A).

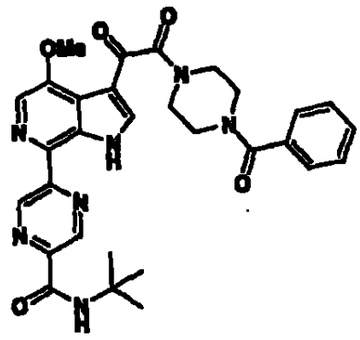
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EJEMPLO 14



El Ejemplo 14, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y ácido piridin-4-il borónico para suministrar 1-benzoil-4-[(4-metoxi-7-(piridin-4-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_5O_4$: 470.18; encontrado 470.32. Tiempo de retención CLAR: 1.02 minutos (columna A).

EJEMPLO 15



Procedimiento típico para el acoplamiento de azaindol con reactivo de estaño aromático (Un ejemplo del procedimiento general descrito abajo para los ejemplos 16-53):

La preparación del Ejemplo 15, 1-benzoil-4-[(4-metoxi-7-(2-(1,1-dimetiletilaminocarbonil)-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina es un ejemplo de la Etapa E como se describió en el Esquema de reacción 15: A un tubo sellado, 1-benzoil-4-[(7-cloro-4-metoxi-6-azaindol-3-il)-oxoacetil]piperazina, Precursor 5b, (20 mg), 2-(1,1-dimetiletilaminocarbonil)-5-tributilestanil-pirazina (1.2 equivalentes, 27 mg.) y $Pd(Ph_3P)_4$ (1 mg) se combinaron en 1.5 mL de dioxano. La reacción se calentó a 110-120°C durante 10 h. Después la mezcla se enfrió bajo temperatura ambiente, esto se vació dentro de 5 mL de agua. La solución se extrajo con EtOAc (4 x 5 mL). El extracto combinado se concentró in vacuo para dar un residuo el cual se purificó usando un sistema CLAR preparativo automatizado Shimadzu para dar el compuesto 1-benzoil-4-[(4-metoxi-7-(2-(1,1-dimetiletilaminocarbonil)-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina (1 mg); EM m/z: $(M+H)^+$ Calculado para $C_{30}H_{32}N_7O_5$: 570.25; encontrado 570.43. Tiempo de retención CLAR: 1.83 minutos (columna B).

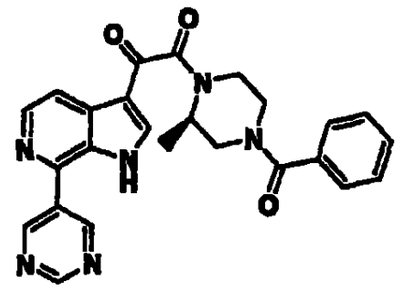
EJEMPLOS 16-54

Los Ejemplos 16-54 se prepararon de acuerdo al siguiente procedimiento general por un método análogo al método descrito por la preparación del Ejemplo 15.

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Procedimiento típico para el acoplamiento de azaindol con reactivo de estaño aromático: A un tubo sellado, un azaindol apropiado (0.049 mmol), un estanano apropiado (0.059 mmol) y $Pd(Ph_3P)_4$ (1 mg) se combinaron en 1.5 mL de dioxano. La reacción se calentó a 110-120°C durante 10 h. Después la mezcla se enfrió bajo temperatura ambiente, esto se vació dentro de 5 mL de agua. La solución se extrajo con EtOAc (4 x 5 mL). El extracto combinado se concentró para dar un residuo el cual se purificó usando un sistema CLAR preparativo automatizado Shimadzu para suministrar el compuesto deseado.

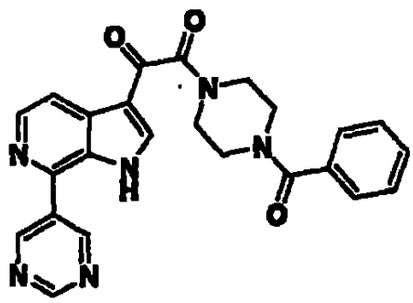
EJEMPLO 16



El Ejemplo 16, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y tributilestaño pirimidin-5-il, Precursor 14-9, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_3$: 455.18; encontrado 455.17. Tiempo de retención CLAR: 1.33 minutos (columna B).

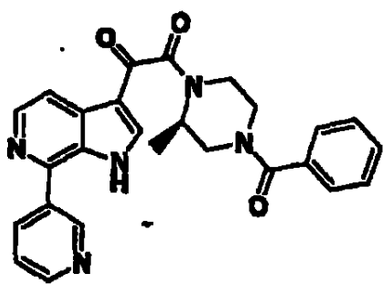
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EJEMPLO 17



EL Ejemplo 17, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y tributilestaño pirimidin-5-il, Precursor 14-9, para suministrar 1-benzoil-4-[(7-(pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ calculado para $C_{25}H_{23}N_6O_3$: 441.17; encontrado 441.07. Tiempo de retención CLAR: 1.30 minutos (columna B).

EJEMPLO 18

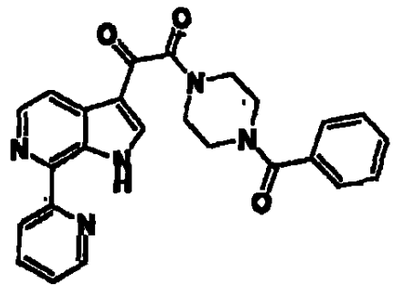


El Ejemplo 18, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y tributilestaño piridin-3-il, Precursor 14a-2, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(piridin-3-il)-6-

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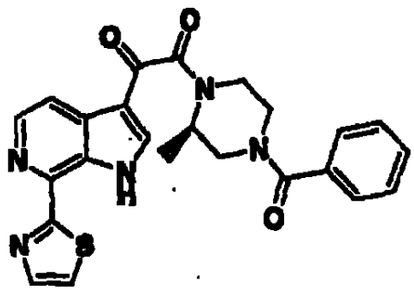
azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_5O_3$: 454.19; encontrado 454.17. Tiempo de retención CLAR: 1.11 minutos (columna A).

EJEMPLO 19



El Ejemplo 19, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y tributilestaño piridin-2-il, Precursor 14a-19, para suministrar 1-benzoil-4-[(7-(piridin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{22}N_5O_3$: 440.17; encontrado 440.07. Tiempo de retención CLAR: 1.40 minutos (columna B).

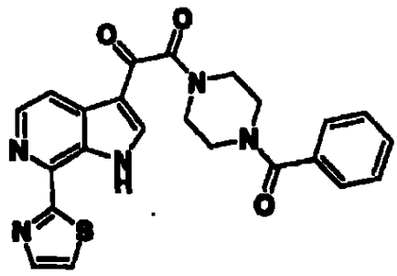
EJEMPLO 20



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El Ejemplo 20, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y tributilestaño tiazol-2-il, Precursor 14a-21, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(tiazol-2-il)-6-azaindol-3-il)oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_5O_3S$: 460.14; encontrado 460.15. Tiempo de retención CLAR: 1.48 minutos (columna B).

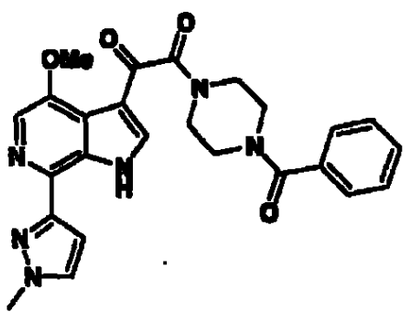
EJEMPLO 21



El Ejemplo 21, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y tributilestaño tiazol-2-il, Precursor 14a-21, para suministrar 1-benzoil-4-[(7-(tiazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{20}N_5O_3S$: 446.13; encontrado 446.03. Tiempo de retención CLAR: 1.44 minutos (columna B).

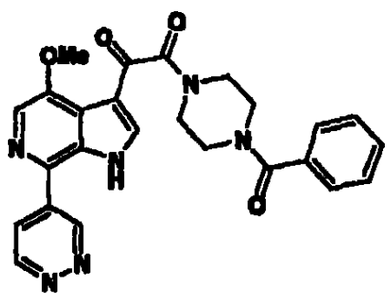
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EJEMPLO 22



El Ejemplo 22, se prepàró de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño 1-metilpirazol-3-il, para suministrar 1-benzoil-4-[(4-metoxi-7-(1-metil-pirazol-3-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{25}N_6O_4$: 473.19; encontrado 473.28. Tiempo de retención CLAR: 1.18 minutos (columna B).

EJEMPLO 23

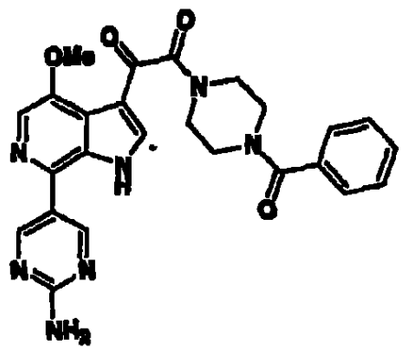


El Ejemplo 23, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y el Intermediario 14-9 para suministrar 1-benzoil-4-[(4-metoxi-7-

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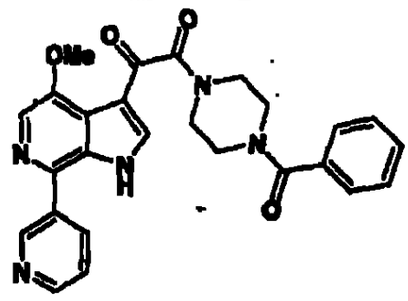
(piridazin-4-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4$: 471.18; encontrado 471.26. Tiempo de retención CLAR: 1.20 minutos (columna B).

EJEMPLO 24



El Ejemplo 24, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño 2-aminopirimidin-5-il, para suministrar 1-benzoil-4-[(4-metoxi-7-(2-amino-pirimidin-5-il))-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_4$: 486.19: encontrado 486.24. Tiempo de retención CLAR: 1.19 minutos (columna A).

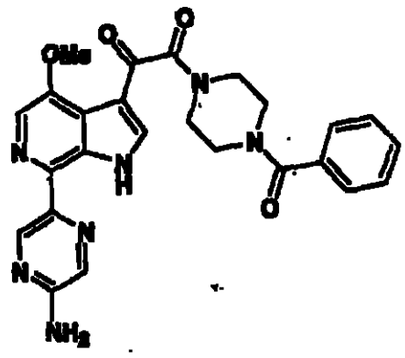
EJEMPLO 25



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El Ejemplo 25, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño piridin-3-il, Precursor 14a-2, para suministrar 1-benzoil-4-[(4-metoxi-7-(piridin-3-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_5O_4$: 470.18; encontrado 470.19. Tiempo de retención CLAR: 1.04 minutos (columna A).

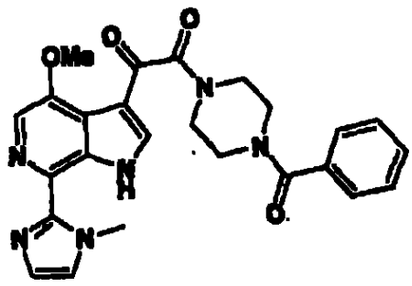
EJEMPLO 26



El Ejemplo 26, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y trimetilestaño 2-aminopirazin-5-il, Precursor 14-28, para suministrar 1-benzoil-4-[(4-metoxi-7-(2-amino-pirazin-5-il))-6-azaindol-3-il)-oxoacetillpiperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 470.19. Tiempo de retención CLAR: 1.13 minutos (columna B).

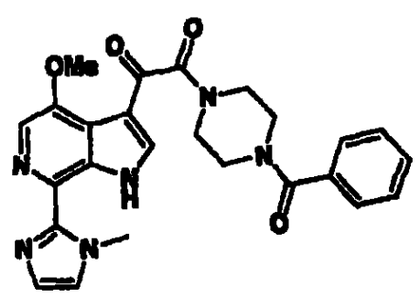
656

EJEMPLO 27



El Ejemplo 27, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y 1-metilimidazol-2-il trimetilestaño, Precursor 14-5, para suministrar 1-benzoil-4-[(4-metoxi-7-(1-metil-imidazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{25}H_{25}N_6O_4$: 473.18; encontrado 473.27. Tiempo de retención CLAR: 1.07 minutos (columna B).

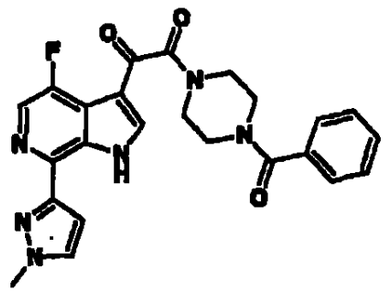
EJEMPLO 28



El Ejemplo 28, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño 1-metilpirrol-2-il, Precursor 14a-15, para suministrar 1-benzoil-4-[(4-metoxi-7-(1-metil-pirrol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado

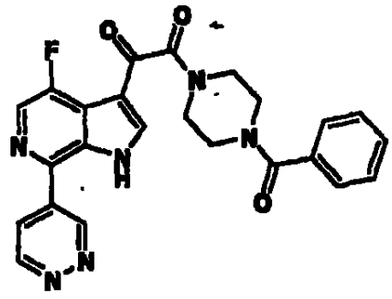
para $C_{26}H_{26}N_5O_4$: 472.20; encontrado 470.26. Tiempo de retención CLAR: 1.11 minutos (columna A).

EJEMPLO 29



El Ejemplo 29, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5i y tributilestaño 1-metilpirazol-3-il, para suministrar 1-benzoil-4-[(4-fluoro-7-(1-metil-pirazol-3-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}FN_6O_3$: 461.17; encontrado 461.24. Tiempo de retención CLAR: 1.36 minutos (columna A).

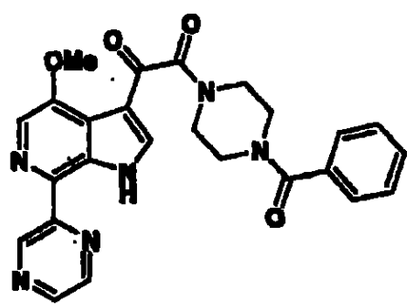
EJEMPLO 30



658

El Ejemplo 30, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5i y tributilestaño piridazin-4-il, Precursor 14-8, para suministrar 1-benzoil-4-[(4-fluoro-7-(piridazin-4-il)-6-azaindol-3-il)-oxoacetil]piperazina ^{1}H RMN (500 MHz, CD_3OD) δ 9.72 (s, 1H), 9.39 (s, 1H), 8.42 (m, 2H), 8.22 (s, 1H), 7.47 (s, 5H), 3.84-3.38 (m, 8H). EM m/z: $(M+H)^+$ calculado para $C_{24}H_{20}FN_6O_3$: 459.16; encontrado 459.25. Tiempo de retención CLAR: 1.26 minutos (columna A).

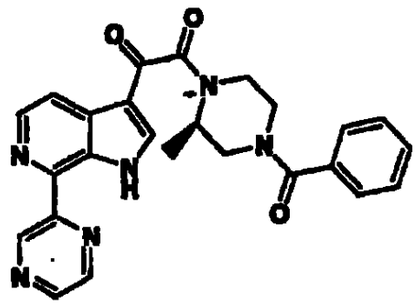
EJEMPLO 32



El Ejemplo 32, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño pirazin-2-il, Precursor 14a-1, para suministrar 1-benzoil-4-[(4-metoxi-7-(pirazin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_3$: 471.18; encontrado 471.17. Tiempo de retención CLAR: 1.35 minutos (columna A).

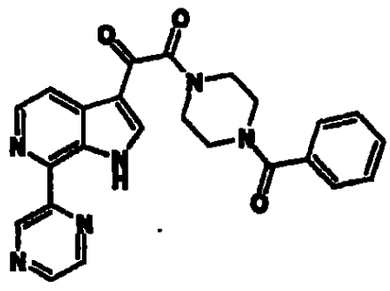
659

EJEMPLO 33



El Ejemplo 33, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y tributilestaño pirazin-2-il, Precursor 14a-1, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(pirazin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_3$: 455.18; encontrado 455.26. Tiempo de retención CLAR: 1.46 minutos (columna A).

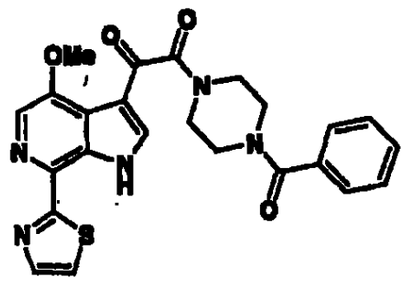
EJEMPLO 34



El Ejemplo 34, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5g y tributilestaño pirazin-2-il, Precursor 14a-1, para suministrar 1-benzoil-4-[(7-(pirazin-2-il)-6-azaindol-3-il)-

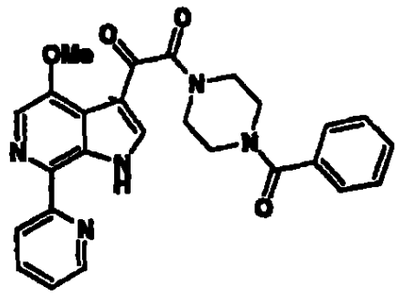
oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{21}N_6O_3$: 441.17; encontrado 441.22. Tiempo de retención CLAR: 1.22 minutos (columna A).

EJEMPLO 35



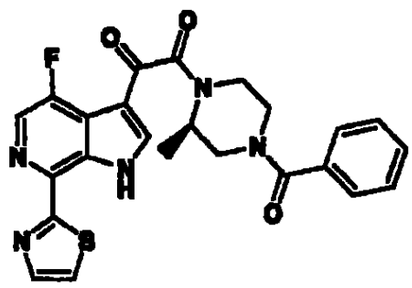
El Ejemplo 35, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño tiazol-2-il, Precursor 14a-21, para suministrar 1-(benzoil)-4-[(4-metoxi-7-(tiazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_5O_3S$: 476.14; encontrado 476.20. Tiempo de retención CLAR: 1.25 minutos (columna B).

EJEMPLO 36



El Ejemplo 36, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño piridin-2-il, Precursor 14a-19, para suministrar 1-benzoil-4-[(4-metoxi-7-(piridin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_5O_4$: 470.18; encontrado 470.17. Tiempo de retención CLAR: 1.04 minutos (columna A).

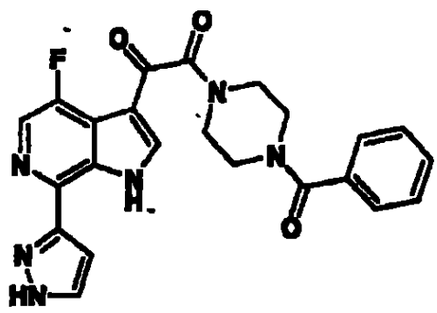
EJEMPLO 37



El Ejemplo 37, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5j y tributilestaño tiazol-2-il, Precursor 14a-21, para suministrar 1-benzoil-3-(R)-metil-4-[(4-fluoro-7-(tiazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{21}FN_5O_3S$: 478.13; encontrado 478.13. Tiempo de retención CLAR: 1.34 minutos (columna A).

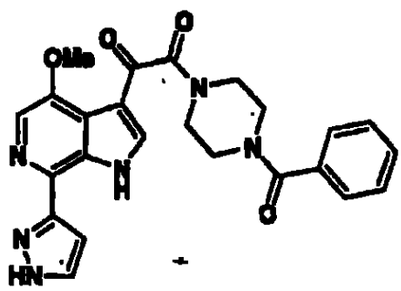
662

EJEMPLO 38



El Ejemplo 38, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5i y tributilestaño pirazol-3-il, para suministrar 1-benzoil-4-[(4-fluoro-7-(pirazol-3-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{20}FN_6O_3$: 447.16; encontrado 447.15. Tiempo de retención CLAR: 1.26 minutos (columna A).

EJEMPLO 39

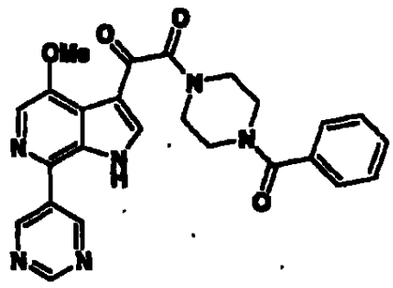


El Ejemplo 39, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño pirazol-3-il, para suministrar 1-benzoil-4-[(4-metoxi-7-(pirazol-3-il)-6-azaindol-3-il)-

663

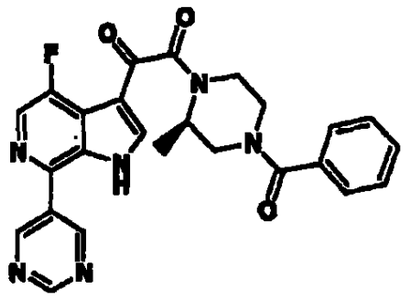
oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{23}N_6O_4$: 459.18; encontrado 459.21. Tiempo de retención CLAR: 1.11 minutos (columna A).

EJEMPLO 40



El Ejemplo 40, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño pirimidin-5-il, Precursor 14-9, para suministrar 1-benzoil-4-[(4-metoxi-7-(pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4$: 471.18; encontrado 471.20. Tiempo de retención CLAR: 1.61 minutos (columna A).

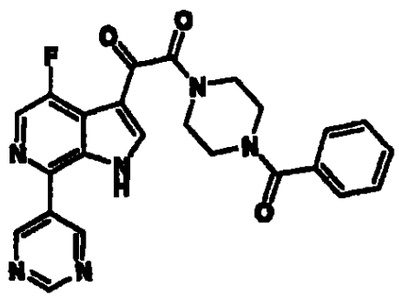
EJEMPLO 41



664

El Ejemplo 41, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5j y tributilestaño pirimidin-5-il, Precursor 14-9, para suministrar 1-benzoil-3-(R)-metil-4-[(4-fluoro-7-(pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina; ^{1}H RMN (500 MHz, CD_3OD) δ 9.26 (m, 3H), 8.39 (m, 2H), 7.56 (m, 5H), 4.72-3.12 (m, 7H), 1.40-0.91 (m, 3H). EM m/z: (M+H)+ Calculado para $C_{25}H_{22}FN_6O_3$: 473.17; encontrado 473.17. Tiempo de retención CLAR: 1.34 minutos (columna A).

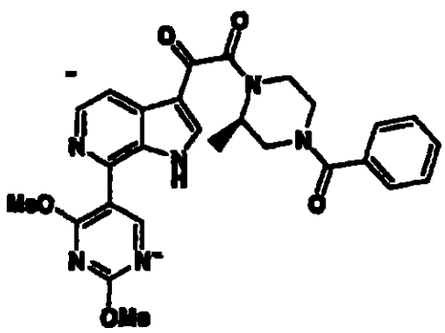
EJEMPLO 42



El Ejemplo 42, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5i y tributilestaño pirimidin-5-il, Precursor 14-9, para suministrar 1-benzoil-4-[(4-fluoro-7-(pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{20}FN_6O_3$: 459.16; encontrado 459.14. Tiempo de retención CLAR: 1.28 minutos (columna A).

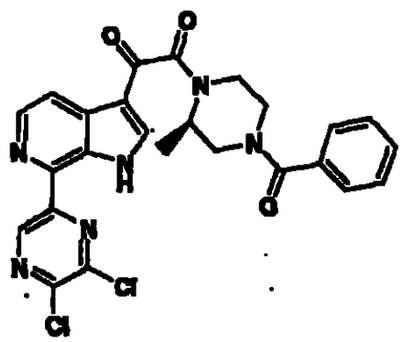
665

Ejemplo 43



El Ejemplo 43, (R)-1-(benzoil)-3-metil-4-[(7-(2,4-dimetoxi-pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{27}N_6O_5$: 515.20; encontrado 515.28. Tiempo de retención CLAR: 1.17 minutos (columna B).

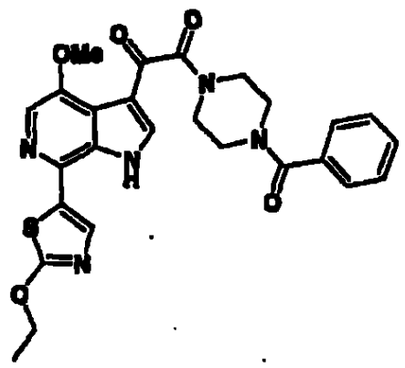
EJEMPLO 44



El Ejemplo 44, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5a y tributilestaño 2,3-dicloropirazin-5-il, Precursor 14-66, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(2,3-dicloro-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+Na)^+$

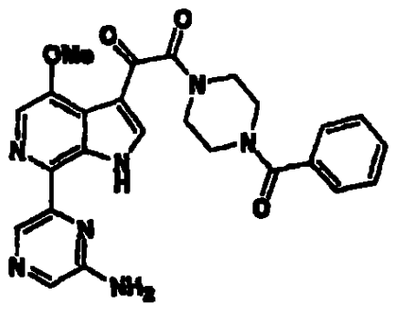
Calculado para $C_{25}H_{20}Cl_2NaN_6O_3$: 545.09; encontrado 545.29. Tiempo de retención CLAR: 1.87 minutos (columna B).

EJEMPLO 45



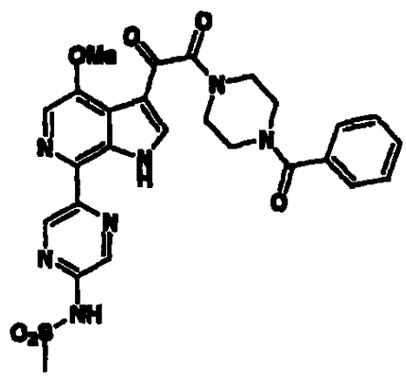
El Ejemplo 45, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño 2-etoxitiazol-5-il, Precursor 14-71, para suministrar 1-benzoil-4-[(4-metoxi-7-(2-etoxi-tiazol-5-il)-6-azaïndol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_5O_5S$: 520.17; encontrado 520.24. Tiempo de retención CLAR: 1.32 minutos (columna A).

EJEMPLO 46



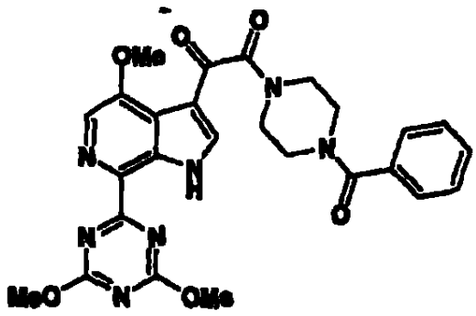
El Ejemplo 46, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y el estanano 2-amino-pirazin-6-il, Precursor 14-68, para suministrar 1-benzoil-4-[(4-metoxi-7-(2-amino-pirazin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 486.31. Tiempo de retención CLAR: 1.22 minutos (columna B).

EJEMPLO 47



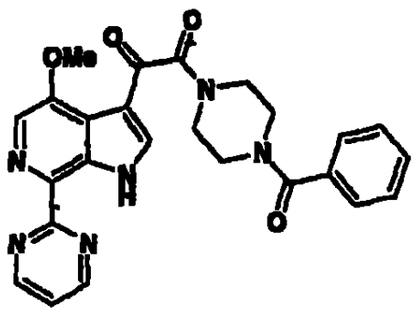
El Ejemplo 47, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y 2-metilsulfonilamino-5-(tri-N-butilestanil)pirazina, Precursor 14-69, para suministrar 1-benzoil-4-[(7-(2-metilsulfonilamino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_7O_6S$: 564.17; encontrado 564.21. Tiempo de retención CLAR: 1.24 minutos (columna A).

EJEMPLO 48



El Ejemplo 48, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño 2,4-dimetoxi-1,3,5-triazin-6-il, Precursor 14-70, para suministrar 1-benzoil-4-[(7-(2,4-dimetoxi-1,3,5-triazin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_7O_6$: 532.19; encontrado 532.12. Tiempo de retención CLAR: 1.28 minutos (columna A).

EJEMPLO 49

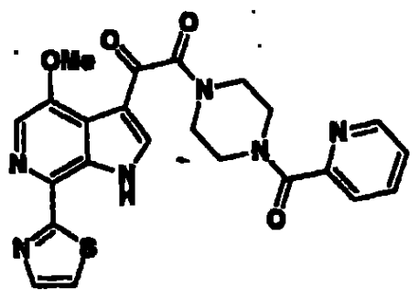


El Ejemplo 49, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5b y tributilestaño pirimidin-2-il, Precursor 14-67, para

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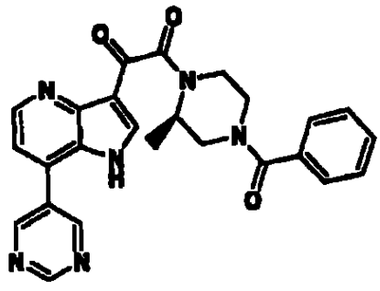
suministrar 1-benzoil-4-[(4-metoxi-7-(pirimidin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4$: 471.18; encontrado 471.29. Tiempo de retención CLAR: 1.21 minutos (columna A).

EJEMPLO 50



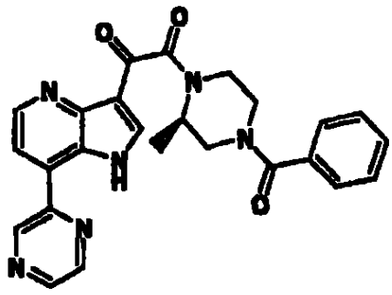
El Ejemplo 50, se preparó a partir de 1-(piridin-2-il)-4-[(4-metoxi-7-cloro-6-azaindol-3-il)-oxoacetil]piperazina y tributilestaño tiazol-2-il, Precursor 14a-21, de acuerdo con el método general antes descrito para suministrar 1-(piridin-2-il)-4-[(4-metoxi-7-(tiazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{25}N_6O_4S$: 477.13; encontrado 477.22. Tiempo de retención CLAR: 0.98 minutos (columna A).

EJEMPLO 51



El Ejemplo 51, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5d y tributilestaño pirimidin-5-il, Precursor 14-9, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(pirimidin-5-il)-4-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{25}H_{23}N_6O_3$: 455.18; encontrado 455.16. Tiempo de retención CLAR: 0.98 minutos (columna A).

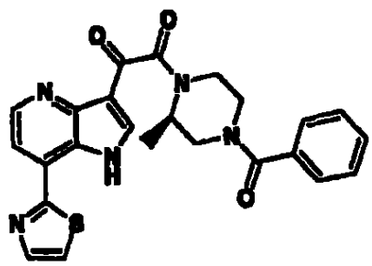
EJEMPLO 52



El Ejemplo 52, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5d y tributilestaño pirimidin-2-il, Precursor 14a-1, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(pirazin-2-il)-4-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_3$: 455.18; encontrado 455.16. Tiempo de retención CLAR: 1.09 minutos (columna A).

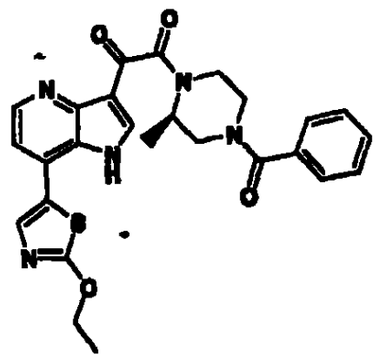
621

EJEMPLO 53



El Ejemplo 53, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5d y tributilestaño tiazol-2-il, Precursor 14a-21, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(tiazol-2-il)-4-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_5O_3S$: 460.14; encontrado 460.26. Tiempo de retención CLAR: 1.02 minutos (columna A).

EJEMPLO 54

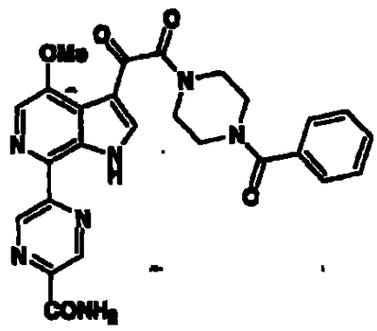


El Ejemplo 54, se preparó de acuerdo con el método general antes descrito partiendo del precursor 5d y tributilestaño 2-etoxitiazol-5-il, Precursor 14-71, para suministrar 1-benzoil-3-(R)-metil-4-[(7-(2-etoxi-tiazol-

672

5-il)-4-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_5O_4S$: 504.17; encontrado 4504.18. Tiempo de retención CLAR: 1.26 minutos (columna A).

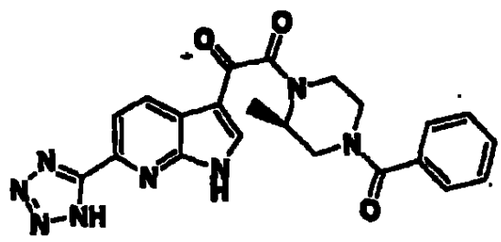
EJEMPLO 55



El compuesto del Ejemplo 15, 1-benzoil-4-[(4-metoxi-7-(2-(1,1-dimetiletilaminocarbonil)-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina (20 mg) se disolvió en 1 gota de ácido sulfúrico concentrado. Después de 30 minutos, la mezcla se diluyó con 2 mL de metanol. La solución resultante se inyectó dentro de un sistema CLAR preparativo automatizado Shimadzu y la purificación CLAR proporcionó el compuesto del Ejemplo 55, 1-benzoil-4-[(4-metoxi-7-(2-aminocarbonil-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina (1 mg); EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_7O_5$: 514.78; encontrado 514.22. Tiempo de retención CLAR: 1.44 minutos (columna B).

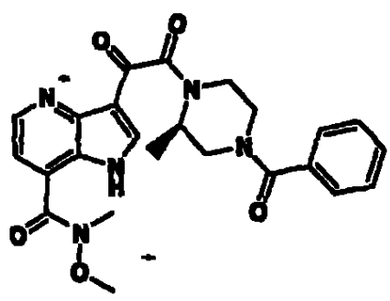
623

EJEMPLO 56



Un exceso de NH_4Cl (27 mg) se agregó dentro de una solución de 1-(benzoil)-3-(R)-metil-4-[(6-ciano-7-azaindol-3-il)-oxoacetil]piperazina (20 mg) y NaN_3 (16 mg) en DMF. La reacción se calentó hasta reflujo durante 12 h. Después del enfriamiento, la mezcla se concentró bajo presión reducida y el residuo se purificó usando Sistema de CLAR preparativa automático Shimadzu para dar 1-benzoil-3-(R)-metil-4-[(6-(tetrazol-1-il)-7-azaindol-3-il)-oxoacetil]piperazina (6.3 mg). EM m/z: $(M+H)^+$ Calculado para $C_{22}H_{21}N_8O_3$: 445.17; encontrado 3445.16. Tiempo de retención CLAR: 1.42 minutos (columna B); Columna B: PHX-LUNA C18 4.6 x 30 mm.

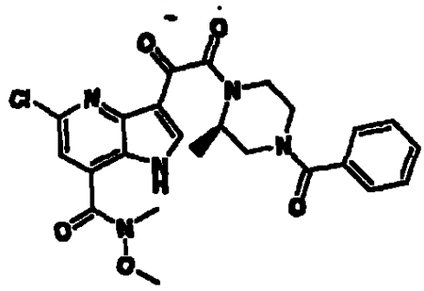
EJEMPLO 57



674

Preparación de 1-benzoil-3-(R)-metil-4-[(7-(metoximetilamino)carbonil)-4-azaindol-3-il)-oxoacetil]piperazina: Una mezcla del Precursor 13 (267 mg), cloruro de hidrógeno N,O-dimetilhidroxilamina (248 mg), tetrabromuro de carbono (844 mg), piridina (202 mg) y trifenilfosfino (668 mg) en diclorometano (10 mL) se agitó a temperatura ambiente durante 10 horas. Después el solvente se removió bajo vacío, el residuo se purificó el usar cromatografía en gel de sílice para resultar 1-(benzoil)-3-(R)-metil-4-[(7-(metoximetilamino)carbonil)-4-azaindol-3-il)-oxoacetil]piperazina (56 mg); EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{26}N_5O_5$: 464.19; encontrado 464.25. Tiempo de retención CLAR: 1.02 minutos (columna A).

EJEMPLO 58

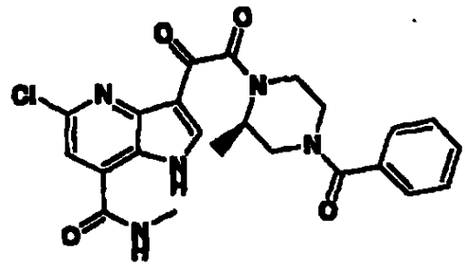


El Ejemplo 58 se preparó de acuerdo con el mismo procedimiento usado en la preparación del Ejemplo 57 con la excepción de que al usar el Precursor 11 como un material de partida en lugar del Precursor 13. El procedimiento proporcionó 1-benzoil-3-(R)-metil-4-[(5-cloro-(7-

(metoximetilamino)carbonil)-4-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{25}ClN_5O_5$: 498.15; encontrado 498.12. Tiempo de retención CLAR: 1.39 minutos (columna A).

Procedimiento general A para preparar CO-NR1R2 del COOH

EJEMPLO 59

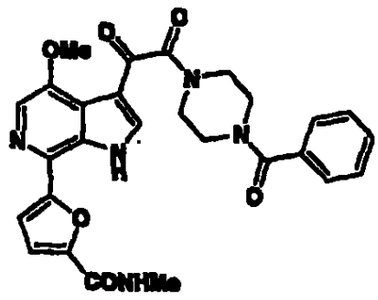


Preparación de 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(metilamino)carbonil)-4-azaindol-3-il)-oxoacetil]piperazina: Una mezcla del Precursor 11 (25 mg), metilamina (2M en THF, 0.08 mL), EDC (26 mg), HOBT (11.2 mg) y diisopropiletilamina (43 mg) en tetrahidrofurano (5 mL) se agitó a temperatura ambiente durante 10 horas. Después el solvente se removió bajo vacío, el residuo se purificó al usar cromatografía en gel de sílice para resultar 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(metilamino)carbonil)-4-azaindol-3-il)-oxoacetil]piperazina (13.6 mg); EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{23}ClN_5O_4$: 468.14; encontrado 468.03. Tiempo de retención CLAR: 1.33 minutos (columna A).

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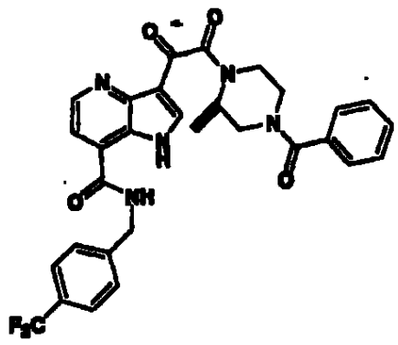
Este procedimiento general A se aplica para preparar los ejemplos 94 y 135:

EJEMPLO 94



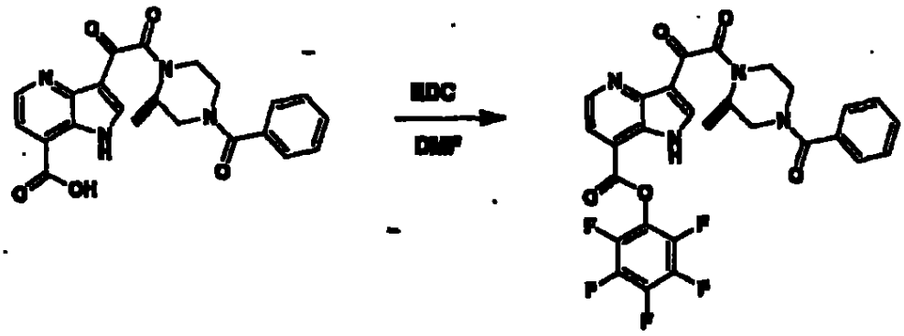
El Ejemplo 94, 1-benzoil-4-[(4-metoxi-7-(2-metilaminocarbonil-furan-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.37 (s, 1H), 8.06 (s, 1H), 7.48-7.26 (m, 7H), 4.08 (s, 3H), 3.83-3.44 (m, 8H), 2.96 (s, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{26}NSO_6$: 516.19; encontrado 516.14. Tiempo de retención CLAR: 1.35 minutos (columna A).

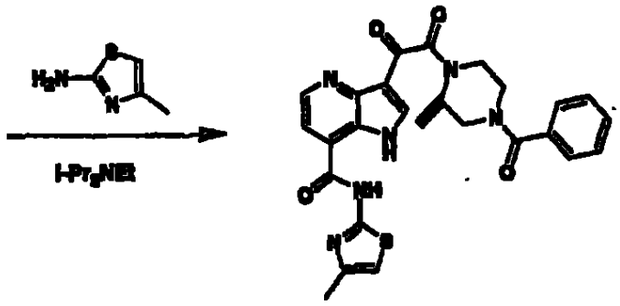
EJEMPLO 135



El Ejemplo 135, (R)-1-benzoil-3-metil-4-[(7-(4-trifluorometilbencilamino)carbonil-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{30}H_{27}F_3N_5O_4$: 578.20; encontrado 578.39. Tiempo de retención CLAR: 1.47 minutos (columna G).

Procedimiento general B para preparar CO-NR1R2 del COOH





Preparación del Ejemplo 136, (R)-1-benzoil-3-metil-4-[(7-(4-metiltiazol-2-il)aminocarbonil-4-azaindol-3-il)-oxoacetil]piperazina:

A una solución del (R)-1-benzoil-3-metil-4-[(7-hidroxilcarbonil-4-azaindol-3-il)-oxoacetil]piperazina (146 mg) en DMF (5 ml) a temperatura ambiente se agregó

678

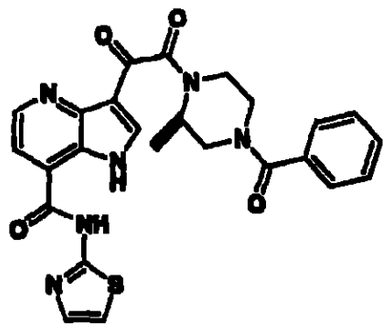
pentafluorofenilo (70.3 mg) seguido por EDC (73.23 mg). La mezcla de reacción se agitó a temperatura ambiente durante 8 horas. El producto crudo se diluyó con cloruro de metileno y se lavó con agua, HCl 0.1 N y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y concentró. El éster de pentafluorofenilo se usó en la siguiente reacción sin purificación adicional.

A una solución agitada de 4-metil-2-amino-tiazol (39.6 mg) y base Hunig (49.4 mg) en DMF (5 ml) a temperatura ambiente se agregó una solución de éster de pentafluorofenilo (1/3 del producto obtenido en la etapa previa descrito arriba) en DMF (2 ml). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. El producto crudo se diluyó con cloruro de metileno y se lavó con Na_2CO_3 (saturado) y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y concentró. El residuo se purificó usando sistema de CLAR preparativa automático Shimadzu para dar (R)-1-benzoil-3-metil-4-[(7-(4-metiltiazol-2-il)aminocarbonil-4-azaindol-3-il)-oxoacetil]piperazina (3.6 mg). EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_6O_4S$: 517.17; encontrado 517.41. Tiempo de retención CLAR: 1.25 minutos (columna A).

Este procedimiento general B se aplica para preparar el ejemplo 137:

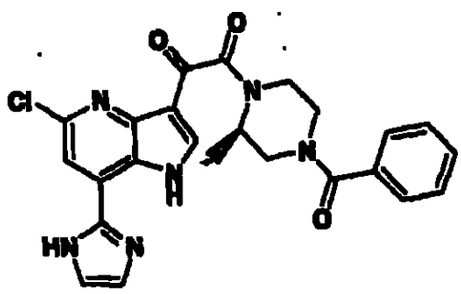
639

EJEMPLO 137



El Ejemplo 137, (R)-1-benzoil-3-metil-4-[(7-(tiazol-2-il)aminocarbonil-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4S$: 503.15; encontrado 503.29. Tiempo de retención CLAR: 1.33 minutos (columna A).

EJEMPLO 60

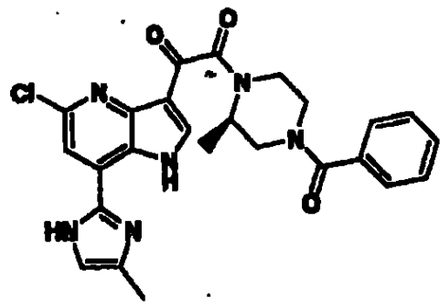


Preparación de 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(imidazol-2-il)-4-azaindol-3-il)-oxoacetil]piperazina: Una mezcla del Precursor 10 (34 mg), glioxal (40% en agua, 0.2 mL) y acetato de amoniaco (139 mg) en metanol se calentó a reflujo durante 10 horas. Después del enfriamiento, la mezcla se concentró bajo presión reducida y el residuo se purificó usando sistema de CLAR preparativa automático Shimadzu para

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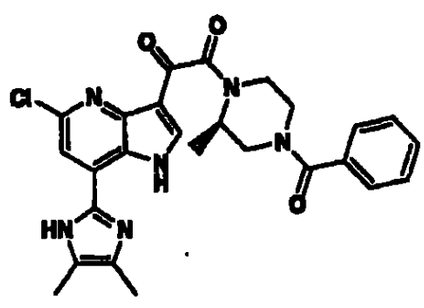
suministrar 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(imidazol-2-il)-4-azaindol-3-il)-oxoacetil]piperazina (1.8 mg); EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}ClN_6O_3$: 477.14; encontrado 477.13. Tiempo de retención CLAR: 1.17 minutos (columna A).

EJEMPLO 61



El Ejemplo 61 se preparó de acuerdo con el mismo procedimiento usado para la preparación del Ejemplo 60 con la excepción de que al usar metilglioxal como un material de partida en lugar de glioxal para suministrar 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(4-metil-imidazol-2-il)-4-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}ClN_6O_3$: 491.16; encontrado 491.13. Tiemp de retención CLAR: 1.26 minutos (columna A).

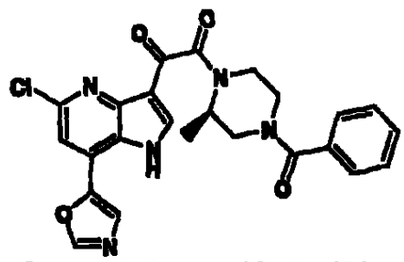
EJEMPLO 62



681

El Ejemplo 62 se preparó de acuerdo con el mismo procedimiento usado para la preparación del Ejemplo 60 con la excepción de que al usar dimetilglioxal como un material de partida en lugar de glioxal para suministrar 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(4,5-dimetil-imidazol-2-il)-4-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}ClN_6O_3$: 505.18; encontrado 505.10. Tiempo de retención CLAR: 1.24 minutos (columna A).

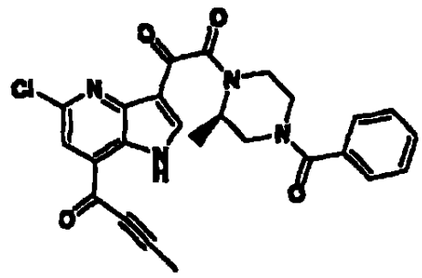
EJEMPLO 63



Preparación de 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(oxazol-5-il)-4-azaindol-3-il)-oxoacetil]piperazina: Una mezcla del Precursor 10 (27.5 mg), tosilmetil isocianuro (12.3 mg) y K_2CO_3 (8.7 mg) en MeOH se calentó a reflujo durante 10 horas. Después del enfriamiento, la mezcla se concentró bajo presión reducida y el residuo se purificó usando sistema de CLAR preparativa automático Shimadzu para suministrar 1-(benzoil)-3-(R)-metil-4-[(5-cloro-7-(oxazol-5-il)-4-azaindol-3-il)-oxoacetil]piperazina (17.7 mg); EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{21}ClN_5O_4$: 478.13; encontrado 478.03. Tiempo de retención CLAR: 1.48 minutos (columna A).

682

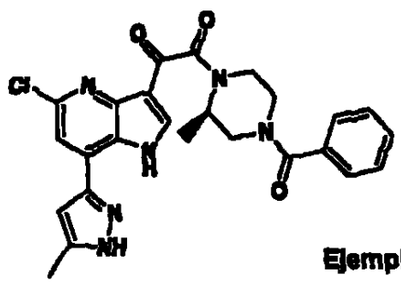
EJEMPLO 64



I-64

Etapa 1: Preparación de I-64, 1-benzoil-3-(R)-metil-4-[(7-(2-propinil)carbonil-4-azaindol-3-il)-oxoacetil]piperazina: Propinillitio (21 mg) se agregó a una solución del Ejemplo 52 (41 mg) en tetrahidrofurano (5 ml) a -78°C. La reacción se apagó con metanol a -25°C en 2 horas. Después de que los solventes se removieron bajo vacío, el residuo se llevó a las reacciones adicionales sin ninguna purificación. I-64, 1-benzoil-3-(R)-metil-4-[(7-(2-propinil)carbonil-4-azaindol-3-il)-oxoacetil]piperazina EM m/z: $(M+H)^+$ calculado para $C_{25}H_{22}ClN_4O_4$: 477.13; encontrado 477.17. Tiempo de retención CLAR: 1.46 minutos (columna A).

Etapa 2: Preparación del Ejemplo 64:



Ejemplo 64

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Preparación del Ejemplo 64, 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(3-metil-pirazol-5-il)-4-azaindol-3-il)-oxoacetil]piperazina: Una mezcla de I-64 (producto crudo de la Etapa 1) e hidrazina (0.22 mL) en EtOAc (2 mL) y agua (2 mL) se agitó a temperatura ambiente durante 24 horas. Luego los solventes se removieron bajo vacío, y el residuo se purificó usando sistema de CLAR preparativa automático Shimadzu para dar 1-benzoil-3-(R)-metil-4-[(5-cloro-7-(3-metil-pirazol-5-il)-4-azaindol-3-il)-oxoacetil]piperazina (9 mg); EM m/z: $(M+H)^+$ calculado para $C_{25}H_{24}ClN_6O_3$: 491.16; encontrado 491.19. Tiempo de retención CLAR: 1.42 minutos (columna A).

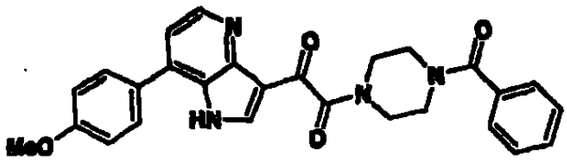
EJEMPLOS 65-67

El procedimiento para la preparación de los Ejemplos 65-67 es el mismo como el que se describió previamente para la preparación del Precursor 5a y es como sigue: 7-(4-metoxifenil)-4-azaindol-3-glioxilato de potasio, Precursor 4c (147 mg, 0.44 mmol), un derivado 1-benzoilpiperazina apropiado (0.44 mmol), 3-(dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona (DEPBT) (101 mg, 0.44 mol) y base Hunig (0.5 mL) se combinaron en 5 mL de DMF. La mezcla se agitó a temperatura ambiente durante 8 horas. Se removió DMF por medio de evaporación a presión reducida y el residuo se purificó usando un sistema CLAR preparativo automatizado

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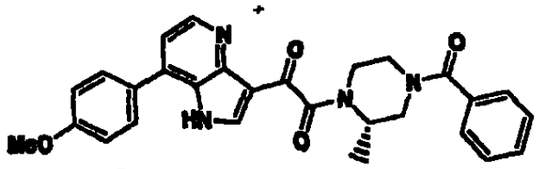
Shimadzu para dar la derivada 1-benzoil-4-[(7-(4-metoxifenil)-4-azaindol-3-il)-oxoacetil]-piperazina correspondiente.

EJEMPLO 65



El Ejemplo 19, 1-(benzoil)-4-[(7-(4-metoxi)-4-azaindol-3-il)-oxoacetil]piperazina se preparó a partir de 7-(4-metoxifenil)-4-azaindol-3-glioxilato de potasio y 1-(benzoil)piperazina según el procedimiento general anterior. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{25}N_4O_4$: 469.19; encontrado 469.16. Tiempo de retención CLAR: 1.26 minutos (columna A).

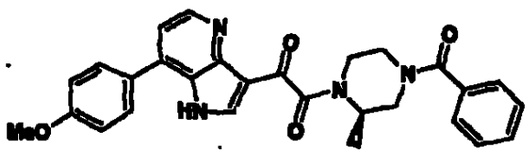
EJEMPLO 66



El Ejemplo 66, 1-benzoil-3-(S)-metil-4-[(7-(4-metoxi)-4-azaindol-3-il)-oxoacetil]piperazina se preparó a partir de 7-(4-metoxifenil)-4-azaindol-3-glioxilato de potasio y la 1-(benzoil)-3-metilpiperazina correspondiente según el procedimiento general anterior. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{27}N_4O_4$: 483.20; encontrado 483.17. Tiempo de retención CLAR: 1.30 minutos (columna A).

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EJEMPLO 67

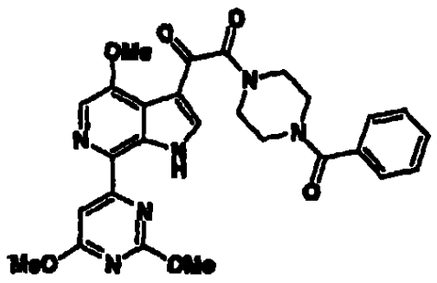


El Ejemplo 67, 1-benzoil-3-(R)-metil-4-[(7-(4-metoxifenil)-4-azaindol-3-il)oxoacetil]piperazina se preparó a partir de 7-(4-metoxifenil)-4-azaindol-3-glioxilato de potasio y la 1-benzoil-3-metilpiperazina correspondiente según el procedimiento general anterior. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{27}N_4O_4$: 483.20; encontrado 483.16. Tiempo de retención CLAR: 1.28 minutos (columna A).

EJEMPLOS 68-79 y 81

Los Ejemplos 68-79 y 81 se prepararon de acuerdo al mismo método general como se describió previamente para los Ejemplos 16-54.

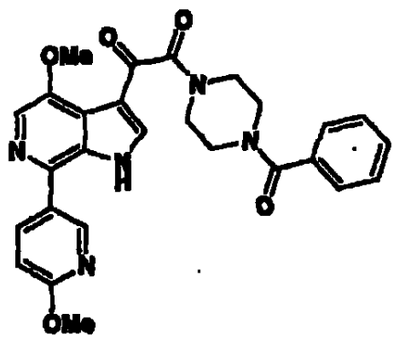
EJEMPLO 68



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El Ejemplo 68, se preparó a partir del Precursor 5b y el 2,4-dimetoxipirimidin-6-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2,6-dimetoxi-pirimidin-4-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.13 (s, 1H), 7.52 (s, 1H), 7.42 (m, 5H), 4.11 (s, 3H), 4.06 (s, 3H), 4.00-3.40 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{27}N_6O_6$: 531.20; encontrado 531.24. Tiempo de retención CLAR: 1.54 minutos (columna A).

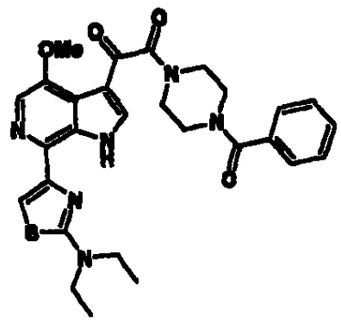
EJEMPLO 69



El Ejemplo 69, se preparó a partir del Precursor 5b y el 6-metoxipiridin-3-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(6-metoxi-piridin-3-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.69 (s, 1H), 8.63 (s, 1H), 8.11 (m, 2H), 7.49 (m, 5H), 7.10 (d, 1H, J = 8.65 Hz), 4.16 (s, 3H), 4.06 (s, 3H), 4.00-3.40 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{26}N_5O_5$: 500.09; encontrado 500.20. Tiempo de retención CLAR: 1.11 minutos (columna A).

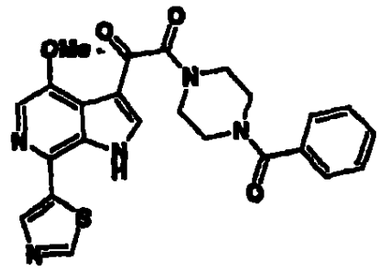
682

EJEMPLO 70



El Ejemplo 70, se preparó a partir del Precursor 5b y el 2-dietilamino-tiazol-4-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-dietilamino-tiazol-4-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.47 (s, 1H), 7.97 (m, 2H), 7.49 (m, 5H), 4.08 (s, 3H), 3.64 (m, 12H), 1.35 (m, 6H). EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{31}N_6O_4S$: 547.21; encontrado 547.22. Tiempo de retención CLAR: 1.35 minutos (columna A).

EJEMPLO 71

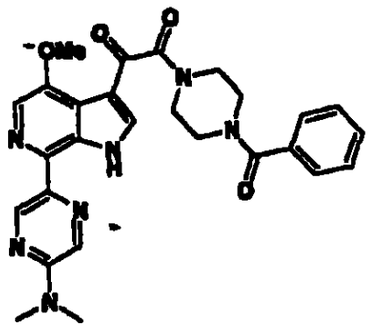


El Ejemplo 71, se preparó a partir del Precursor 5b y el tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(tioazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H

688

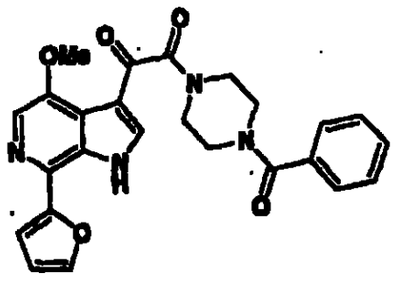
RMN (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.64 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.46 (m, 5H), 4.00 (s, 3H), 3.55 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_5O_4S$: 476.14; encontrado 476.17. Tiempo de retención CLAR: 1.13 minutos (columna A).

EJEMPLO 72



El Ejemplo 72, se preparó a partir del Precursor 5b y el 2-dimetilamino-pirazin-5-il estanano para suministrar 1-(benzoil)-4-[(4-metoxi-7-(2-dimetilamino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{28}N_7O_4$: 514.22; encontrado 514.29. Tiempo de retención CLAR: 1.27 minutos (columna A).

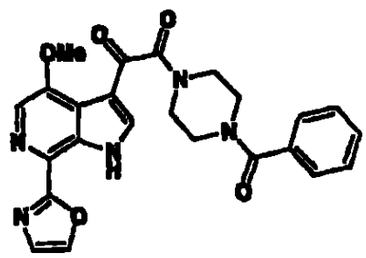
EJEMPLO 73



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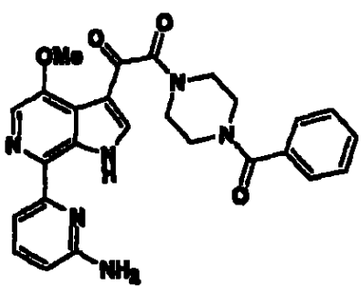
El Ejemplo 73, se preparó a partir del Precursor 5b y el furan-2-il estanano para suministrar 1-(benzoil)-4-[(4-metoxi-7-(furan-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_5$: 459.17; encontrado 459.25. Tiempo de retención CLAR: 1.15 minutos (columna A).

EJEMPLO 74



El Ejemplo 74, se preparó a partir del Precursor 5b y el oxazol-2-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(oxazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^1H RMN (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.64 (s, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.46 (m, 5H), 4.00 (s, 3H), 3.55 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_5O_5$: 460.16; encontrado 460.23. Tiempo de retención CLAR: 1.22 minutos (columna A).

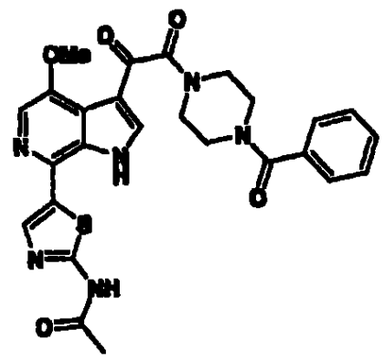
EJEMPLO 75



691

El Ejemplo 77, se preparó a partir del Precursor 5b y el 6-metoxipiridin-2-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-metoxi-piridin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{26}N_5O_5$: 500.19; encontrado 500.23. Tiempo de retención CLAR: 1.26 minutos (columna A).

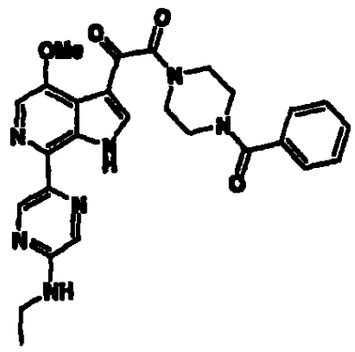
EJEMPLO 78



El Ejemplo 78, se preparó a partir del Precursor 5b y el 2-acetilamino-tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-acetilamino-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_6O_5S$: 533.16; encontrado 533.18. Tiempo de retención CLAR: 1.21 minutos (columna A).

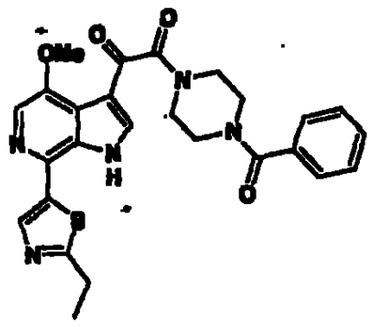
692

EJEMPLO 79



El Ejemplo 79, se preparó a partir del Precursor 5b y el 2-etilamino-pirazin-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-etilamino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{28}N_7O_4$: 514.22; encontrado 514.18. Tiempo de retención CLAR: 1.31 minutos (columna A).

EJEMPLO 88

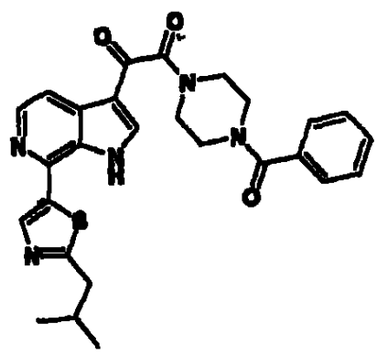


El Ejemplo 88, se preparó a partir del Precursor 5b y el 2-etil-tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-etil-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para

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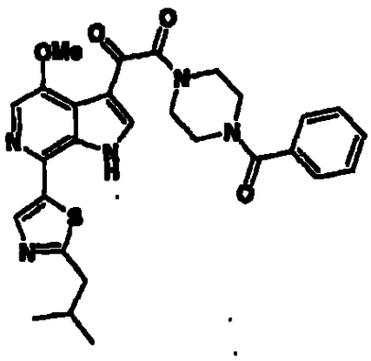
$C_{26}H_{26}N_5O_4S$: 504.17; encontrado 514.32. Tiempo de retención CLAR: 1.50 minutos (columna A).

EJEMPLO 89



El Ejemplo 89, se preparó a partir del Precursor 5k y el 2-isobutil-tiazol-5-il estanano para suministrar 1-benzoil-4-[(7-(2-isobutil-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{28}N_5O_3S$: 502.19; encontrado 502.26. Tiempo de retención CLAR: 1.56 minutos (columna E).

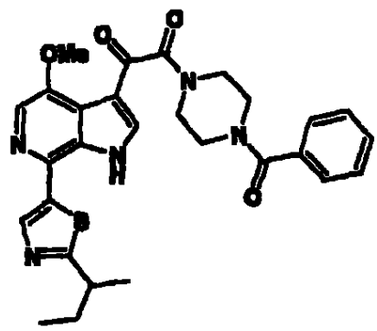
EJEMPLO 90



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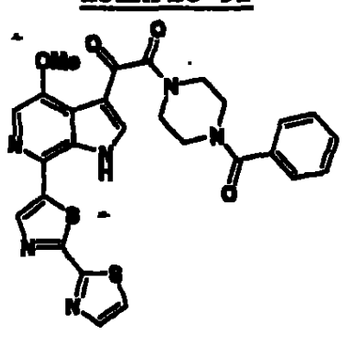
El Ejemplo 90, se preparó a partir del Precursor 5b y el 2-isobutil-tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-isobutil-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{30}N_5O_4S$: 532.20; encontrado 532.27. Tiempo de retención CLAR: 1.57 minutos (columna E).

EJEMPLO 91



El Ejemplo 91, se preparó a partir del Precursor 5b y el 2-(2-butil)-tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-(2-butil)-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{30}N_5O_4S$: 532.20; encontrado 532.27. Tiempo de retención CLAR: 1.57 minutos (columna E).

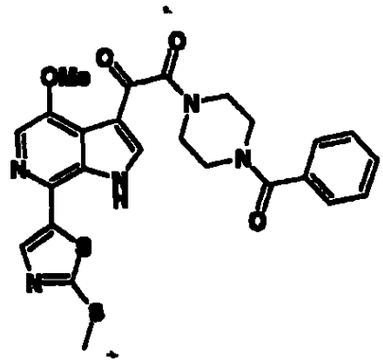
EJEMPLO 92



645

El Ejemplo 92, se preparó a partir del Precursor 5b y el 2-(tiazol-2-il)-tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-(tiazol-2-il)-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{23}N_6O_4S_2$: 559.12; encontrado 559.18. Tiempo de retención CLAR: 1.55 minutos (columna E).

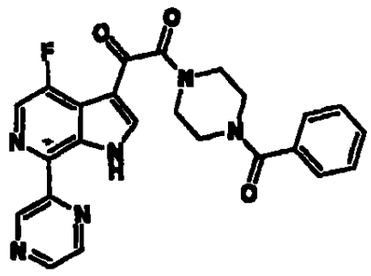
EJEMPLO 93



El Ejemplo 93, se preparó a partir del Precursor 5b y el 2-metiltio-tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-metiltio-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_5O_4S_2$: 522.13; encontrado 522.17. Tiempo de retención CLAR: 1.45 minutos (columna E).

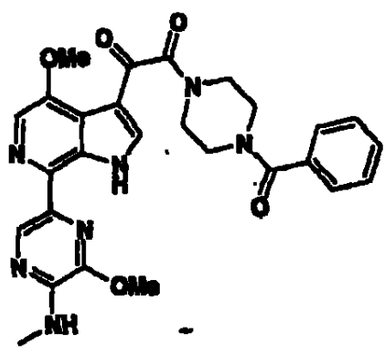
696

EJEMPLO 95



El Ejemplo 95, se preparó a partir del Precursor 5i y el pirazin-2-il estanano para suministrar 1-benzoil-4-[(4-fluoro-7-(pirazin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.70-8.34 (m, 4H), 7.46 (m, 5H), 3.80-3.50 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{20}FN_6O_3$: 459.16; encontrado 459.33. Tiempo de retención CLAR: 1.46 minutos (columna G).

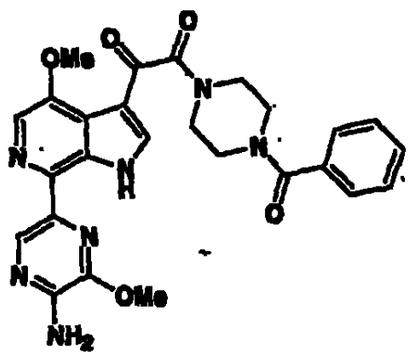
EJEMPLO 100



El Ejemplo 100, se preparó a partir del Precursor 5b y el 2-metilamino-3-metoxi-pirazin-5-il estanano para

suministrar 1-benzoil-4-[(4-metoxi-7-(2-metilamino-3-metoxi-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.65 (s, 1H), 8.43 (s, 1H), 7.95 (s, 1H), 7.45 (m, 5H), 4.21 (s, 3H), 4.12 (s, 3H), 3.89-3.32 (m, 8H), 3.06 (s, 3H). EM m/z: (M+H)+ calculado para $C_{27}H_{28}N_7O_5$: 530.22; encontrado 530.19. Tiempo de retención CLAR: 1.31 minutos (columna A).

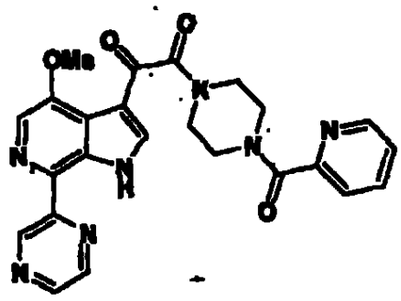
EJEMPLO 101



El Ejemplo 101, se preparó a partir del Precursor 5b y el 2-amino-3-metoxi-pirazin-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-amino-3-metoxi-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.67 (s, 1H), 8.34 (s, 1H), 7.96 (s, 1H), 7.48 (m, 5H), 4.22 (s, 3H), 4.12 (s, 3H), 3.92-3.32 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_7O_5$: 516.20; encontrado 516.23. Tiempo de retención CLAR: 1.27 minutos (columna A).

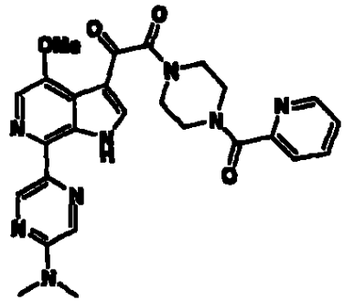
698

EJEMPLO 102



El Ejemplo 102, se preparó a partir del Precursor 51 y el pirazin-2-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(pirazin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 9.59 (s, 1H), 8.79-7.51 (m, 8H), 4.13 (s, 3H), 3.95-3.34 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_7O_4$: 472.17; encontrado 472.25. Tiempo de retención CLAR: 1.15 minutos (columna A).

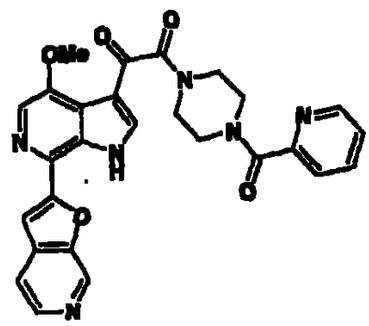
EJEMPLO 103



El Ejemplo 103, se preparó a partir del Precursor 51 y el 2-dimetilamino-pirazin-5-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(2-dimetilamino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{26}H_{27}N_8O_4$: 515.22; encontrado 515.16. Tiempo de retención CLAR: 1.29 minutos (columna A).

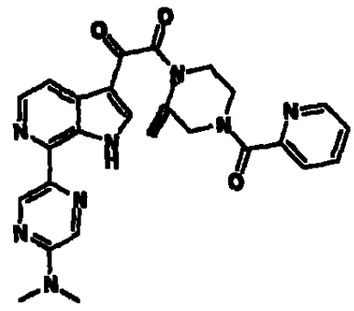
699

EJEMPLO 104



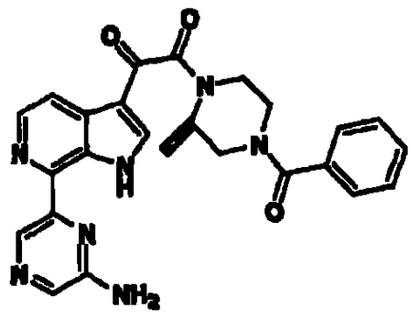
El Ejemplo 104, se preparó a partir del Precursor 5b y el 6-aza-benzofuran-2-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(6-aza-benzofuran-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.48 (d, 1H, J = 8.5 Hz), 8.36 (s, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.64 (d, 1H, J = 8.55 Hz), 7.41 (m, 4H), 6.92 (s, 1H), 4.12 (s, 3H), 3.87-3.38 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{24}N_5O_5$: 510.18; encontrado 510.33. Tiempo de retención CLAR: 1.33 minutos (columna A).

EJEMPLO 105



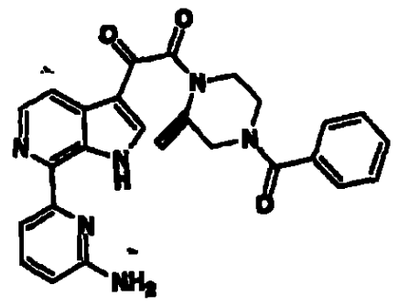
El Ejemplo 105, se preparó a partir del Precursor 5m y el 2-dimetilamino-pirazin-5-il estanano para suministrar (R)-1-picolinoil-3-metil-4-[(7-(2-dimetilamino-pirazin-5-il)-6-

EJEMPLO 111



El Ejemplo 111, se preparó a partir del Precursor 5f y el 2-amino-pirazin-6-il estanano para suministrar (R)-1-benzoil-3-metil-4-[(7-(2-amino-pirazin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.68-7.45 (m, 10H), 4.89-3.13 (m, 7H), 1.39-0.99 (m, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_3$: 470.19; encontrado 470.31. Tiempo de retención CLAR: 1.30 minutos (columna A).

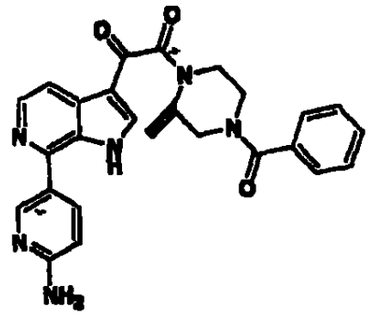
EJEMPLO 112



El Ejemplo 112, se preparó a partir del Precursor 5f y el 2-amino-piridin-6-il estanano para suministrar (R)-1-benzoil-3-metil-4-[(7-(2-amino-piridin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.65-6.89

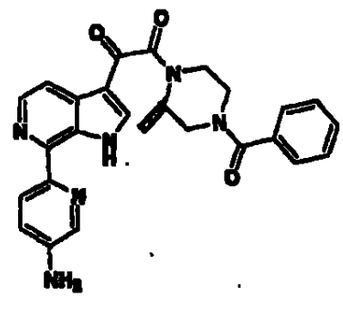
(m, 11H), 4.90-3.12 (m, 7H), 1.39-0.99 (m, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_6O_3$: 469.20; encontrado 469.32. Tiempo de retención CLAR: 1.26 minutos (columna A).

EJEMPLO 113

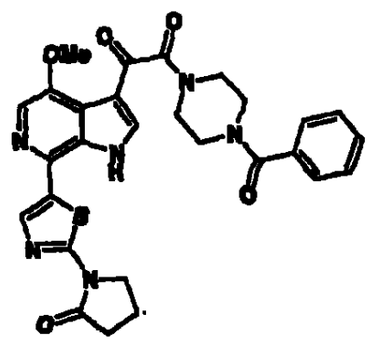


El Ejemplo 113, se preparó a partir del Precursor 5f y el 2-amino-piridin-5-il estanano para suministrar (R)-1-benzoil-3-metil-4-[(7-(2-amino-piridin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^1H RMN (500 MHz, CD_3OD) δ 8.75-7.19 (m, 11H), 4.91-3.12 (m, 7H), 1.38-1.25 (m, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_6O_3$: 469.20; encontrado 469.34. Tiempo de retención CLAR: 1.05 minutos (columna A).

EJEMPLO 114

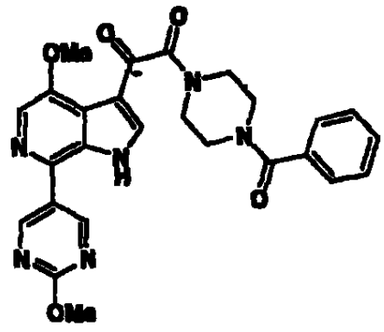


EJEMPLO 116



El Ejemplo 116, se preparó a partir del Precursor 5b y el 2-(2-pirrolidinon-1-il)-tiazol-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-((2-pirrolidinon-1-il)-tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{27}N_6O_5S_2$: 559.18; encontrado 559.11. Tiempo de retención CLAR: 1.39 minutos (columna E).

EJEMPLO 117

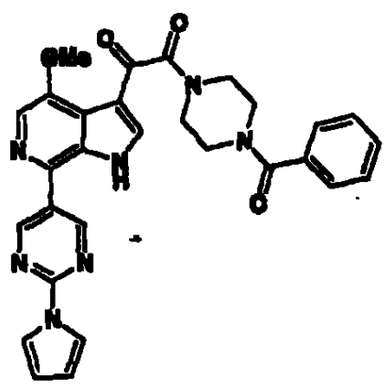


El Ejemplo 117, se preparó a partir del Precursor 5b y el 2-metoxi-pirimidin-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-metoxi-pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para

706

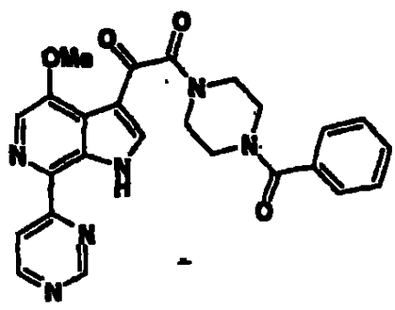
$C_{26}H_{25}N_6O_5$: 501.19; encontrado 501.12. Tiempo de retención CLAR: 1.21 minutos (columna E).

EJEMPLO 118



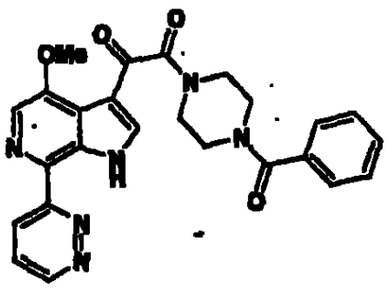
El Ejemplo 118, se preparó a partir del Precursor 5b y el 2-(pirrol-1-il)-pirimidin-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-(pirrol-1-il)-pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{29}H_{26}N_7O_4$: 536.20; encontrado 536.33. Tiempo de retención CLAR: 1.44 minutos (columna C).

EJEMPLO 119



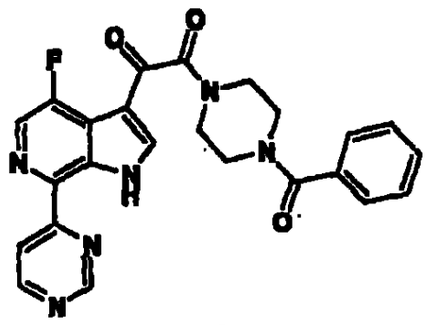
El Ejemplo 119, se preparó a partir del Precursor 5b y el pirimidin-4-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 9.29 (s, 1H), 8.88 (d, 1H, J = 5.4 Hz), 8.48 (d, 1H, J = 5.25 Hz), 8.26 (s, 1H), 8.18 (s, 1H), 7.43 (m, 5H), 4.13 (s, 3H), 3.85-3.47 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N6O4$: 471.18; encontrado 471.32. Tiempo de retención CLAR: 1.35 minutos (columna G).

EJEMPLO 120



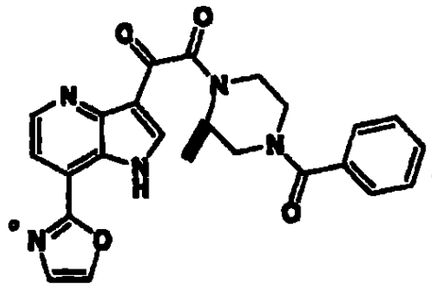
El Ejemplo 119, se preparó a partir del Precursor 5b y el piridazin-3-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(piridazin-3-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 9.16 (s, 1H), 8.77 (d, 1H, J = 8.5 Hz), 8.26 (d, 1H, J = 3.05 Hz), 8.18 (s, 1H), 7.68 (m, 1H), 7.43 (m, 5H), 4.13 (s, 3H), 3.85-3.47 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4$: 471.18; encontrado 471.16. Tiempo de retención CLAR: 1.35 minutos (columna G).

EJEMPLO 125



El Ejemplo 125, se preparó a partir del Precursor 5i y el pirimidin-4-il estanano para suministrar 1-benzoil-4-[(4-fluoro-7-(pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 9.36 (s, 1H), 8.96 (d, 1H, J = 5.35 Hz), 8.58 (d, 1H, J = 5.10 Hz), 8.43 (s, 1H), 8.38 (s, 1H), 7.43 (m, 5H), 3.85-3.47 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{20}FN_6O_2$: 459.16; encontrado 459.15. Tiempo de retención CLAR: 1.48 minutos (columna A).

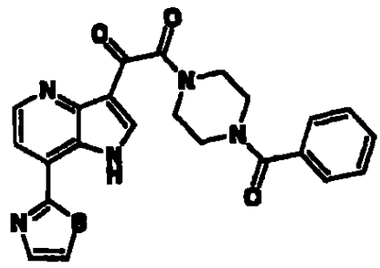
EJEMPLO 126



El Ejemplo 126, se preparó a partir del Precursor 5i y el oxazol-2-il estanano para suministrar (R)-1-benzoil-3-metil-4-[7-(oxazol-2-il)-4-azaindol-3-il)-

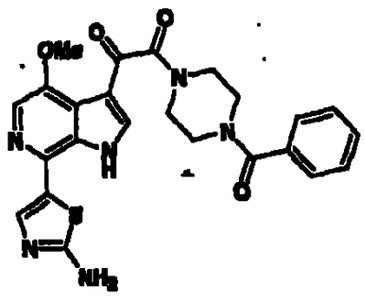
oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_5O_4$: 444.17; encontrado 444.25. Tiempo de retención CLAR: 1.13 minutos (columna A).

EJEMPLO 131



El Ejemplo 131, se preparó a partir del Precursor 5P y el tiazol-2-il estanano para suministrar 1-benzoil-4-[7-(tiazol-2-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{20}N_5O_3S$: 446.13; encontrado 446.04. Tiempo de retención CLAR: 1.12 minutos (columna A).

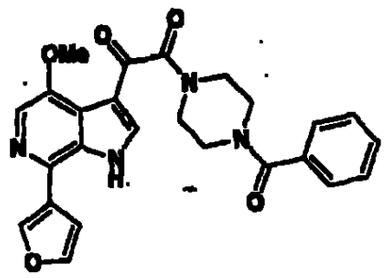
EJEMPLO 80



Preparación del Ejemplo 80, 1-benzoil-4-[(4-metoxi-7-(2-amino-tioazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina: Una mezcla de Ejemplo 78 (9 mg), TFA (3 mL) y agua (1 mL) se agitó a

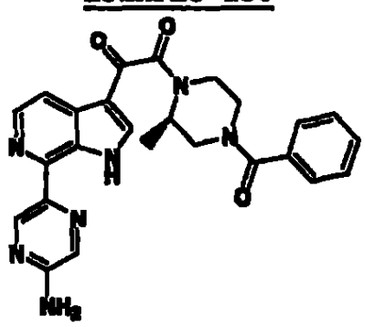
80°C durante 10 horas. Después de que el solvente se removió bajo vacío, el residuo se purificó al usar cromatografía en gel de sílice para resultar 1-benzoil-4-[(4-metoxi-7-(2-amino-tioazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina (3 mg); EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{23}N_6O_5S$: 491.15; encontrado 491.21. Tiempo de retención CLAR: 1.20 minutos (columna A).

EJEMPLO 81



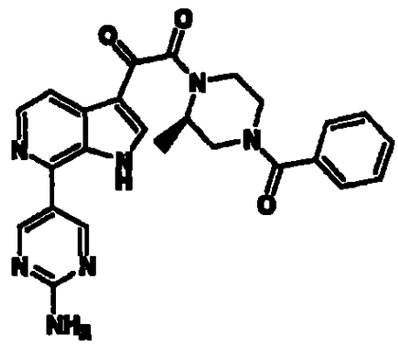
El Ejemplo 81, se preparó a partir del Precursor 5b y el furan-3-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(furan-3-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_5$: 459.17; encontrado 459.24. Tiempo de retención CLAR: 1.13 minutos (columna A).

EJEMPLO 150



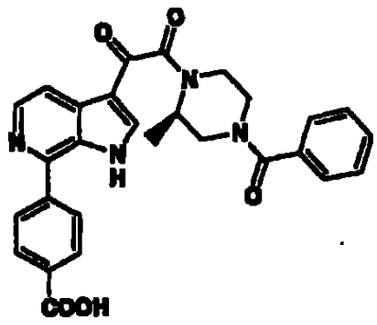
El Ejemplo 150, se preparó a partir del Precursor 5f y el 5-amino-pirazin-2-il estanano para suministrar (R)-1-benzoil-3-metil-4-[(7-(5-amino-pirazin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_3$: 470.19; encontrado 470.19. Tiempo de retención CLAR: 1.14 minutos (columna G).

EJEMPLO 153



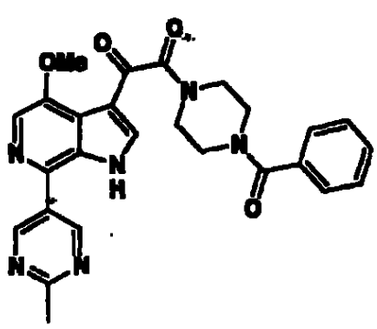
El Ejemplo 153, se preparó a partir del Precursor 5f y el 2-amino-pirimidin-5-il estanano para suministrar (R)-1-benzoil-3-metil-4-[(7-(2-amino-pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_3$: 470.19; encontrado 470.22. Tiempo de retención CLAR: 1.07 minutos (columna G).

EJEMPLO 170



El Ejemplo 170, se preparó a partir del Precursor 5f y el ácido 4-borono-benzóico para suministrar (R)-1-benzoil-3-metil-4-[(7-(hidroxilcarbonil-bencen-4-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{25}N_4O_5$: 497.18; encontrado 497.10. Tiempo de retención CLAR: 1.25 minutos (columna H).

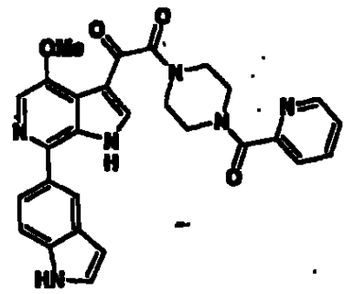
EJEMPLO 171



El Ejemplo 171, se preparó a partir del Precursor 5b y el 2-metil-pirimidin-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-metil-pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para

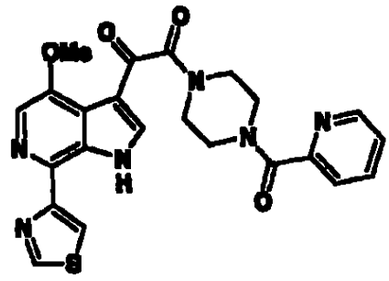
$C_{26}H_{25}N_6O_4$: 485.19; encontrado 485.20. Tiempo de retención CLAR: 1.14 minutos (columna C).

EJEMPLO 172



El Ejemplo 172, se preparó a partir del Precursor 51 y el ácido 5-indol borónico para suministrar 1-picolinoil-4-[(4-metoxi-7-(indol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{25}N_6O_4$: 509.19; encontrado 509.33. Tiempo de retención CLAR: 1.14 minutos (columna J).

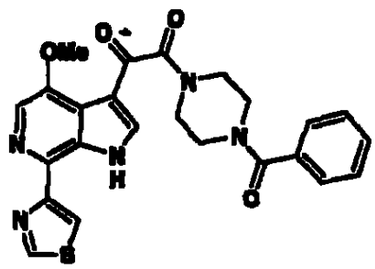
EJEMPLO 173



El Ejemplo 173, se preparó a partir del Precursor 51 y el tiazol-4-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(tiazol-4-il)-6-azaindol-3-il)-oxoacetil]piperazina.

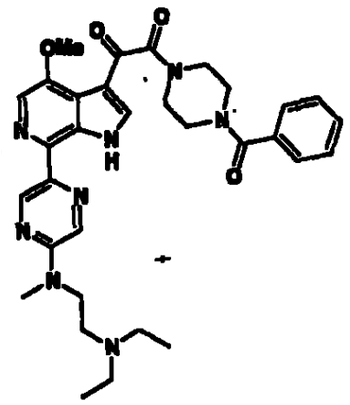
EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{21}N_6O_4S$: 477.13; encontrado 477.06. Tiempo de retención CLAR: 0.92 minutos (columna G).

EJEMPLO 174



El Ejemplo 174, se preparó a partir del Precursor 5b y el tiazol-4-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(tiazol-4-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{22}N_5O_4S$: 476.14; encontrado 476.13. Tiempo de retención CLAR: 1.12 minutos (columna G).

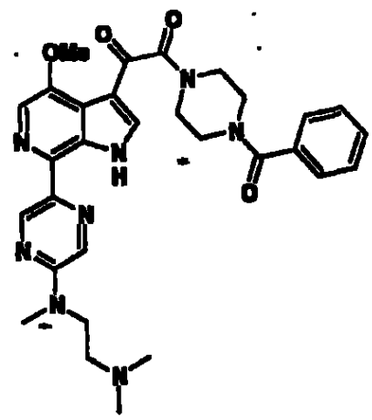
EJEMPLO 175



El Ejemplo 175, se preparó a partir del Precursor 5b y el 2-(N-dietilaminoetil-N-metil)aminopirazin-5-il

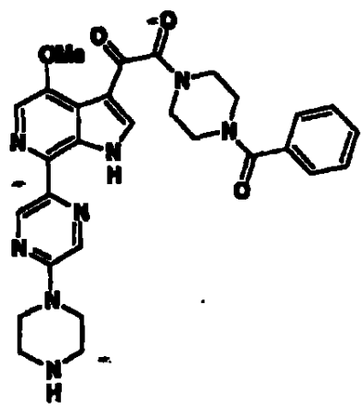
estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-(N-dietilaminoetil-N-metil)aminopirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{32}H_{39}N_8O_4$: 599.31; encontrado 599.29. Tiempo de retención CLAR: 1.11 minutos (columna G).

EJEMPLO 176



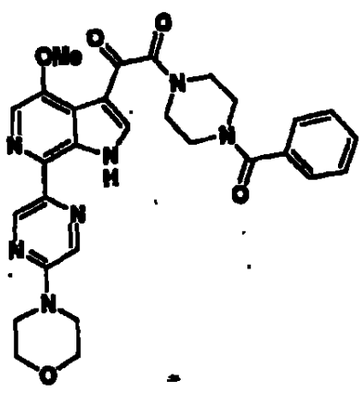
El Ejemplo 176, se preparó a partir del Precursor 5b y el estanano 2-(N-dimetilaminoetil-N-metil)aminopirazin-5-il para suministrar 1-benzoil-4-[(4-metoxi-7-(2-(N-dimetilaminoetil-N-metil)aminopirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{30}H_{35}N_8O_4$: 571.28; encontrado 571.23. Tiempo de retención CLAR: 1.06 minutos (columna G).

EJEMPLO 177



El Ejemplo 177, se preparó a partir del Precursor 5b y el 2-(N-piperazinil)-pirazin-5-il estanano para suministrar 1-benzoil-4-[(4-metoxi-7-(2-(N-piperazinil)-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{31}N_8O_4$: 555.25; encontrado 555.19. Tiempo de retención CLAR: 1.05 minutos (columna G).

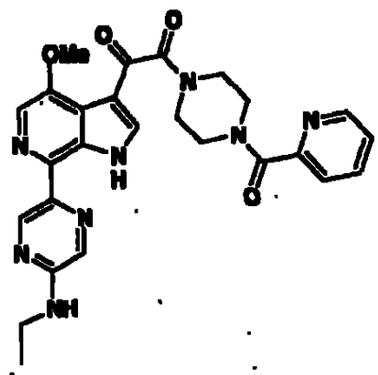
EJEMPLO 178



El Ejemplo 178, se preparó a partir del Precursor 5b y el 2-(4-morfolinil)-pirazin-5-il estanano para suministrar 1-

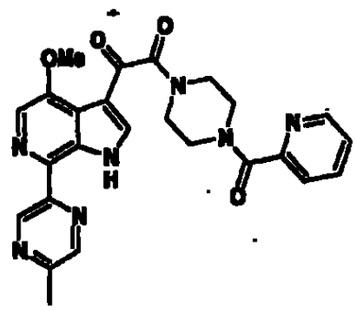
benzoil-4-[(4-metoxi-7-(2-(4-morfolinil)-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{30}N_7O_5$: 556.23; encontrado 556.18. Tiempo de retención CLAR: 1.27 minutos (columna G).

EJEMPLO 179



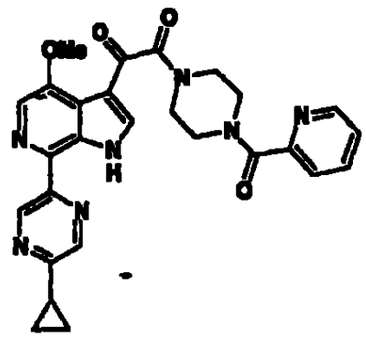
El Ejemplo 179, se preparó a partir del Precursor 51 y el 2-etilaminopirazin-5-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(2-etilaminopirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{27}N_8O_4$: 515.22; encontrado 515.14. Tiempo de retención CLAR: 1.13 minutos (columna G).

EJEMPLO 180



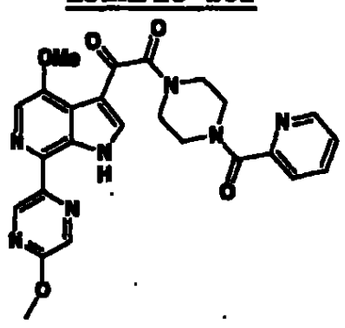
El Ejemplo 180, se preparó a partir del Precursor 51 y el 2-metilpirazin-5-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(2-metilpirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: (M+H)+ Calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 486.16. Tiempo de retención CLAR: 1.08 minutos (columna G).

EJEMPLO 181



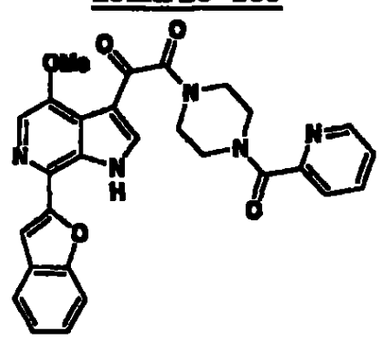
El Ejemplo 181, se preparó a partir del Precursor 51 y el 2-ciclopropanil-pirazin-5-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(2-ciclopropanil-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{26}N_7O_4$: 512.20; encontrado 512.12. Tiempo de retención CLAR: 1.35 minutos (columna G).

EJEMPLO 182



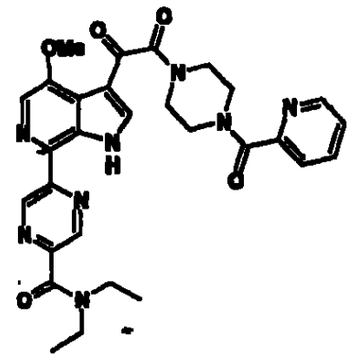
El Ejemplo 182, se preparó a partir del Precursor 51 y el 2-metoxi-pirazin-5-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(2-metoxi-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_5$: 502.18; encontrado 502.08. Tiempo de retención CLAR: 1.15 minutos (columna G).

EJEMPLO 183



El Ejemplo 183, se preparó a partir del Precursor 51 y el ácido 2-benzofuran borónico para suministrar 1-picolinoil-4-[(4-metoxi-7-(benzofuran-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{24}N_5O_5$: 510.18; encontrado 510.08. Tiempo de retención CLAR: 1.33 minutos (columna G).

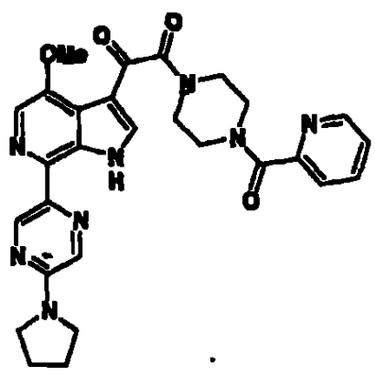
EJEMPLO 184



720

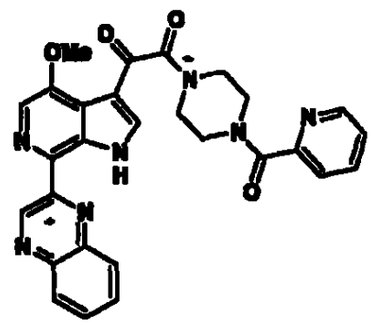
El Ejemplo 184, se preparó a partir del Precursor 51 y el 2-dietilaminocarbonil-pirazin-5-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(2-dietilaminocarbonil-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{31}N_8O_5$: 571.24; encontrado 571.19. Tiempo de retención CLAR: 1.55 minutos (columna J).

EJEMPLO 185



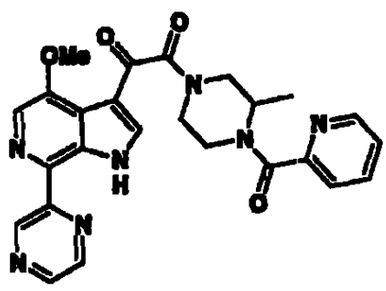
El Ejemplo 185, se preparó a partir del Precursor 51 y el 2-(N-pirrolinil)-pirazin-5-il estanano para suministrar la 1-picolinoil-4-[(4-metoxi-7-(2-(N-pirrolinil)-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{29}N_8O_4$: 541.23; encontrado 541.18. Tiempo de retención CLAR: 1.30 minutos (columna J).

EJEMPLO 186



El Ejemplo 186, se preparó a partir del Precursor 51 y el quinoxalin-2-il estanano para suministrar 1-picolinoil-4-[(4-metoxi-7-(quinoxakin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{28}H_{24}N_7O_4$: 522.19; encontrado 522.14. Tiempo de retención CLAR: 1.68 minutos (columna J).

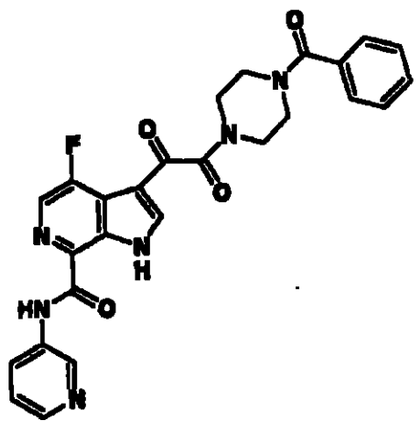
EJEMPLO 194



El Ejemplo 194, se preparó a partir del Precursor 5v y el pirazin-2-il estanano para suministrar 2-metil-1-picolinoil-4-[(4-metoxi-7-(pirazin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 486.14. Tiempo de retención CLAR: 1.50 minutos (columna G).

722

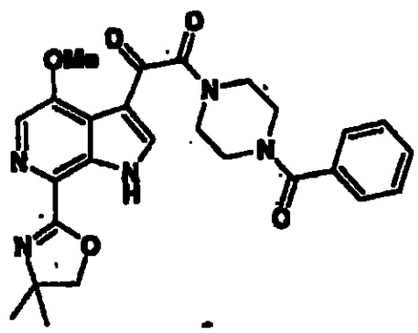
EJEMPLO 147



El Precursor 5i (16.5 mg, 0.05 mmol) en DMF (1 mL) se trató con clorohidrato N-benzoilpiperazina, DEBPT (15 mg, 0.05 mmol) y base Hunig (34 µL, 0.2 mmol) a temperatura ambiente durante 18 horas. El solvente se removió en vacío y el residuo se purificó por CLAR preparativa de fase inversa. Las fracciones muestran la CL/EM (ES^+) m/z $(M+H)^+$ = 501 correcta, se colectaron, concentraron y purificaron nuevamente al usar un TLC preparativo (5% $MeOH/CH_2Cl_2$) para resultar el compuesto del título como un sólido blanco. ^1H-RMN (500 MHz, $CDCl_3$) δ 11.2 (s, 1H), 10.0 (s, 1H), 9.21 (s, 1H), 8.51 (s, 1H), 8.41 (s, 1H), 8.40 (m, 1H), 8.32 (s, 1H), 7.62 (m, 1H), 7.45 (m, 5H), 3.90-3.50 (bm, 8H);

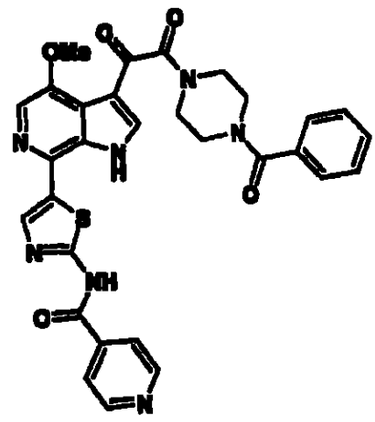
723

EJEMPLO 156



El Ejemplo 156, se preparó a partir del Precursor 5b y el 4,4-dimetiloxazolin-2-il estanano para suministrar 1-benzoil-4-[(7-(4,4-dimetiloxazolin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{27}H_{28}N_5O_5$: 490.21; encontrado 490.22. Tiempo de retención CLAR: 1.20 minutos (columna C).

EJEMPLO 169



El Ejemplo 169, se preparó a partir del Precursor 5b y el estanano 2-(4-piridincarboxamido)-tiazol-5-il para suministrar 1-benzoil-4-[(7-(2-(4-piridincarboxamido)-

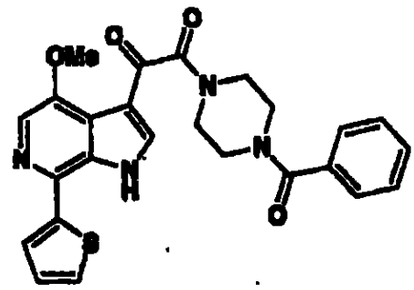
724

tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{30}H_{26}N_7O_5S$: 596.17; encontrado 596.14. Tiempo de retención CLAR: 1.32 minutos (columna C).

EJEMPLOS 82-86, 98, 107, 108, 129, 130, 132, 133, 134

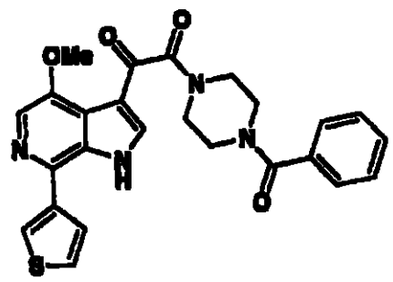
Los Ejemplos 82-86, 98, 107, 108, 127, 128, 129, 130, 132, 133 y 134 se prepararon de acuerdo al procedimiento general como se describió previamente para los Ejemplos 2-14.

EJEMPLO 82



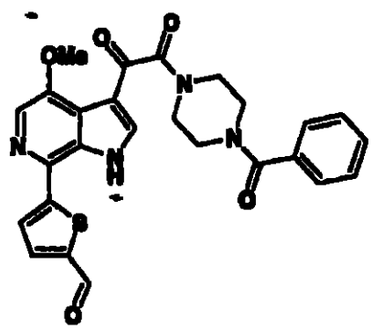
El Ejemplo 82, se preparó a partir del Precursor 5b y ácido tien-2-il borónico para suministrar 1-benzoil-4-[(4-metoxi-7-(tiofen-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_4S$: 475.14; encontrado 475.31. Tiempo de retención CLAR: 1.14 minutos (columna A).

EJEMPLO 83



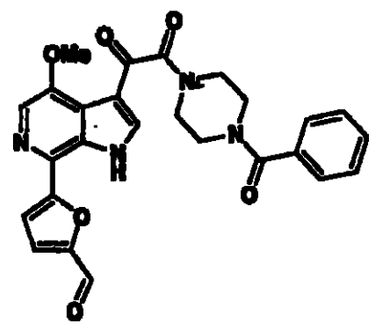
El Ejemplo 83, se preparó a partir del Precursor 5b y ácido tien-2-il borónico para suministrar 1-benzoil-4-[(4-metoxi-7-(tiofen-3-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_4S$: 475.14; encontrado 475. 33. Tiempo de retención CLAR: 1.16 minutos (columna A).

EJEMPLO 84



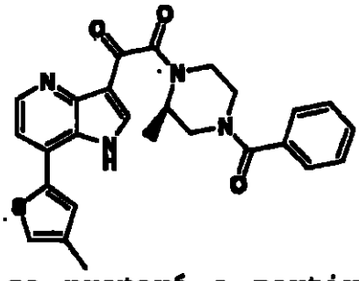
El Ejemplo 84, se preparó a partir del Precursor 5b y ácido 5-carboniltien-2-il borónico para suministrar 1-benzoil-4-[(4-metoxi-7-(5-carbonil-tiofen-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{23}N_4O_5S$: 503.14; encontrado 503.23. Tiempo de retención CLAR: 1.31 minutos (columna A).

EJEMPLO 85



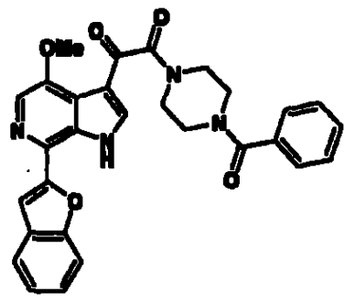
El Ejemplo 76, se preparó a partir del Precursor 5b y ácido 5-carbonilfuran-2-il borónico para suministrar 1-(benzoil)-4-[(4-metoxi-7-(5-carbonil-furan-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{26}H_{23}N_4O_6$: 487.16; encontrado 487.28. Tiempo de retención CLAR: 1.44 minutos (columna A).

EJEMPLO 86



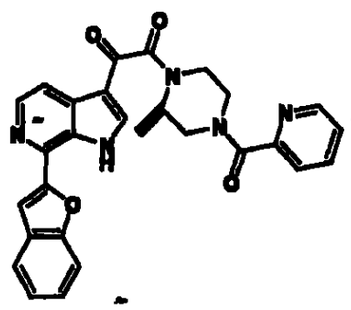
El Ejemplo 86, se preparó a partir del Precursor 5d y ácido 4-metiltien-2-il borónico para suministrar 1-benzoil-3-(R)-metil-4-[(7-(4-metil-tiofen-2-il)-4-azaindol-3-il)-oxoacetillpiperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_4O_3S$: 473.16; encontrado 473.26. Tiempo de retención CLAR: 1.28 minutos (columna A).

EJEMPLO 98



El Ejemplo 98, se preparó a partir del Precursor 5d y ácido 2-benzofuranilo borónico para suministrar 1-benzoil-3-(R)-metil-4-[(7-(benzofuran-2-il)-4-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.09 (s, 1H), 7.70-7.26 (m, 10H), 4.03 (s, 3H), 3.97-3.49 (m, 8H). EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{25}N_4O_5$: 509.18; encontrado 509.18. Tiempo de retención CLAR: 1.50 minutos (columna A).

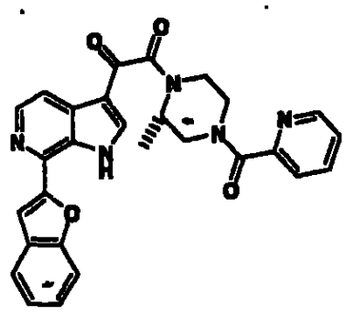
EJEMPLO 107



El Ejemplo 107, se preparó a partir del Precursor 5m y ácido 2-benzofuranilo borónico para suministrar (R)-1-picolinoil-3-metil-4-[(7-(benzofuran-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 8.77-7.38 (m,

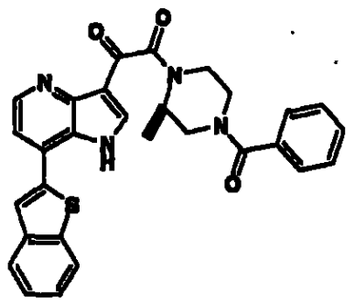
12H), 4.99-3.16 (m, 7H), 1.44-1.27 (m, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{24}N_5O_4$: 494.18; encontrado 494.24. Tiempo de retención CLAR: 1.35 minutos (columna A).

EJEMPLO 108



El Ejemplo 108, se preparó a partir del Precursor 5n y ácido 2-benzofuranilo borónico para suministrar (S)-1-picolinoil-3-metil-4-[(7-(benzofuran-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{24}N_5O_4$: 494.18; encontrado 494.23. Tiempo de retención CLAR: 1.37 minutos (columna A).

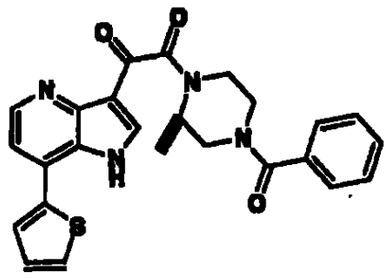
EJEMPLO 127



El Ejemplo 127, se preparó a partir del Precursor 5i y el ácido benzotiofen-2-il borónico para suministrar (R)-1-

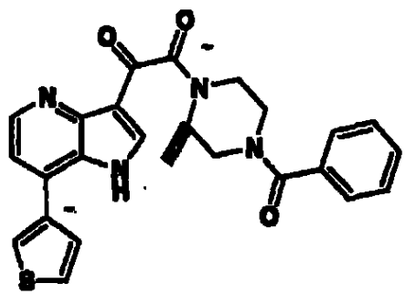
benzoil-3-metil-4-[7-(benzotiofen-2-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{25}N_4O_3S$: 509.16; encontrado 509.21. Tiempo de retención CLAR: 1.42 minutos (columna A).

EJEMPLO 128



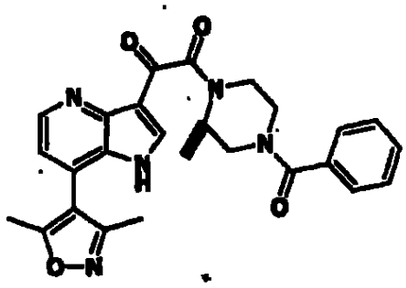
El Ejemplo 128, se preparó a partir del Precursor 5i y el ácido tiofen-2-il borónico para suministrar (R)-1-benzoil-3-metil-4-[7-(tiofen-2-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_3S$: 459.15; encontrado 459.27. Tiempo de retención CLAR: 1.22 minutos (columna A).

EJEMPLO 129



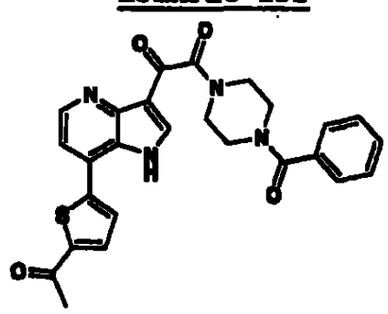
El Ejemplo 129, se preparó a partir del Precursor 5i y el ácido tiofen-3-il borónico para suministrar (R)-1-benzoil-3-metil-4-[7-(tiofen-3-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_3S$: 459.15; encontrado 459.34. Tiempo de retención CLAR: 1.31 minutos (columna A).

EJEMPLO 130



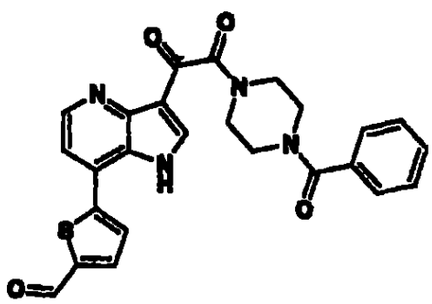
El Ejemplo 130, se preparó a partir del Precursor 5i y el ácido 2,5-dimetil-isoxazol-4-il borónico para suministrar (R)-1-benzoil-3-metil-4-[7-(2,5-dimetil-isoxazol-4-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_5O_4$: 472.20; encontrado 472.28. Tiempo de retención CLAR: 1.14 minutos (columna A).

EJEMPLO 132



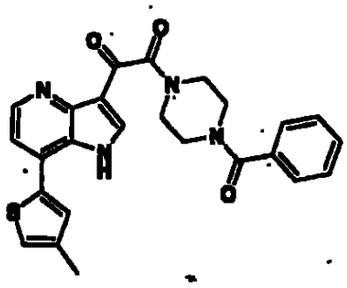
El Ejemplo 132, se preparó a partir del Precursor 5p y el ácido 2-metilcarbonil-tiofen-5-il borónico para suministrar 1-benzoil-4-[7-(2-metilcarbonil-tiofen-5-il)-4-azaindol-3-il)-oxoacetil]piperàzina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{23}N_4O_4S$: 487.14; encontrado 487.20. Tiempo de retención CLAR: 1.14 minutos (columna A).

EJEMPLO 133



El Ejemplo 133, se preparó a partir del Precursor 5p y el ácido 2-carbonil-tiofen-5-il borónico para suministrar 1-benzoil-4-[7-(2-carbonil-tiofen-5-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{21}N_4O_4S$: 473.13; encontrado 473.11. Tiempo de retención CLAR: 1.14 minutos (columna A).

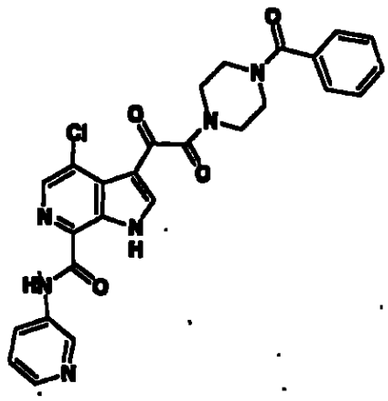
EJEMPLO 134



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El Ejemplo 134, se preparó a partir del Precursor 5p y el ácido 4-metil-tiofen-2-il borónico para suministrar 1-benzoil-4-[7-(4-metil-tiofen-2-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_4O_3S$: 459.15; encontrado 459.08. Tiempo de retención CLAR: 1.26 minutos (columna G).

EJEMPLO 152



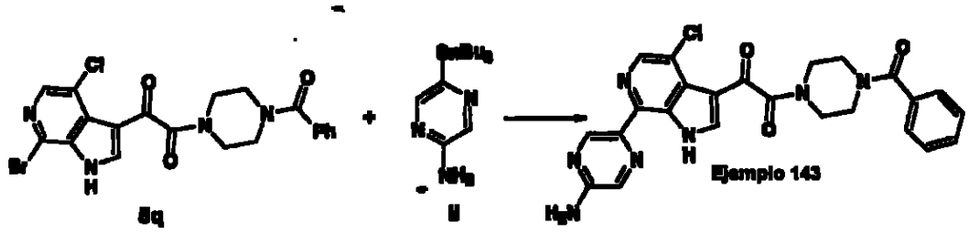
Preparación del Ejemplo 152:

A una mezcla del **precursor 16 ácido** (30 mg, 68 µmol), 3-aminopiridina (26 mg, 0.27 mmol) y DMAP (50 mg, 0.41 mmol) se agregó THF (2 ml), y luego EDC (60 mg, 0.31 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. El análisis CL/EM indicó que el producto mayor fue el éster activado. La mezcla de reacción se agregó luego dentro de una solución DMF (2 ml) de 3-aminopiridina (400 mg, 4.25 mmol) y se agitó a temperatura ambiente durante 16 horas. Después de la adición de MeOH (4 ml), la mezcla de reacción se purificó

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por CLAR de fase inversa preparativa para dar la sal TFA del compuesto del título al usar el método: Inicio % B = 30, Final % B = 75, Tiempo de gradiente = 25 min, Relación de flujo = 25 ml/min, Columna: YMC C18 5um 20 x 100mm, Fracción colectada: 10.41-11.08 min. ^{1}H RMN: (DMSO-D_6) δ 13.04 (s, 1H), 11.17 (s, 1H), 9.17 (s, 1H), 8.53 (s, 1H), 8.35 (m, 3H), 7.44 (b s, 6H), 3.75-3.37 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 517, 519; CLAR T_r = 1.653.

EJEMPLO 143



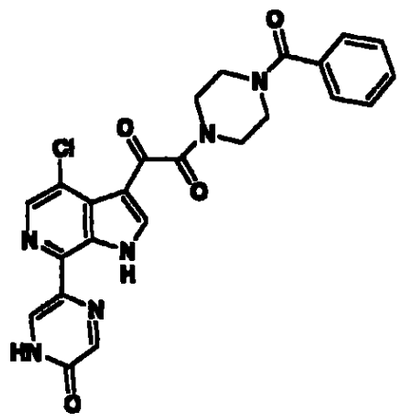
Preparación del Ejemplo 143:

A una mezcla del Precursor 5q (31 mg, 65 µmol) y $Pd(PPh_3)_4$ (20 mg, 17 µmol) se agregó 1,4-dioxano (1 ml) y ii (30 mg, 78 µmol). La mezcla de reacción se calentó en un tubo sellado a 145°C durante 4 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se agregó MeOH (4 ml) y luego se filtró. el filtrado se purificó por CLAR de fase inversa preparativa para dar la sal TFA del compuesto del título al usar el método: Inicio % B = 25, Final % B = 90, Tiempo de gradiente = 20 min, Relación de flujo = 25

734

ml/min, Columna: YMC C18 5um 20 x 100 mm, Fracción colectada: 11.14-11.92 min. ^{1}H RMN: (DMSO-D_6) δ 12.71 (s, 1H), 9.01 (s, 1H), 8.36 (s, 1H), 8.27 (s, 1H), 8.08 (s, 1H), 7.44 (b s, 5H), 7.44 (b s, 2H), 3.75-3.37 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 490, 492; CLAR T_r = 2.250.

EJEMPLO 149



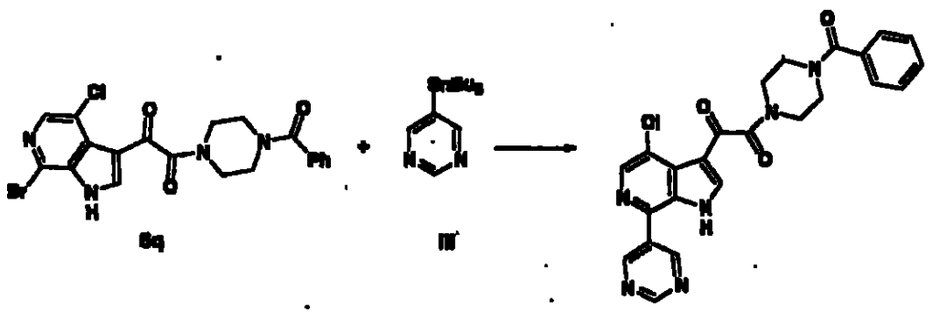
Preparación del Ejemplo 49:

A una suspensión del compuesto del Ejemplo 143 (12 mg, 24 μmol) en ácido sulfúrico (5%, 2 ml), se cargó nitrato de sodio (22 mg, 0.32 mol) a 0°C. La mezcla de reacción se agitó a 0°C durante 30 minutos y luego a temperatura ambiente durante 1 hora. Después de la adición de MeOH (4 ml), la mezcla de reacción se purificó por CLAR de fase inversa preparativa para dar un solvato TFA del compuesto del título al usar el método: Inicio % B = 20, Final % B = 85, Tiempo de gradiente = 15 min, Relación de flujo = 25 ml/min, Columna: YMC C18 5um 20 x 100 mm, Fracción colectada: 10.67-11.36 min.

735

^{1}H RMN: (DMSO-d_6) δ 12.62 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 8.18 (s, 1H), 7.44 (b s, 5H), 3.80-3.30 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 491, 493; CLAR T_r = 2.193.

EJEMPLO 144

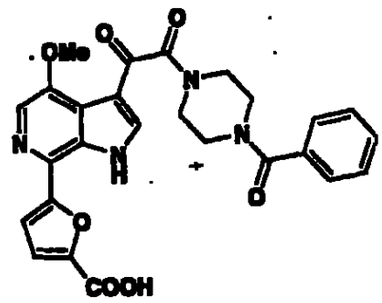


Preparación del Ejemplo 144:

A una mezcla del Precursor 5q (50 mg, 105 µmol) y $Pd(PPh_3)_4$ (50 mg, 43 µmol) se agregó 1,4-dioxano (1 ml) y iii (77 mg, 210 mol). La mezcla de reacción se calentó en un tubo sellado a 145°C durante 16 horas. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se agregó MeOH (4 ml) y luego se filtró. El filtrado se purificó por CLAR de fase inversa para dar la sal TFA del compuesto del título al usar el método: Inicio % B = 15, Final % B = 100, Tiempo de gradiente = 20 min, Relación de flujo = 25 ml/min, Columna: YMC C18 5um 20 x 100 mm, Fracción colectada: 11.80-12.31 min. ^{1}H RMN: (CD_3OD) δ 9.32 (s, 1H), 9.25 (s, 2H), 8.50 (s, 1H), 8.44 (s, 1H), 7.47 (b s, 5H), 4.00-3.44 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 475, 477; CLAR T_r = 1.833.

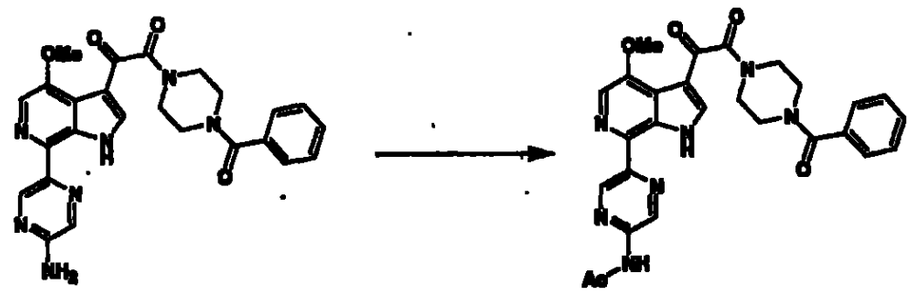
736

EJEMPLO 87



Preparación del Ejemplo 87, 1-benzoil-4-[(4-metoxi-7-(2-hidroxicarbonil-furan-5-il)-6-azaindol-3-il)-oxoacetil]piperazina: Una mezcla del compuesto del Ejemplo 85 (19 mg), $NaClO_2$ (9.2 mg) en una solución mezclada de CH_3CN (3 mL) y agua (0.5 mL) se agitó a temperatura ambiente durante 24 horas. Después de que la reacción se apagó por solución NaOH 1N (1 ml), la mezcla se extrajo con éter de dietilo (3 x 10 mL). La fase acuosa se hizó ácida con HCl 1N para dar un precipitado sólido amarillo (5 mg) el cual fue el producto mostrado. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{23}N_6O_7$: 503.16; encontrado 503.19. Tiempo de retención CLAR: 1.37 minutos (columna A).

Procedimiento general de conversión de grupo $-NH_2$ a grupo -NHCOR



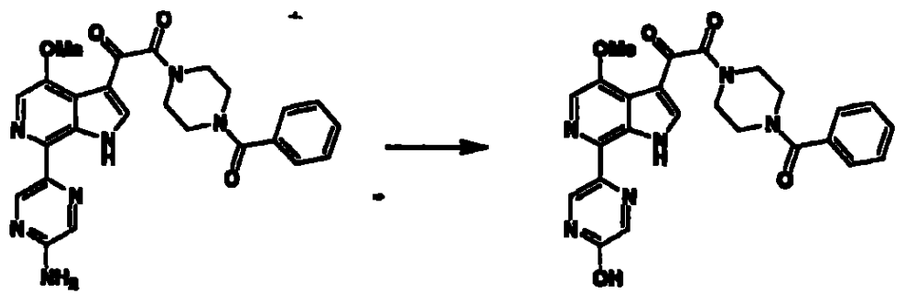
Preparación del Ejemplo 99, 1-(benzoil)-4-[(4-metoxi-7-(2-acetilamino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina: 1-(benzoil)-4-[(4-metoxi-7-(2-amino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina (4 mg) y anhídrido acético (20 mg) se disolvieron en piridina (0.5 ml). La reacción se agitó durante tres horas a temperatura ambiente. Después de que la reacción se apagó con MeOH (1mL), los solventes se concentraron para dar un residuo el cual se purificó usando un sistema CLAR preparativo automatizado Shimadzu para suministrar, 3.0 mg del compuesto deseado, 1-(benzoil)-4-[(4-metoxi-7-(2-acetilamino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^{1}H RMN (500 MHz, CD_3OD) δ 9.58 (s, 1H), 9.25 (s, 1H), 8.45 (s, 1H), 8.10 (s, 1H), 7.49 (m, 5H), 4.12 (s, 3H), 3.84-3.35 (m, 8H), 2.27 (s, 3H). EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{26}N_7O_5$: 528.20; encontrado 528.22. Tiempo de retención CLAR: 1.33 minutos (columna A).

Procedimiento general de conversión de grupo $-NH_2$ a grupo -OH

Preparación del Ejemplo 97, 1-(benzoil)-4-[(4-metoxi-7-(2-hidroxil-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina: 1-(benzoil)-4-[(4-metoxi-7-(2-amino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina (15 mg) y $NaNO_2$ (10 mg) se agregó dentro de una solución H_2SO_4 (0.1 ml de H_2SO_4 concentrado diluido con 0.3 ml de agua). La reacción se agitó a temperatura ambiente durante una hora. Luego, la

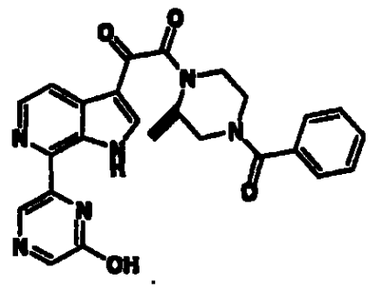
738

mezcla de reacción se neutralizó con una solución Na_2CO_3 saturada (10 ml). Los solventes se concentraron para dar un residuo el cuál se purificó usando un sistema CLAR preparativo automatizado Shimadzu para suministrar 4.2 mg del compuesto deseado, 1-(benzoil)-4-[(4-metoxi-7-(2-hidroxil-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. ^1H RMN (500 MHz, CD_3OD) δ 8.55 (s, 1H), 8.44 (s, 1H), 8.31 (s, 1H), 8.01 (s, 1H), 7.49 (m, 5H), 4.12 (s, 3H), 3.84-3.64 (m, 8H). EM m/z: $(M+H)^+$ calculado para $C_{25}H_{23}N_6O_5$: 487.17; encontrado 487.22. Tiempo de retención CLAR: 1.13 minutos (columna A).



Este procedimiento general se aplica para preparar los ejemplos 121, 122, 123, 124, 155, 157, y 162.

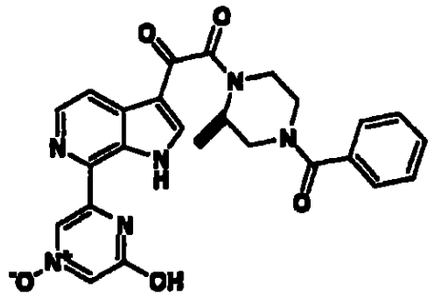
EJEMPLO 121



739

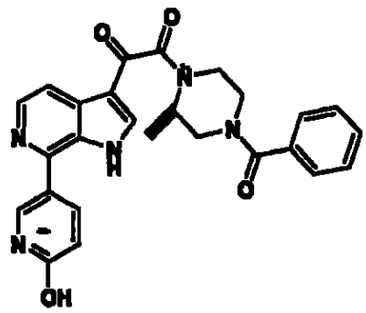
El Ejemplo 121, (R)-1-(benzoil)-3-metil-4-[(4-metoxi-7-(2-hidroxil-pirazin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4$: 471.17; encontrado 471.17. Tiempo de retención CLAR: 1.39 minutos (columna G).

EJEMPLO 121-2



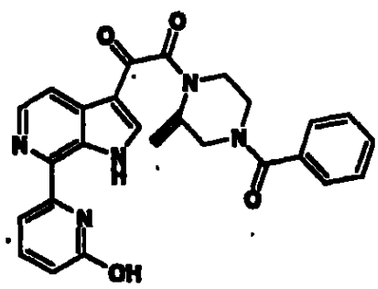
El Ejemplo 121-2, (R)-1-(benzoil)-3-metil-4-[(4-metoxi-7-(2-hidroxil-4-oxo-pirazin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina se aisló durante la preparación del Ejemplo 121. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_5$: 487.17; encontrado 487.17. Tiempo de retención CLAR: 1.08 minutos (columna G).

EJEMPLO 122



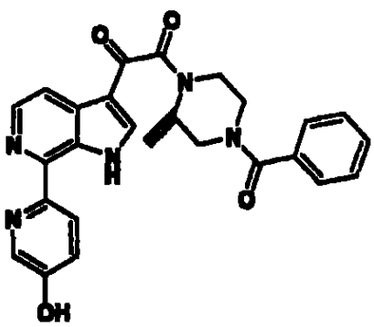
El Ejemplo 122, (R)-1-(benzoil)-3-metil-4-[(4-metoxi-7-(2-hidroxil-piridin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_5O_4$: 470.18; encontrado 470.17. Tiempo de retención CLAR: 1.03 minutos (columna G).

EJEMPLO 123



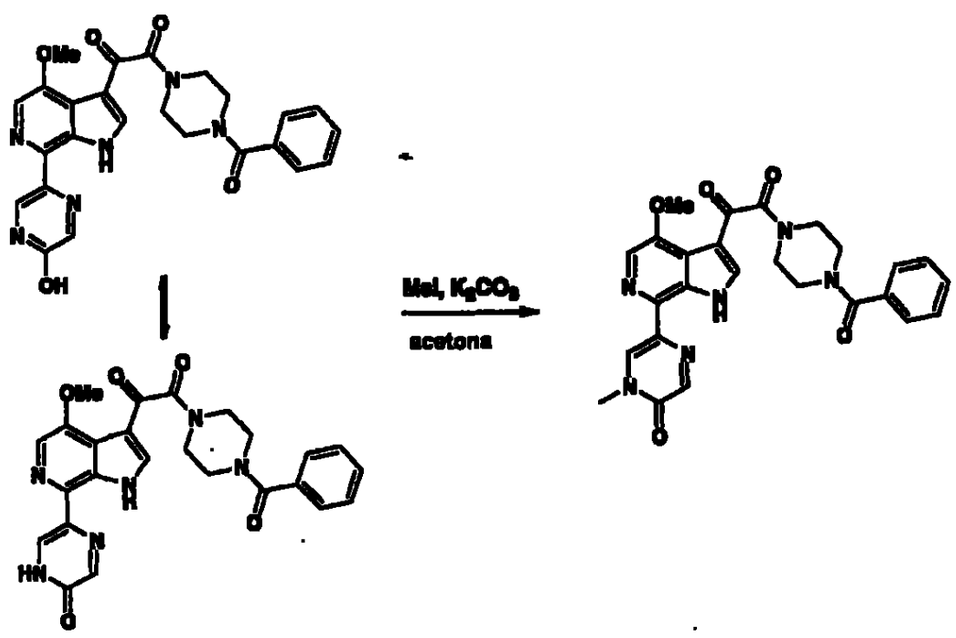
El Ejemplo 123, (R)-1-(benzoil)-3-metil-4-[(4-metoxi-7-(2-hidroxil-piridin-6-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_5O_4$: 470.18; encontrado 470.14. Tiempo de retención CLAR: 1.28 minutos (columna G).

EJEMPLO 124



El Ejemplo 124, (R)-1-(benzoil)-3-metil-4-[(4-metoxi-7-(5-hidroxil-piridin-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}N_5O_4$: 470.18; encontrado 470.13. Tiempo de retención CLAR: 1.21 minutos (columna G).

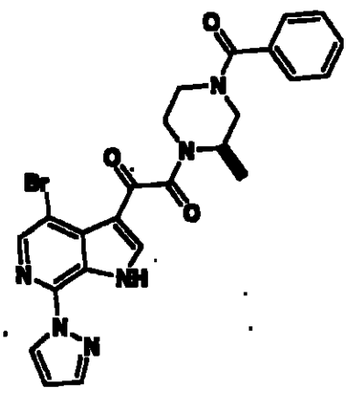
Preparación del Ejemplo 138



Preparación del Ejemplo 138, 1-(benzoil)-4-[(4-metoxi-7-(1-metilpirazin-2-on-5-il)-6-azaindol-3-il)-oxoacetil]piperazina: 1-(benzoil)-4-[(4-metoxi-7-(2-hidroxil-pirazin-5-il)-6-azaindol-3-il)-oxoacetil] piperazina (6 mg), MeI (5 mg) y K_2CO_3 (4 mg) se disolvieron en acetona (5 ml). La reacción se agitó durante cuatro horas a temperatura

ambiente. Después el sólido se filtró nuevamente, el licor madre se concentró para dar un residuo el cual se purificó usando un sistema CLAR preparativo automatizado Shimadzu para suministrar 3.0 mg del compuesto deseado, 1-(benzoil)-4-[(4-metoxi-7-(1-metilpirazin-2-on-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_6O_5$: 501.19; encontrado 501.14. Tiempo de retención CLAR: 1.08 minutos (columna G).

EJEMPLO 139



Precursor 4i se disolvió en DMF (2 ml), y al cual clorohidrato N-benzoil-(R)-metilpiperazina (0.092 g, 0.45 mmol) y 3-(dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona (DEPBT, 0.180 g, 0.60 mmol) se agregaron, seguido por N,N-diisopropiletilamina (0.15 ml, 0.87 mmol). La mezcla de reacción se agitó durante 2 horas a temperatura ambiente, y luego el volátil se evaporó bajo alto vacío. Se agregó agua a la mezcla para inducir la precipitación, y los sólidos se

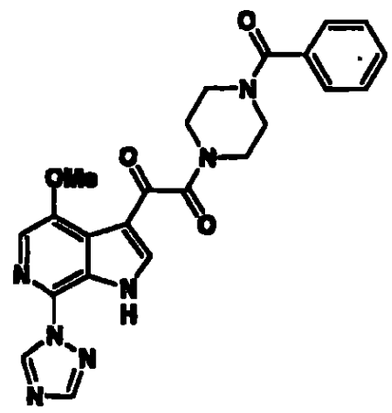
743

filtraron y secaron in vacuo. La purificación del sólido crudo por cromatografía de capa delgada preparativa (5% MeOH/CH_2Cl_2), y subsecuentemente lavando con éter dio el compuesto del título; ^1H RMN: ($CDCl_3$) δ 8.78 (s, 1H), 8.32 (s, 1H), 8.28 (s, 1H) 7.84 (s, 1H), 7.44 (b s, 5H), 6.56 (s, 1H), 5.00-3.00 (b m, 7H), 1.45-1.20 (b s, 3H); CL/EM: (ES+) m/z $(M+H)^+$ = 521, 523; CLAR T_r = 1.677.

Preparación de Derivados Heterocíclicos de Azaindol enlazados a N a partir del Bromuro o Cloruro correspondiente. Un ejemplo de un procedimiento típico:

La condición de reacción general se muestra con la preparación del Ejemplo 187. Otros análogos, ejemplos 188-193, se prepararon por medio de la condición de reacción.

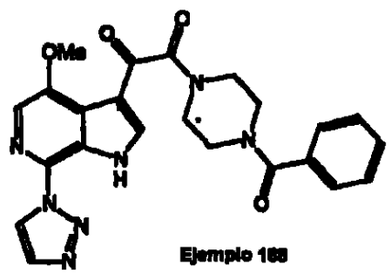
EJEMPLO 187



Preparación de compuesto del Ejemplo 187: Precursor 5b (30 mg), 1,2,4-triazol (145 mg), Cu (4.4 mg) y K_2CO_3 (9.6 mg) se

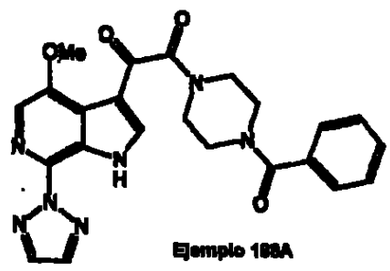
combinaron en un tubo sellado el cual se desgasificó posteriormente estando sellado. La mezcla se calentó a 160°C durante 8 horas. Después de permitir enfriarse bajo temperatura ambiente, la mezcla se diluyó con MeOH (14 ml) y diclorometano (7 ml). Después de la filtración, el filtrado se concentró para dar un residuo el cual se purificó usando un sistema CLAR preparativo automatizado Shimadzu para suministrar 12.9 mg del compuesto deseado 187, 1-benzoil-4-[(4-metoxi-7-(1,2,4-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{22}N_7O_4$: 460.17; encontrado 460.33. Tiempo de retención CLAR: 1.45 minutos (columna J).

EJEMPLO 188 y EJEMPLO 188A



Ejemplo 188

y



Ejemplo 188A

El Ejemplo 188 y 188A, se prepararon de acuerdo con el método general descrito arriba partiendo del precursor 5z y 1,2,3-triazol para suministrar Ejemplo 188 y Ejemplo 188A.

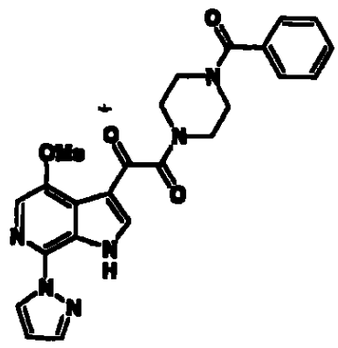
El precursor 5z (0.050 g), 0.050 g polvo Cu, 0.025 g K2CO3 y 6 equivalentes de 1,2,3 triazol se calentaron a 150C durante 16 horas. La reacción se permitió para enfriar a

temperatura ambiente y se disolvió en MeOH y se purificó por CLAR preparativa como se describe arriba en los métodos generales para suministrar el Ejemplo 188 (0.0237 g sólido café, rendimiento 44%) y el otro isomero del Ejemplo 188a.

Ejemplo 188, 1-benzoil-4-[(4-metoxi-7-(1,2,3-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{22}N_7O_4$: 460.17; encontrado 460.34. Tiempo de retención CLAR: 1.50 minutos (columna J); 1.29 minutos (columna L). ^1H RMN (500 MHz, CD_3OD) δ 8.86 (s, 1H), 8.34 (s, 1H), 7.97 (m, 2H), 7.48 (b, 5H), 4.08 (s, 3H), 3.89-3.56 (m, 8H).

Ejemplo 188A, 1-benzoil-4-[(4-metoxi-7-(1,2,3-triazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{22}N_7O_4$: 460.17; encontrado 460.34. Tiempo de retención CLAR: 1.39 minutos (columna J). ^1H RMN (500 MHz, CD_3OD) δ 8.32 (s, 1H), 7.76 (s, 1H), 7.45 (b, 7H), 4.07 (s, 3H), 3.80-3.30 (m, 8H).

EJEMPLO 189

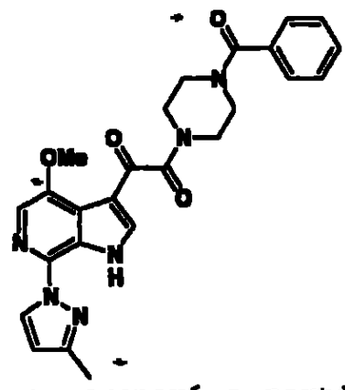


El Ejemplo 189, se preparó a partir del Precursor 5b y pirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(1-

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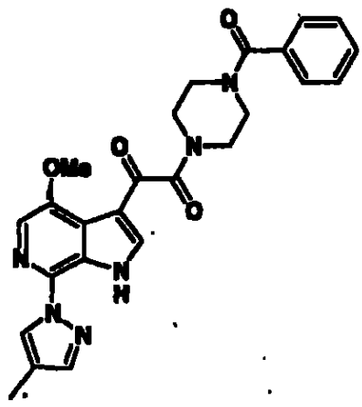
pirazolil)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{24}H_{23}N_6O_4$: 459.18; encontrado 459.01. Tiempo de retención CLAR: 0.92 minutos (columna G).

EJEMPLO 190



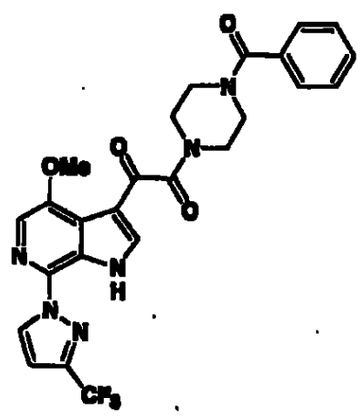
El Ejemplo 190, se preparó a partir del Precursor 5b y 3-metilpirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-metilpirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: . $(M+H)^+$ Calculado para $C_{25}H_{25}N_6O_4$: 473.19; encontrado 473.09. Tiempo de retención CLAR: 1.49 minutos (columna G).

EJEMPLO 191



El Ejemplo 191, se preparó a partir del Precursor 5b y 4-metilpirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(4-metilpirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{25}N_6O_4$: 473.19; encontrado 473.09. Tiempo de retención CLAR: 1.52 minutos (columna G).

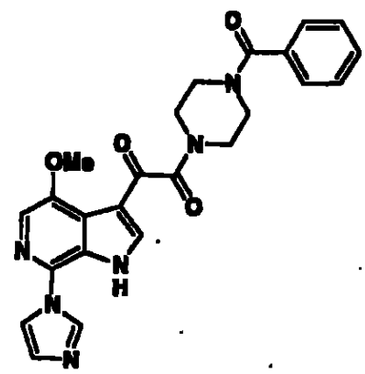
EJEMPLO 192



El Ejemplo 192, se preparó a partir del Precursor 5b y 3-trifluorometilpirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-trifluorometilpirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{22}F_3N_6O_4$: 527.17; encontrado 527.09. Tiempo de retención CLAR: 1.64 minutos (columna G).

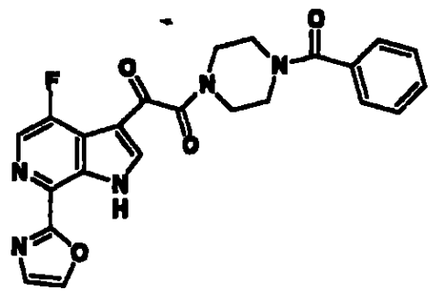
748

EJEMPLO 193



El Ejemplo 193, se preparó a partir del Precursor 5b y imidazol para suministrar 1-benzoil-4-[(4-metoxi-7-(1-imidazolil)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{24}H_{23}N_6O_4$: 459.18; encontrado 459.26. Tiempo de retención CLAR: 1.22 minutos (columna G).

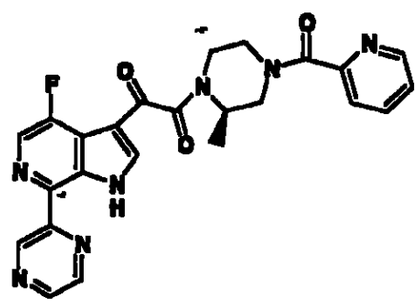
EJEMPLO 140



El compuesto del título se preparó de acuerdo a los procedimientos generales descritos abajo (acoplamiento Sn). H RMN: 8.41 (m, 1H); 8.33 (m, 1H); 8.16 (m, 1H); 7.53 (m, 1H); 7.47 (bs, 5H); 3.97-3.54 (m, 8H). CL/EM: (ES+) m/z $(m+H)^+$ = 448, Tr = 1.28 min.

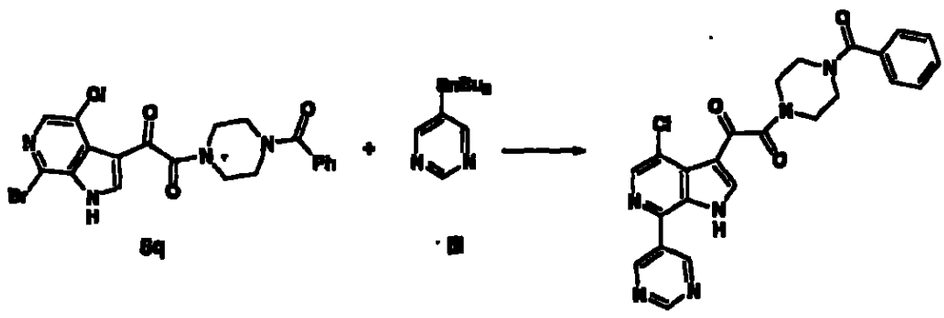
749

EJEMPLO 141



El compuesto del título se preparó de acuerdo a los procedimientos generales descritos abajo (acoplamiento Sn). ^{1}H-RMN: 9.71-9.70 (m, 1H); 8.80-8.79 (m, 1H); 8.66-8.42 (m, 2H); 8.41-8.35 (m, 2H); 7.99-7.92 (m, 1H), 7.69-7.53 (m, 1H); 7.48-7.44 (m, 1H); 5.05-3.15 (m, 8H). CL/EM: (ES+) m/z $(m+H)^+$ = 474. T_r = 1.26 min.

EJEMPLO 144

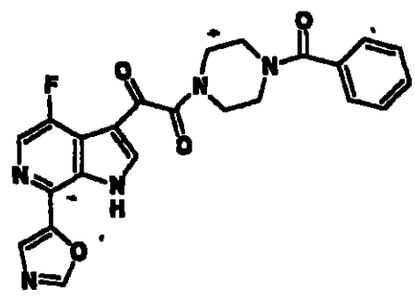


Preparación del Ejemplo 144:

A una mezcla del Precursor 5q (50 mg, 105 µmol) y $Pd(PPh_3)_4$ (50 mg, 43 µmol) se agregó 1,4-dioxano (1 ml) y iii (77 mg, 210 µmol). La mezcla de reacción se calentó en un tubo sellado a 145°C durante 16 horas.

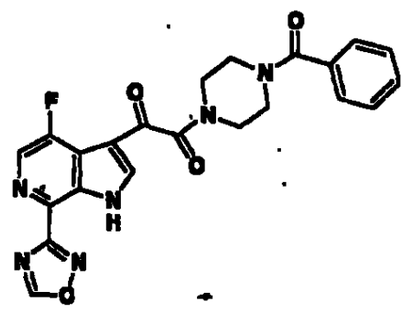
Después del enfriamiento a temperatura ambiente, a la mezcla de reacción se agregó MeOH (4 ml) y luego se filtró. El filtrado se purificó por CLAR de fase inversa para dar la sal TFA del compuesto del título al usar el método: Inicio % B = 15, Final % B = 100, Tiempo de gradiente = 20 min, Relación de flujo = 25 ml/min, Columna: YMC C18 SUM 20 x 100 mm, Fracción colectada: 11.80-12.31 min. ^{1}H RMN: (CD_3OD) δ 9.32 (s, 1H), 9.25 (s, 2H), 8.50 (s, 1H), 8.44 (s, 1H), 7.47 (b s, 5H), 4.00-3.44 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 475, 477; CLAR T_r = 1.833.

EJEMPLO 145



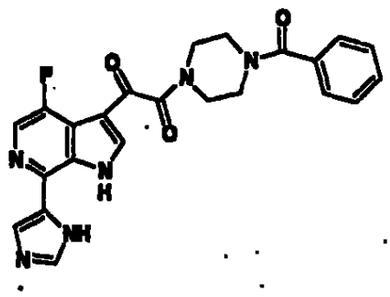
El compuesto del título se preparó siguiendo el procedimiento descrito abajo para el ejemplo 146 y el precursor 4k. ^{1}H RMN: 8.35-8.33 (m, 2H); 8.11 (s, 1H); 7.89 (s, 1H); 7.43 (bs, 5H); 3.89-3.49 (m, 8H). CL/EM: (ES+) m/z $(M+H)^+$ = 448. T_r = 1.18 min.

EJEMPLO 146



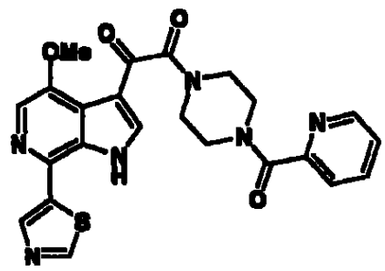
El precursor 4m (0.26 mmol) se disolvió en DMF (1 mL) y se trató con clorohidrato de N-benzoilpiperazina (59 mg, 0.26 mmol), DEBPT (79 mg, 0.26 mmol) y base Hunig (90 µL, 0.52 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. El solvente se removió in vacuo y el residuo se purificó por CLAR preparativa de fase inversa. Las fracciones mostraron CL/EM: (ES+) m/z $(M+H)^+$ = 449 correcta, se colectaron, concentraron y purificaron nuevamente al usar CCD preparativa (5% $MeOH/CH_2Cl_2$) para resultar el compuesto del título como un sólido blanco. ^{1}H-RMN (500 MHz, $CDCl_3$) δ 10.7 (s, 1H), 9.00 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 7.45 (M, 5H), 3.9-3.5 (bm, 8H).

EJEMPLO 148



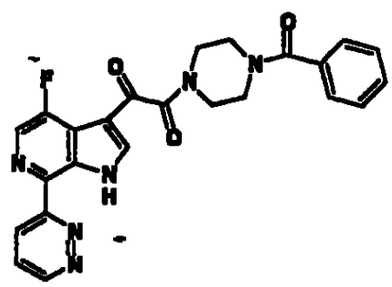
El compuesto del título se preparó a partir del precursor 4n al usar las mismas condiciones de acoplamiento descritas para la última etapa de la preparación del Precursor 5i. ^{1}H RMN: 8.82 (m, 1H); 8.48-8.45 (m, 1H); 8.37-8.33 (m, 1H); 8.26-8.23 (m, 1H); 7.47 (bs, 5H); 3.97-3.54 (m, 8H). CL/EM: (ES+) m/z $(m+H)^+$ = 447 T_r. = 0.94 min.

EJEMPLO 151



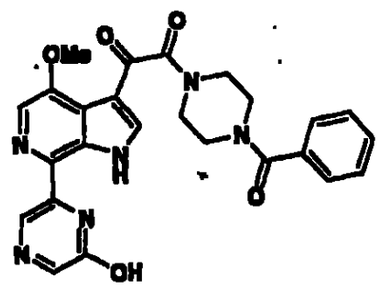
El Ejemplo 151, se preparó a partir del Precursor 51 y el estanano tiazol-5-il para suministrar 1-picolinoil-4-[(4-metoxi-7-(tiazol-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{21}N_6O_4S$: 477.13; encontrado 477.13. Tiempo de retención CLAR: 0.94 minutos (columna G).

EJEMPLO 154



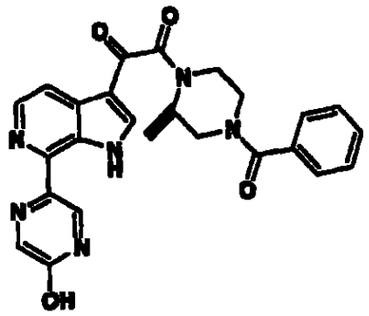
El compuesto del título se preparó de acuerdo a los procedimientos generales descritos abajo (acoplamiento Sn). ^{1}H-RMN: 9.23-9.22 (m, 1H); 8.83-8.81 (m, 1H); 8.43 (m, 1H); 8.36 (m, 1H); 7.75-7.73 (m, 1H), 7.44 (bs, 5H); 3.85-3.49 (m, 8H). CL/EM: (ES+) m/z $(M+H)^+$ = 459. T_r = 1.39 min.

EJEMPLO 155



El Ejemplo 155, 1-(benzoil)-4-[(4-metoxi-7-(2-hidroxil-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_5$: 487.17; encontrado 487.14. Tiempo de retención CLAR: 1.30 minutos (columna G).

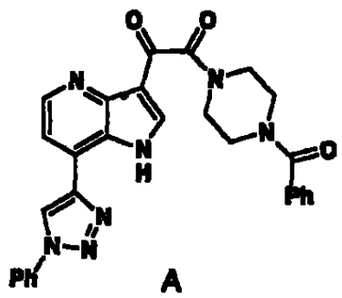
EJEMPLO 157



Ejemplo 157, (R)-1-(benzoil)-3-metil-4-[(4-metoxi-7-(5-hidroxil-pirazin-2-il)-6-azaindol-3-il)-

oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4$: 471.18; encontrado 471.16. Tiempo de retención CLAR: 1.09 minutos (columna G).

EJEMPLO 161

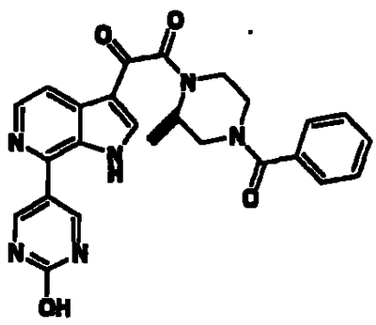


A

$C_{28}H_{23}N_7O_3$
Masa Exacta: 505.19
Peso Mol: 505.53

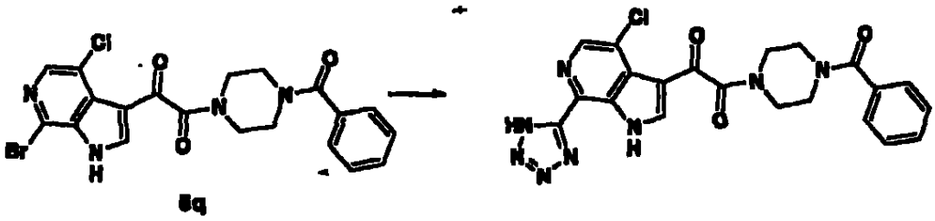
Ejemplo 161 se preparó a partir del precursor 5p y 3-fenil-5-tributilestanil-1,2,3-triazol al usar el procedimiento general de acoplamiento con estaño proporcionado previamente: ^{1}H RMN (500 MHz, DMSO) δ 9.67 (s, 1H), 8.81 (s, 1H), 8.72 (d, J = 5.4 Hz, 1H), 8.25 (d, J = 6.1 Hz, 1H), 8.00 (dd, J = 8.2, 1.8 Hz, 1H), 7.68 (dd, J = 8.2, 7.4 Hz, 2H), 7.60 (tt, J = 7.4, 1.8 Hz, 2H), 7.48 (br s, 5H), 4.04-3.46 (m, 8H). EM m/z: $(M+H)^+$ calculado para $C_{28}H_{24}N_7O_3$: 506.19; encontrado 506.15. Tiempo de retención CLAR: 1.21 minutos (XTERRA C18 S7 3.0 x 50 mm)).

EJEMPLO 162



El Ejemplo 162, (R)-1-(benzoil)-3-metil-4-[(4-metoxi-7-(2-hidroxil-pirimidin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{23}N_6O_4$: 471.18; encontrado 471.13. Tiempo de retención CLAR: 0.95 minutos (columna G).

EJEMPLO 163

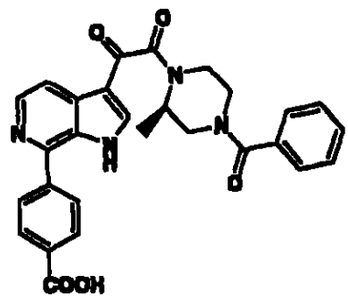


5q

A una solución del precursor 5q (50 mg, 0.11 mmol) en DMF (1 ml) se agregó CuCN (30 mg, 0.335 mmol). La mezcla de reacción se calentó a 170°C durante 30 min. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se diluyó con MeOH (15 ml), se filtró bajo gravedad, y el filtrado se evaporó in vacuo para resultar un residuo tono café el cual es un cianoprecursor. Al residuo en DMF (1 ml)

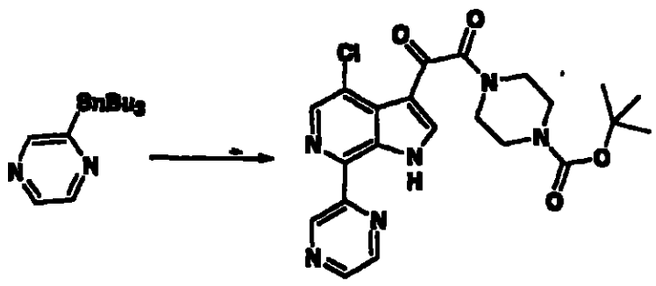
se agregó azida de sodio (61 mg, 0.95 mmol) y cloruro de amonio (50 mg, 0.95 mmol). La mezcla se calentó a 90°C durante una hora. La mezcla de reacción luego se diluyó con MeOH (4 ml), se filtró, y el filtrado se purificó por CLAR de fase inversa preparativa al usar el método: Inicio % B = 20, Final % B = 80, Tiempo de gradiente = 15 min, Relación de flujo = 40 ml/min, Columna: XTERRA C18 5 um 30 x 100 mm, Fracción colectada: 11.26-11.71 min. El material se hizo homogéneo por ^{1}H RMN y CLAR, no obstante el espectro de masa indicó un pico extra a $(M+H)^+$ = 431; ^{1}H RMN: (CD_3OD) 8.41 (s, 1H), 8.12 (s, 1H), 7.47 (b s, 5H), 3.97-3.47 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$ = 465, 467; CLAR T_r = 1.937

EJEMPLO 164



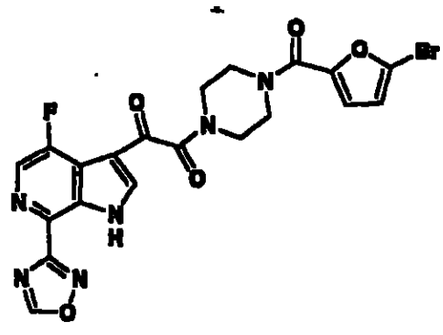
El Ejemplo 164, se preparó a partir del precursor 5a y el ácido 4-hidroxicarbonilfenil borónico para suministrar 1-benzoil-4-[7-(4-hidroxicarbonilfenil)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{25}N_4O_5$: 497.18; encontrado 497.22. Tiempo de retención CLAR: 1.20 minutos (columna C).

EJEMPLO 165



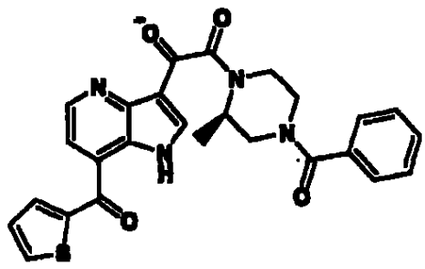
El compuesto del Ejemplo 165 se preparó en una forma similar al compuesto del Ejemplo 143 partiendo con precursor 5r, pero a 125°C durante 22 horas y la purificación por cromatografía de capa delgada preparativa (4% $MeOH/CH_2Cl_2$). ^1H RMN: ($CDCl_3$) δ 11.85 (s, 1H), 9.91 (d, J = 1.6 Hz, 1H), 8.70 (d, J = 2.6 Hz, 1H), 8.65 (dd, J = 1.6, 2.6 Hz, 1H), 8.52 (s, 1H), 8.35 (d, J = 3.1 Hz, 1H), 3.73 (b m, 2H), 3.56 (b m, 4H), 3.53 (b m, 2H), 1.48 (s, 9H); CL/EM: (ES+) m/z $(M+H)^+$ = 471, 473; CLAR T_r = 1.690.

EJEMPLO 167



El precursor 4m (0.098 mmol) se disolvió en DMF (1 mL) y se trató con clorohidrato N-[5-(2-bromofuroil)]piperazina (30 mg, 0.098 mmol), DEBPT (60 mg, 0.19 mmol) y base Hunig (70 µL, 0.19 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. El solvente se removió in vacuo y el residuo se purificó por CLAR preparativa de fase inversa. Las fracciones mostraron la CL/EM: (ES+) m/z $(M+H)^+$ = 518, 520 correcta, se recolectaron, concentraron y purificaron nuevamente al usar un TLC preparativo (5% $MeOH/CH_2Cl_2$) para resultar el compuesto del título como un sólido blanco. ^1H-RMN (500 MHz, $CDCl_3$) δ 10.7 (s, 1H), 9.00 (s, 1H), 8.54 (s, 1H), 8.40 (s, 1H), 7.06 (d, J = 3.4 Hz, 1H), 6.46 06 (d, J = 3.4 Hz, 1H), 3.90-3.66 (bm, 8H).

EJEMPLO 168



El Ejemplo 168, 1-benzoil-3-(R)-metil-4-[(7-(2-tienilcarbonil)-4-azaindol-3-il)-oxoacetil]piperazina, se preparó a partir de una reacción 1-benzoil-3-(R)-metil-4-[(7-

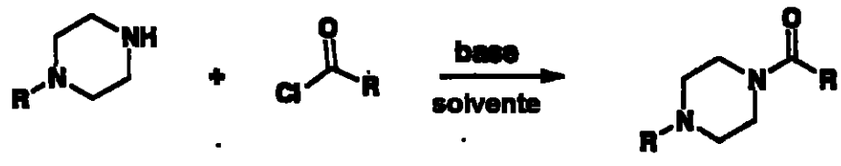
759

(metoximetilamino)carbonil)-4-azaindol-3-il)-oxoacetil]piperazina y 2-tienil litio al usar el mismo procedimiento para la preparación de I-64, 1-benzoil-3-(R)-metil-4-[(7-(2-propinil)carbonil-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{23}N_4O_4S$: 487.14; encontrado 487.11. Tiempo de retención CLAR: 1.31 minutos (columna A).

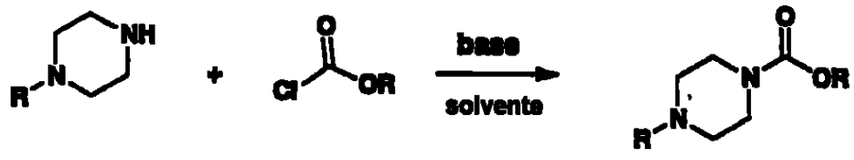
Procedimiento general para la preparación de amidas o carbamidas de piperazina:

El átomo de nitrógeno libre de piperazina se puede ocultar como amidas o carbamidas por medio de reacciones de piperazina con haluros de acilo, ácidos de acilo o formatos de halo acilo, los cuales se muestran en los siguientes esquemas de reacción 80 y 81.

Esquema de reacción 80

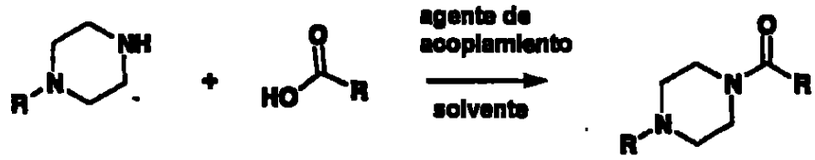


base = Et_3N, IPr_2NEt, piridina, DBU, DMAP
solvente = THF, éter, CH_2Cl_2, DMF, dioxano, benceno



base = Et_3N, IPr_2NEt, piridina, DBU, DMAP
solvente = THF, éter, CH_2Cl_2, DMF, dioxano, benceno

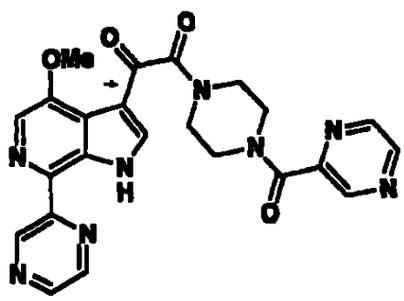
Esquema de reacción 81



agente de acoplamiento = DDC, EDAC, DEBPT
solvente = THF, éter, CH_2Cl_2, dioxano, DMF, benceno

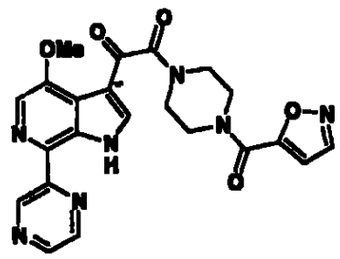
Los Ejemplos 195-199 se prepararon por medio de un procedimiento que se demostró en el Esquema de reacción 80. El procedimiento típico se presenta en la síntesis del Ejemplo 195.

EJEMPLO 195



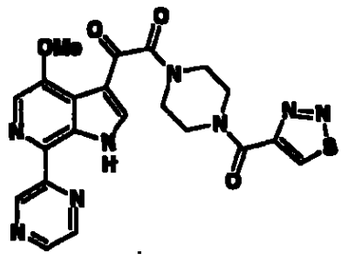
Ejemplo 195: Precursor 5u (40 mg), cloruro de piperazin carbonilo (50 mg) y I-Pr_2NEt (0.2 g) se combinaron en 1 ml de THF. Después de que la reacción se agitó a temperatura ambiente durante 16 horas, la mezcla se concentró in vacuo para dar un residuo el cual se purificó usando un sistema CLAR preparativa automatizado Shimadzu para suministrar el compuesto deseado 195 (4.7 mg). EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{21}N_8O_4$: 473.17; encontrado 473.42. Tiempo de retención CLAR: 1.14 minutos (columna C).

EJEMPLO 196



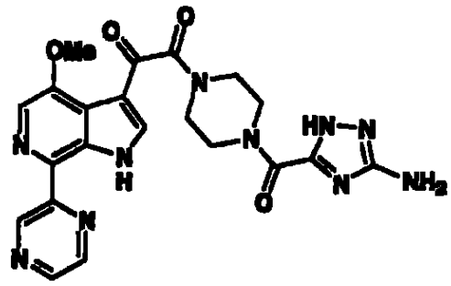
Ejemplo 196, se preparó a partir del Precursor 5u y cloruro de 4-isoxazol carbonilo. EM m/z: $(M+H)^+$ calculado para $C_{22}H_{20}N_7O_5$: 462.15; encontrado 462.41. Tiempo de retención CLAR: 1.09 minutos (columna C).

EJEMPLO 197



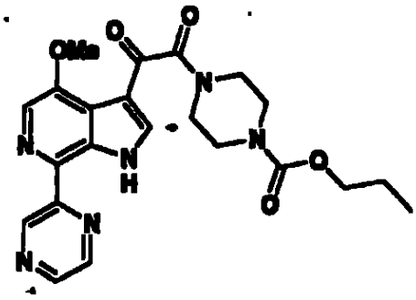
Ejemplo 197, se preparó a partir del Precursor 5u y cloruro de 4-(1,2,3-tiodiazol)-carbonilo. EM m/z: $(M+H)^+$ Calculado para $C_{21}H_{19}N_8O_4S$: 479.12; encontrado 479.31. Tiempo de retención CLAR: 1.17 minutos (columna C).

EJEMPLO 198



Ejemplo 198, se preparó a partir del Precursor 5u y cloruro de 5-(3-amino-1,2,4-triazol)-carbonilo. EM m/z: $(M+H)^+$ Calculado para $C_{21}H_{21}N_{10}O_4$: 477.17; encontrado 477.36. Tiempo de retención CLAR: 0.97 minutos (columna C).

EJEMPLO 199

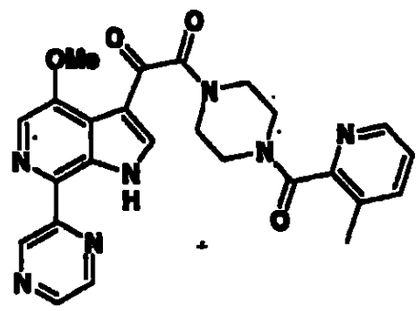


Ejemplo 199, se preparó a partir del Precursor 5u y cloro formato de propanilo. EM m/z: $(M+H)^+$ Calculado para $C_{22}H_{25}N_6O_5$: 453.19; encontrado 453.17. Tiempo de retención

CLAR: 1.53 minutos (columna M).

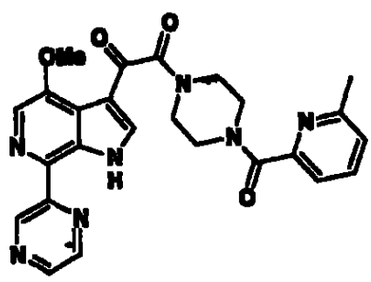
Los Ejemplo 200-201 se prepararon por medio de un procedimiento demostrado en el esquema de reacción 81. El procedimiento típico se presentó en la síntesis del Ejemplo 200.

EJEMPLO 200



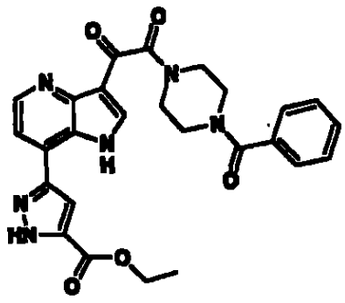
Ejemplo 200: ácido 3-metil-2-picolínico (140 mg), EDAC (190 mg) pentafluorofenol (180 mg) se combinaron en DMF, y, la reacción se agitó durante 12 horas. El precursor 3u se agregó entonces y la mezcla resultante se agitó a temperatura ambiente durante otras 16 horas. Los solventes se removieron in vacuo para dar un residuo el cual se purificó usando un sistema CLAR preparativa automatizado Shimadzu para suministrar el compuesto deseado 200 (28 mg). EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 486.14. Tiempo de retención CLAR: 1.08 minutos (columna G).

EJEMPLO 201



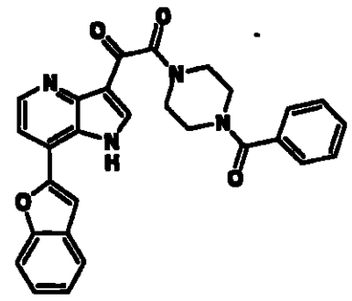
Ejemplo 201, se preparó a partir del Precursor 5u y ácido 6-metil-2-picolínico. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 486.28. Tiempo de retención CLAR: 1.44 minutos (columna G).

EJEMPLO 202



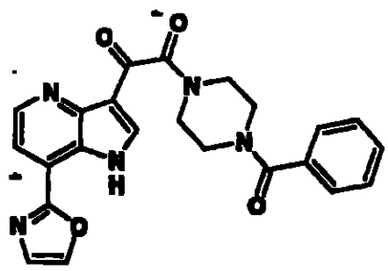
El Ejemplo 202, se preparó a partir del Precursor 5p y el carboxilato de pirazol-5-il etilo estanano para suministrar éster de etilo del ácido 5-{3-[2-(4-benzoil-piperazin-1-il)-2-oxo-acetil]-1H-pirrolo[3,2-b]piridin-7-il}-2H-pirazol-3-carboxílico. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_6O_5$: 501.18; encontrado 501.13. Tiempo de retención CLAR: 1.14 minutos (columna G).

EJEMPLO 203



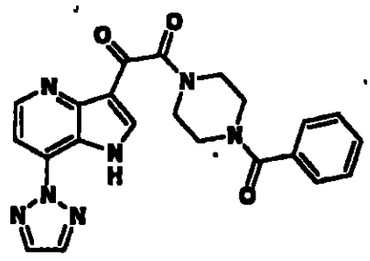
El Ejemplo 202, se preparó a partir del Precursor 5p y el benzofuran-2-il estanano para suministrar 1-(7-benzofuran-2-il-1H-pirrolo[3,2-b]piridin-3-il)-2-(4-benzoil-piperazin-1-il)-etano-1,2-diona. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{21}N_4O_4$: 479.16; encontrado 479.07. Tiempo de retención CLAR: 1.31 minutos (columna G).

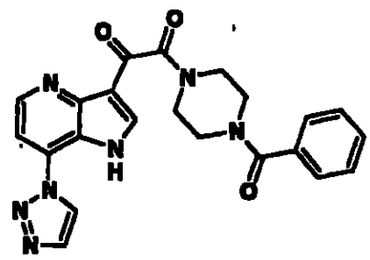
EJEMPLO 204



El Ejemplo 204, se preparó a partir del Precursor 5p y el oxazol-2-il estanano para suministrar 1-benzoil-4-[7-(oxazol-2-il)-4-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{23}H_{20}N_5O_4$: 430.14; encontrado 430.07. Tiempo de retención CLAR: 2.08 minutos (columna E, gradiente de 10 minutos).

EJEMPLO 205 y EJEMPLO 206

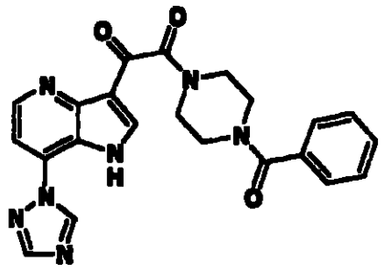




Ejemplo 205 y 206. En un tubo sellado se calentaron -(4-benzoil-piperazin-1-il)-2-(7-cloro-1H-pirrolo[3,2-b]piridin-3-il)-etano-1,2-diona (30 mg, 0.076 mmol), 1H-1,2,3-triazol (160 mg, 2.3 mmol), Cu(0) (10 mg, 0.16 mmol) y K_2CO_3 (11 mg, 0.080 mmol) a 160°C durante 16 horas. La mezcla de reacción se diluyó con MeOH, se filtró a través de celite y se concentró. La mezcla de reacción se diluyó con MeOH, se filtró a través de celite y se concentró. El residuo se purificó por preparación CLAR para suministrar 1-(4-benzoil-piperazin-1-il)-2-(7-[1,2,3]triazol-2-il-1H-pirrolo[3,2-b]piridin-3-il)-etano-1,2-diona: ^{1}H RMN (300 MHz, CD_3OD) δ 8.79 (d, J = 6.6 Hz, 1H), 8.79 (s, 1H), 8.48 (d, J = 6.6 Hz, 1H), 8.40 (s, 2H), 7.48 (br s, 5H), 4.00-3.55 (m, 8H). EM m/z $(M+H)^+$ Calculado para $C_{22}H_{20}N_7O_3$: 430.15; encontrado 430.29. Tiempo de retención CLAR 0.91 min (columna G); y 1-(4-benzoil-piperazin-1-il)-2-(7-[1,2,3]triazol-1-il-1H-pirrolo[3,2-b]piridin-3-il)-etano-1,2-diona: ^{1}H RMN (300 MHz, CD_3OD) δ 8.97 (d, J = 81.2 Hz, 1H), 8.70 (d, J = 5.6 Hz, 1H), 8.48 (s, 1H), 8.06 (d, J = 1.2 Hz, 1H), 7.80 (d, J = 5.6 Hz,

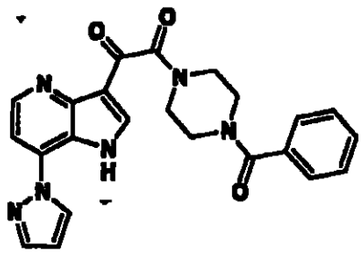
1H), 7.47 (br s, 5H), 4.00-3.45 (m, 8H). EM m/z $(M+H)^+$ calculado para $C_{22}H_{20}N_7O_3$: 430.15; encontrado 430.29. Tiempo de retención CLAR 0.90 min (columna G).

EJEMPLO 207



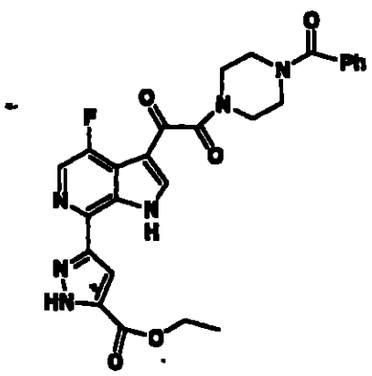
El Ejemplo 207, se preparó como en el Ejemplo 205 del Precursor 5p y 1,2,4-triazol para suministrar 1-(4-benzoil-piperazin-1-il)-2-(7-[1,2,4]triazol-1-il-1H-pirrolo[3,2-b]piridin-3-il)-etano-1,2-diona. ^1H RMN (300 MHz, CD_3OD) δ 9.73 (s, 1H), 8.82 (d, J=6.6 Hz, 1H), 8.77 (s, 1H), 8.55 (s, 1H), 8.32 (d, J=6.6 Hz, 1H), 7.48 (br s, 5H), 4.00-3.45 (m, 8H). EM m/z $(M+H)^+$ Calculado para $C_{22}H_{20}N_7O_3$: 430.15; encontrado 430.27. Tiempo de retención CLAR 0.87 min (columna G).

EJEMPLO 208



El Ejemplo 208, se preparó como en el Ejemplo 205 del Precursor 5p y pirazol para suministrar 1-(4-benzoil-piperazin-1-il)-2-(7-pirazol-1-il-1H-pirrolo[3,2-b]piridin-3-il)-etano-1,2-diona. ^{1}H RMN (300 MHz, CD_3OD) δ 8.87 (d, J = 2.7 Hz, 1H), 8.70 (s, 1H), 8.68 (d, J = 6.6 Hz, 1H), 8.18 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 6.6 Hz, 1H), 7.48 (br s, 5H), 6.85 (dd, J = 2.7, 1.5 Hz, 1H), 4.00-3.50 (m, 8H). EM m/z $(M+H)^+$ calculado para $C_{23}H_{21}N_6O_3$: 429.16; encontrado 429.23. Tiempo de retención CLAR 0.87 min (columna G).

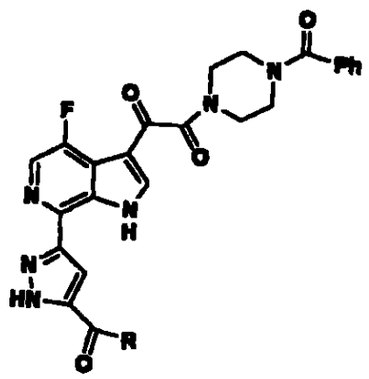
EJEMPLO 209



El compuesto del Ejemplo 209 se preparó de acuerdo con el método general antes descrito a partir del precursor 5i y etil éster-5-tributilestaño pirazol-3-carboxílico preparado como se describe en la siguiente referencia: Heterociclos, 1992, 33(2), 813-18. Después del enfriamiento a temperatura ambiente, la mezcla de reacción se concentró in vacuo. El residuo se filtró a través de papel filtro

y se lavó con metanol. El sólido amarillo resultante se secó en aire para suministrar el Compuesto X; ^{1}H RMN (500 MHz, $CDCl_3$): 8.33 (s, 1H); 8.31 (s, 1H); 7.66 (s, 1H); 7.46-7.39 (m, 5H); 4.47-4.42 (q, 2H); 3.98-3.45 (m, 8H); 1.43-1.40 (t, 3H). CL/EM: (ES+) m/z $(M+H)^+$ = 519. T_r = 1.43 min.

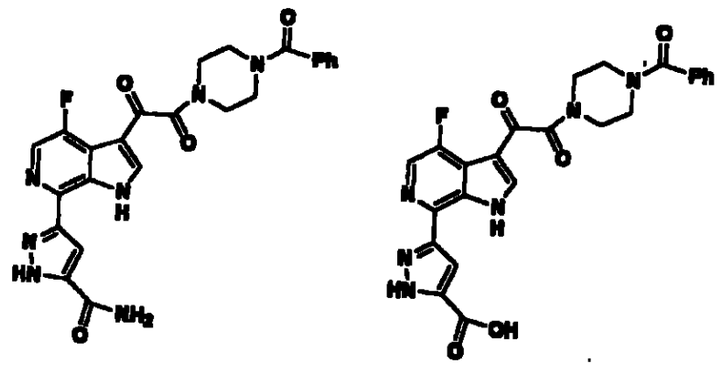
EJEMPLOS 210-213



Procedimiento general para la preparación de los ejemplos 210-213

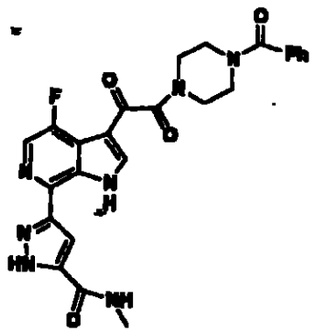
El compuesto del ejemplo 209 se trató con un exceso (>5eq.) de la amina correspondiente y se agitó en un tubo sellado a temperatura ambiente o 70°C (R = NH_2) por 20 hr. La solución resultante se concentró en un evaporador rotatorio y se purificó por CLAR preparativa de fase inversa.

EJEMPLOS 210 y 214



Los compuestos del ejemplo 210 y 214 se prepararon del compuesto del ejemplo 209 e hidróxido de amonio siguiendo el procedimiento arriba descrito. X1a: ^{1}H RMN (500 MHz, CD_3OD_3): 8.40-8.37 (m, 1H); 8.28-8.27 (m, 1H); 7.58-7.39 (m, 6H); 3.97-3.43 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$= 490. Tr = 1.14 min. X1b: 8.43 (s, 1H); 8.29 (s, 1H); 7.56 (s, 1H); 7.45-7.55 (m, 5H); 3.99-3.45 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$= 491. Tr= 1.12 min.

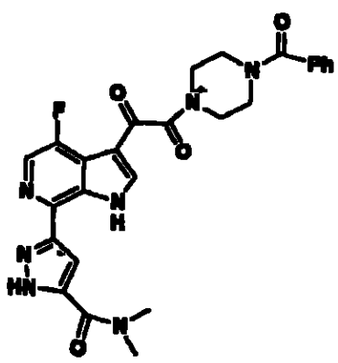
EJEMPLO 211



El compuesto del ejemplo 211 se preparó a partir del compuesto del ejemplo 209 y metilamina siguiendo el procedimiento arriba descrito. ^{1}H RMN (500 MHz, CD_3OD_3): 8.43

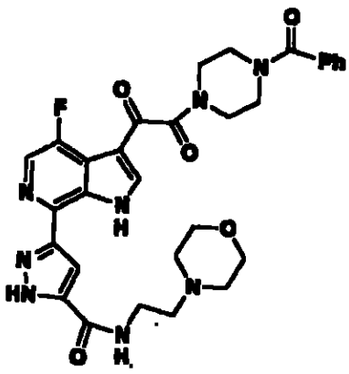
(s, 1H); 8.31 (s, 1H); 7.49 (bs, 5H); 7.45 (s, 1H) 3.97-3.48 (m, 8H); 2.97 (s, 3H). CL/EM: (ES$^+$) m/z (M+H)$^+$= 504. Tr= 1.31 min.

EJEMPLO 212



El compuesto del ejemplo 212 se preparó a partir del compuesto del ejemplo 209 y dimetilamina siguiendo el procedimiento arriba descrito. CL/EM: (ES$^+$) m/z (M+H)$^+$= 518. Tr= 122 min.

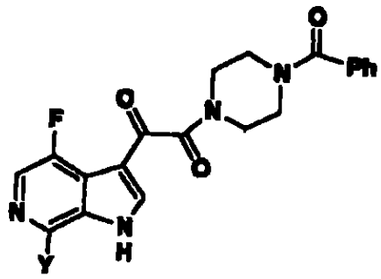
COMPUESTO 213



El compuesto del ejemplo 213 se preparó a partir del compuesto del ejemplo 209 y N-aminoetilmorfolina siguiendo el

procedimiento arriba descrito. ^1H RMN (500 MHz, CD_3OD_3): 8.41 (s, 1H); 8.31 (s, 1H); 7.52-7.49 (m, 6H); 4.19-3.20 (m, 20H); CL/EM: (ES^+) m/z $(M+H)^+$= 603. Tr= 1.03 min.

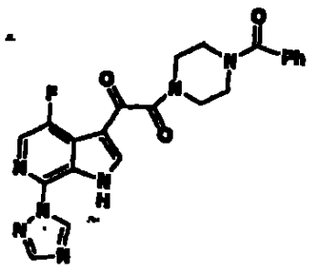
COMPUESTOS DE LOS EJEMPLOS 215-222



Procedimiento general para la preparación de los compuesto de los ejemplos 215-222

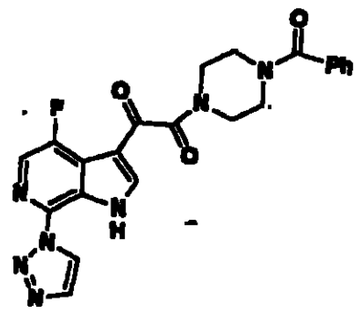
Una mezcla del precursor 5i, 30 equivalentes de la amina correspondiente, 1 equivalente de polvo de cobre y 1 equivalente de carbonato de potasio se calentó a 160°C por 4-7 hr en un tubo sellado. La reacción se enfrió hasta temperatura ambiente y se filtró a través de papel filtro. El filtrado se diluyó con metanol y se purificó por CLAR preparativa.

EJEMPLO 215



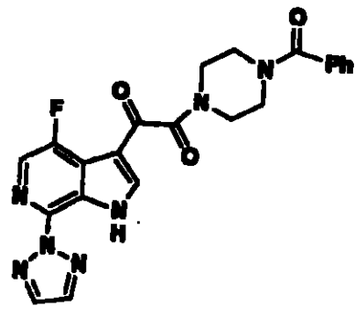
El ejemplo 215 se preparó a partir del precursor 5i y 1,2,4-triazol siguiendo el procedimiento arriba descrito. ^1H RMN (500 MHz, $CDCl_3$): 11.15 (bs, 1H); 9.28 (s, 1H); 8.33-8.34 (m, 1H); 8.22 (s, 1H); 8.10 (s, 1H); 7.46-7.42 (m, 5H); 3.90-3.48 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$= 448. Tr = 1.21 min.

EJEMPLO 216



El ejemplo 216 se preparó a partir del precursor 5i y 1,2,3-triazol siguiendo el procedimiento arriba descrito. ^1H RMN (500 MHz, $CDCl_3$): 11.16 (bs, 1H); 8.75 (s, 1H); 8.37-8.37 (s, 1H); 8.15 (s, 1H); 7.92 (s, 1H); 7.43 (bs, 5H); 3.99-3.48 (m 8H). CL/EM: (ES^+) m/z $(M+H)^+$= 448. Tr= 1.28 min.

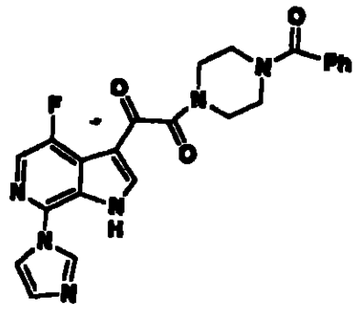
EJEMPLO 217



El ejemplo 217 se preparó a partir del precursor 5i y

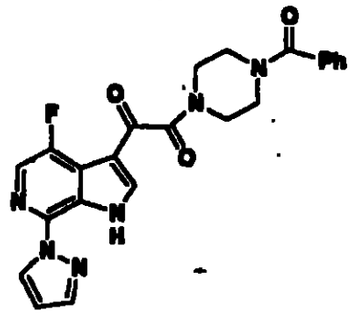
1,2,3-triazol siguiendo el procedimiento arriba descrito. ^{1}H RMN (500 MHz, $CDCl_3$): 11.12 (bs, 1H); 8.78-8.77 (m, 1H); 8.37-8.36 (m, 1H); 8.02-8.0 (m, 2H); 7.45-7.41 (m, 5H); 4.11-3.45 (m, 8H). CL/EM: (ES$^+$) m/z $(M+H)^+$= 448. Tr= 1.03 min.

EJEMPLO 218



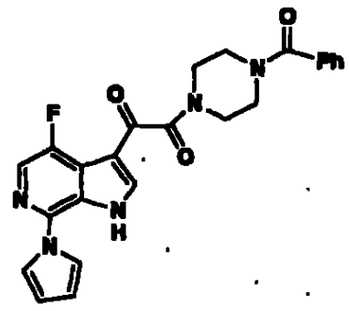
El ejemplo 218 se preparó a partir del precursor 5i e imidazol siguiendo el procedimiento arriba descrito. ^{1}H RMN (500 MHz, $CDCl_3$): 13.35 (bs, 1H); 9.49 (s, 1H); 8.35-8.30 (m, 1H); 8.20 (s, 1H); 7.97 (s, 1H); 7.56-7.53 (m, 1H); 7.46-7.41 (m, 5H); 3.98-3.40 (m, 8H). CL/EM: (ES$^+$) m/z $(M+H)^+$= 447. Tr= 1.25 min.

EJEMPLO 219



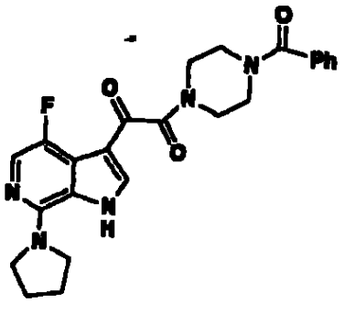
El ejemplo 219 se preparó a partir del precursor 5i y pirazol siguiendo el procedimiento arriba descrito. ^{1}H RMN (500 MHz, $CDCl_3$): 11.52 (bs, 1H); 8.65-8.64 (m, 1H); 8.27-8.26 (m, 1H); 8.05-8.04 (m, 1H); 7.81-7.80 (m, 1H); 7.50-7.35 (m, 5H); 6.54-6.53 (m, 1H); 4.01-3.47 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$= 447. Tr= 1.25 min.

EJEMPLO 220



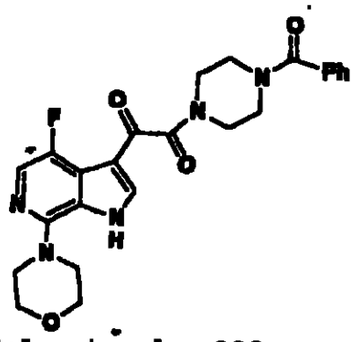
El ejemplo 220 se preparó a partir del precursor 5i y pirrol siguiendo el procedimiento arriba descrito. ^{1}H RMN (300 MHz, CD_3OD_3): 8.33-8.29 (m, 2H); 7.49-7.40 (m, 5H); 7.38-7.37 (m, 2H); 6.42-6.41 (m, 2H); 3.91-3.40 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$= 446. Tr= 1.34 min.

EJEMPLO 221

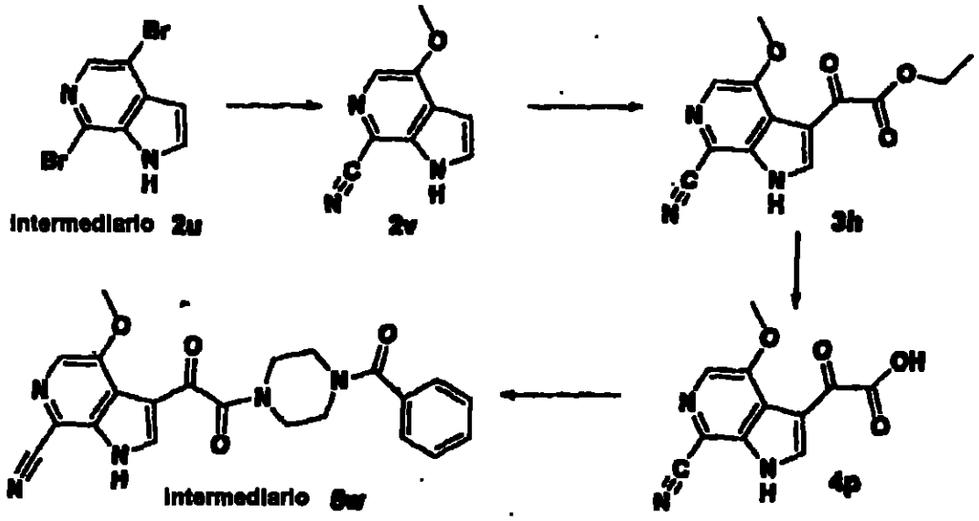


El ejemplo 221 se preparó a partir del precursor 5i y pirrolidina siguiendo el procedimiento arriba descrito. ^{1}H RMN (300 MHz, CD_3OD_3): 8.37 (s, 1H); 7.61-7.59 (m, 1H); 7.51-7.38 (m, 5H); 4.08-3.23 (m, 12H); 2.25-2.15 (m, 4H). CL/EM: (ES$^+$) m/z $(M+H)^+$= 450. Tr= 0.89 min.

EJEMPLO 222



El compuesto del ejemplo 222 se preparó a partir del precursor 5i y morfolina siguiendo el procedimiento arriba descrito. ^{1}H RMN (300 MHz, CD_3OD_3): 8.38 (s, 1H); 7.86-7.84 (m, 1H); 4.14-3.25 (m, 16H). CL/EM: (ES$^+$) m/z $(M+H)^+$= 466. Tr= 0.988 min.



Preparación del precursor 5w:

A una mezcla de 2u (2.0 g, 7.3 mmol) y CuCN (1.0 g, 11 mmol) se agregó DMF (20 ml). La mezcla de reacción se calentó a 150°C por 1 hora. Después de enfriar a temperatura ambiente, a la mezcla de reacción se agregó NaOMe (20 ml, 25 % peso en solución de MeOH), y se calentó a 110°C por 10 minutos. Después de enfriar a temperatura ambiente, la mezcla de reacción se vació en una solución acuosa de acetato de amonio (sat. 500 ml). La mezcla resultante se filtró a través de una almohadilla corta de Celite®. El filtrado se extrajo con EtOAc (500 ml x 4). Los extractos combinados se secaron sobre $MgSO_4$ y evaporaron in vacuo para dar un residuo color café, que se trituró con MeOH (5 ml x 3) para proporcionar el precursor 2v como un sólido amarillo (317 mg, 25%). La estructura se soportó por los experimentos NOE. ^1H RMN: (DMSO-d_6) 12.47 (s, 1H), 8.03 (s, 1H), 7.65 (t, J=2.8, 1H), 6.70 (dd, J=2.8, 1.8, 1H), 4.08 (s, 3H); CL/EM: (ES^+) m/z $(M+H)^+$= 174; CLAR (condiciones alternas B, columna G) Tr= 1.320.

Preparación del precursor 3h:

Al cloruro de 1-etil-3-metilimidazolio (85 mg, 0.58 mmol) en un vial cerrado se le agregó rápidamente cloruro de aluminio (231 mg, 1.73 mmol). La mezcla se agitó vigorosamente a temperatura ambiente hasta la formación de

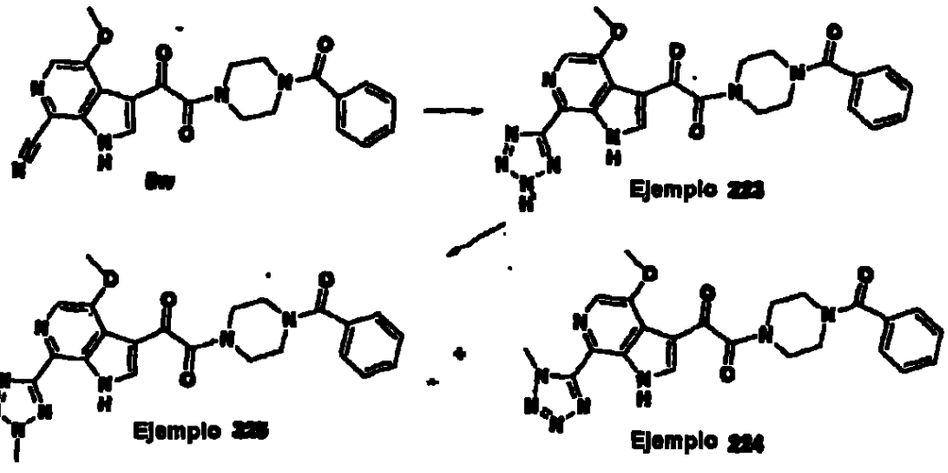
líquido iónico. Después de enfriar a temperatura ambiente, el líquido iónico se agregó el compuesto 2v (50 mg, 0.29 mmol) y etil clorooxoacetato (0.2 ml, 1.79 mmol). La mezcla de reacción se agitó a temperatura ambiente por tres horas, se enfrió a 0°C y se apagó cuidadosamente al agregar hielo -agua (15 ml). Los precipitados se filtraron, se lavaron con agua (5 ml x 3) y se secaron in vacuo para dar 3h como un sólido amarillo grisáceo (50 mg, 63%). ^{1}H RMN: (DMSO-d_6) 13.73 (s, 1H), 8.54 (s, 1H), 8.26 (s, 1H), 4.35 (q, J=7.0, 2H), 4.06 (s, 3H), 1.29 (t, J=7.0, 3H); CL/EM: (ES+) m/z $(M+H)^+$= 274; CLAR (condiciones alternas B, columna G) Tr= 1.527.

Preparación del precursor 4p:

A una mezcla de 3h (200 mg, 0.73 mmol) en MeOH (1 ml) se agregó NaOH (2.5 ml, 1N acuoso). La mezcla de reacción se agitó a temperatura ambiente por 30 minutos, y luego se acidificó con ácido clorhídrico (1N, ~3 ml) a un pH de alrededor de 2. El sólido se filtró, se lavó con agua (5 ml x 4), y se secó in vacuo para dar 4p como un sólido de tono café (160 mg, 89%). El compuesto 4p se usó directamente en la siguiente reacción sin purificación adicional. CL/EM: (ES+) m/z $(M+H)^+$= 246; CLAR (condiciones alternas B, columna G) Tr= 0.777.

Preparación del precursor 5w;

A una mezcla de 4p (160 mg, 0.65 mmol), DEPBT (390 mg, 1.31 mmol) y clorhidrato de benzoilpiperazina (222 mg, 0.98 mmol) se agregó DMF (2 ml) y N,N-diisopropiletilamina (1.2 ml, 6.9 mmol). La mezcla de reacción se agitó a temperatura ambiente por 16 horas, y se concentró para retirar la mayoría del solvente. El residuo se diluyó con MeOH (10 ml) y luego se filtró. El filtrado se purificó por CLAR preparativa de fase inversa usando el método: Inicio %B = 15, Final %B = 70, Tiempo de gradiente = 30 min, Relación de flujo = 40 ml/min, Longitud de onda = 220 nm. Columna: XTERRA C18 5 µm 30 x 100 mm, A = 10% MeOH,- 90% H_2O-0.1% TFA, B = 90% MeOH-10% H_2O-0.1% TFA, Recolección de la fracción: 14.03-15.43 min. La estructura se soportó por experimentos NOE. ^1H RMN: (DMSO-d_6) 13.66 (s, 1H), 8.45 (s, 1H), 8.25 (s, 1H), 7.45 (s, 5H), 4.07 (s, 3H), 3.80-3.40 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$= 418 CLAR (condiciones alternas B, columna G) Tr= 1.447.



Preparación del ejemplo 223:

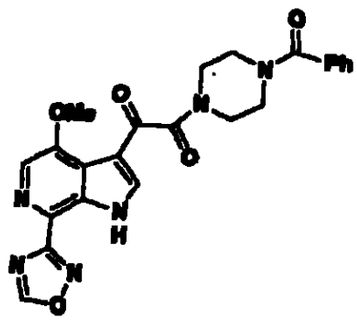
A una mezcla de 5w (15 mg, 0.036 mmol), NaN_3 (24 mg, 0.36 mmol), y NH_4Cl (19 mg, 0.36 mmol) se agregó DMF (1 ml). La mezcla de reacción se calentó a 100°C por tres horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se agregó MeOH (4 ml) y luego se filtró. El filtrado se purificó por CLAR preparativa de fase inversa usando el método: Inicio %B =15, Final %B = 75, Tiempo de gradiente = 15 min. Relación de flujo = 40 ml/min. Longitud de Onda = 220 nm. Columna: XTERRA C18 5 µm 30 x 100 mm, A = 10% MeOH, -90% H_2O-0.1% TFA, B=90% MeOH-10% H_2O-0.1% TFA, Recolección de la fracción: 8.48-9.78 min. ^1H RMN: (DMSO-d_6) 12.68 (b s, 1H), 8.26 (s, 1H), 8.24 (s, 1H), 7.46 (s, 5H), 4.09 (s, 3H), 3.86-3.30 (b m, se traslapó con un pico amplio de agua, 8H), no se observó un protón intercambiable debido a la presencia de agua en la muestra. CL/EM: (ES+) m/z $(M+H)^+$= 461 CLAR (condiciones alternas B, columna G) Tr= 1.392.

Preparación de los ejemplos 224 y 225:

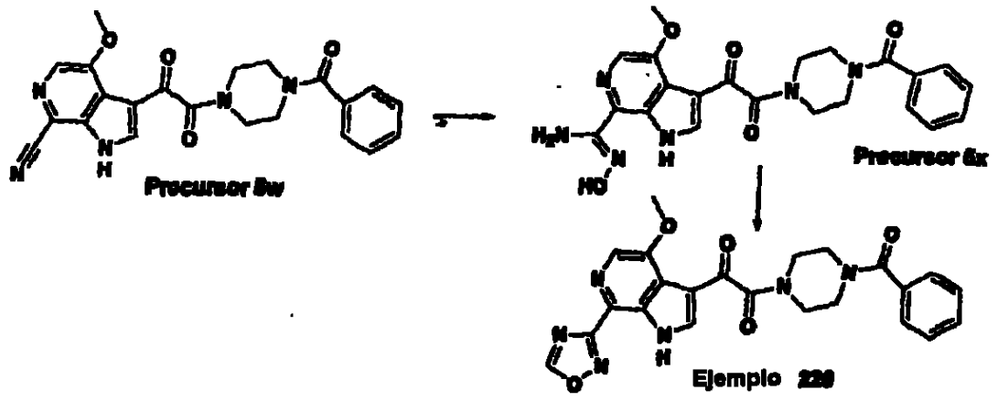
A la mezcla de 5w (10 mg, 0.022 mmol) en MeOH (0.2 ml) y benceno (0.4 ml) se agregó $TMSCHN_2$ (0.4 ml, 0.1 M*). La mezcla de reacción se agitó a temperatura ambiente por 1.5 horas, seguido por la purificación sobre CCD preparativa (1 x 20 x 20 cm, 500 micras) con 10% $MeOH/CH_2Cl_2$ para dar los dos compuesto como

sólidos blancos. El ejemplo 224 (2.7 mg, 26%); ^{1}H RMN: (DMSO-d_6) 12.60 (b s, 1H), 8.31 (s, 1H), 8.23 (s, 1H), 7.46 (s, 5H), 4.50 (s, 3H), 4.15 (s, 3H), 3.80-3.30 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$= 475, CLAR (condiciones alternas B, columna G) Tr= 1.672. El ejemplo 225 (1.4 mg, 13%), ^{1}H RMN: (DMSO-d_6) 12.40 (b s, 1H), 8.22 (s, 1H), 8.20 (s, 1H), 7.46 (s, 5H), 4.52 (s, 3H), 4.04 (s, 3H), 3.80-3.30 (b m, 8H); CL/EM: (ES+) m/z $(M+H)^+$= 475, CLAR (condiciones alternas B, columna G) Tr= 1.373. Estas dos estructuras se soportan además por análisis de nitrógeno HMBC. *$TMSCHN_2$ (0.1 M) se preparó al diluir $TMSCHN_2$ comercialmente disponible (0.2 ml, 2.0 M) con hexano (3.8 ml).

EJEMPLO 226



Esquema de Reacción para la prep del ejemplo 226



Preparación del ejemplo 226

A una mezcla de 5w (85 mg, 0.204 mmol) y clorhidro de hidroxilamina (22 mg, 0.305 mmol) en etanol anhidro (3 ml, 200 grado) se agregó trietilamina (60 µl, 0.4 mmol). La mezcla de reacción se calentó en un vial cerrado a 100°C por 6 horas. La separación del solvente dio el precursor 5x como un sólido blanco, al cual se agregó trietil ortoformiato (3 ml). La mezcla luego se calentó en un vial cerrado a 100°C por 12 horas. Después de separar la mayoría del exceso del trietil ortoformiato, el residuo se diluyó con MeOH (6 ml), seguido por filtración. El filtrado se purificó por CLAR preparativa de fase inversa usando el método: Inicio %B = 30, Final %B = 50, Tiempo de gradiente = 20 min. Relación de flujo = 40

ml/min, Columna: XTERRA C18 5 µm 30 x 100 mm; Recolección de la fracción: 7.57-7.98 min. ^{1}H RMN (DMSO-d_6) 12.41 (s, 1H), 9.87 (s, 1H), 8.27 (s, 1H), 8.24 (s, 1H), 7.45 (s, 5H), 4.06 (s, 3H), 3.68-3.20 (b m, traslape con un pico de agua amplio, 8H); Las siguientes condiciones CLAR para la LCMS analítica se usaron: Columna: Xterra C18 S7 3 x 50 mm; Tiempo de gradiente = 3 min; Relación de flujo = 4 ml/min. CL/EM: (ES+) m/z $(M+H)^+$= 461 CLAR Tr= 1.390. El producto de una corrida similar suministró los siguientes espectros 1H RMN (metanol-d6) δ 9.32 (s, 1H), 8.28 (s, 2H), 7.83 (s, 1H), 7.45 (multiplete estrecho, 6H), 4.05 (s,3H), 3.80 (bm, 4H), 3.56 (bm, 4H).

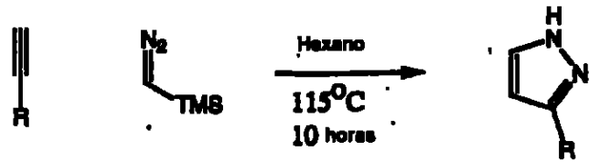
EJEMPLOS 227 al 229

Los ejemplos 227 al 230 (Tabla 2-1) se preparó de manera análoga al ejemplo 194 excepto que se utilizó la piperazina apropiada substituida. La preparación de las piperazinas apropiadas substituidas se describe para los precursores 17a-d o en la referencia 90b.

Procedimientos generales para la preparación de pirazoles

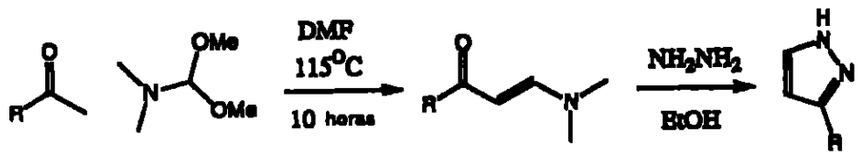
los pirazoles 3-Substituidos se pueden preparar por medio de las siguientes rutas:

Ruta *P-A*



El alquino (1 eq.) se disolvió en una solución de 2 M de diazometano (5-10 eq.) en hexano y la mezcla resultante se calentó a 110-115°C durante 12 horas. Después la reacción se apagó con MeOH, la remoción de los solventes proporcionó un residuo el cual se usó en la siguiente etapa sin ninguna purificación.

Ruta *P-B*

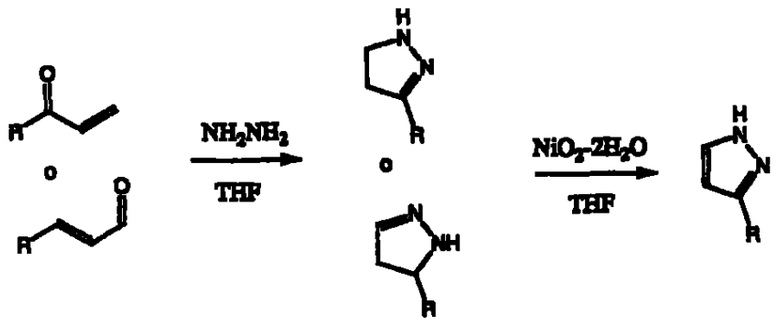


La metil cetona (1 eq.) se agregó en una solución de dimetoxi-DMF (5-10 eq.) en DMF y la mezcla resultante se calentó a 110-115°C durante 12 horas. Los solventes luego se removieron bajo vacío para suministrar un residuo.

El residuo anterior se mezcló con hidrazina (5-10 eq.)

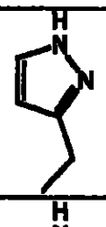
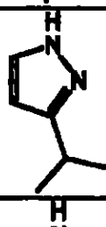
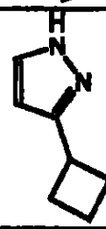
en etanol y la reacción se mantuvo en reflujo durante 12 horas. La eliminación de los solventes in vacuo dio un residuo, el cual se llevó a cabo en las reacciones adicionales sin purificación.

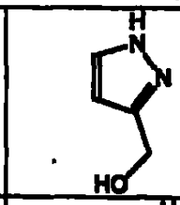
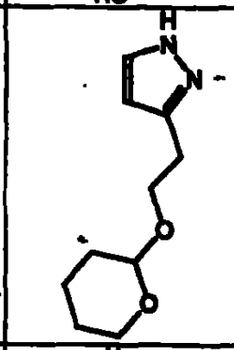
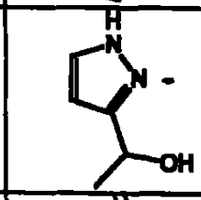
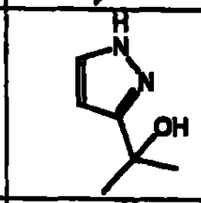
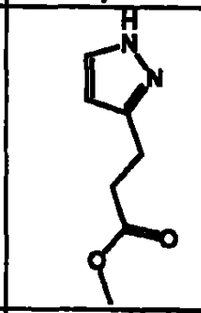
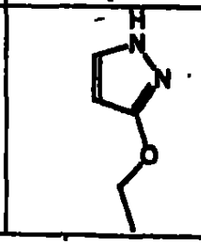
Ruta P-C

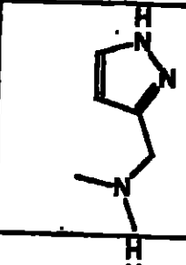
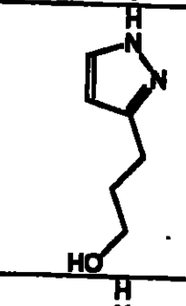
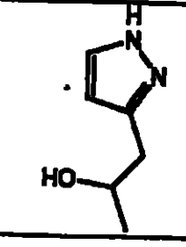


La hidrazina (10-20 eq.) se agregó en una solución de alquenona o alquenal (1 eq.) en THF y la mezcla resultante se calentó a 110-115°C durante 12 horas. Después de que la mezcla se enfrió bajo temperatura ambiente, un exceso de NiO2-2H2O (5-10 eq.) luego se agregó en la mezcla de reacción y la reacción se agitó a temperatura ambiente durante otras 12 horas. Los materiales insolubles luego se filtraron y la concentración bajo vacío proporcionó un residuo que se usó en las reacciones adicionales sin purificación.

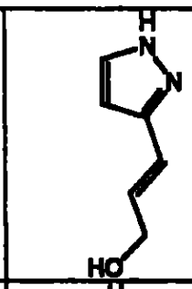
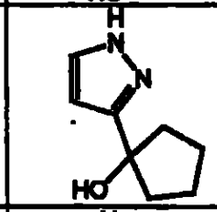
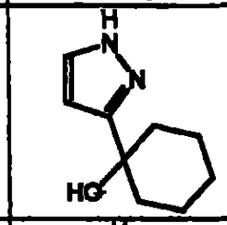
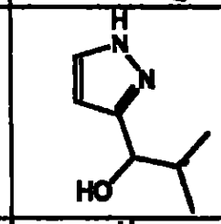
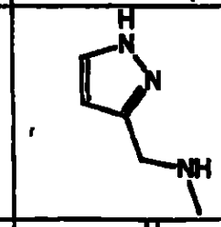
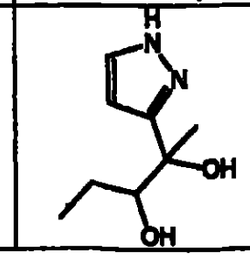
Tabla I-5 Preparación de Pirazoles

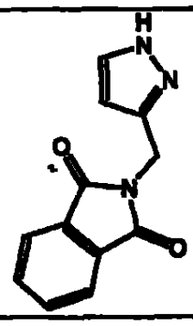
Compuesto*	Estructura	Método usado	CLAR R_t (columna)/MS $(M+H)^+$ o $(M+Na)^+$
Pirázol-001		P-A	0.35 min (columna L)
Pirazol -002		P-A	0.59 min (columna L)
Pirazol-003		P-A	1.07 min (columna L) / EM $(M+H)^+$: Calculado 139.12 Encontrado 139.18
Pirazol-004		P-A, P-B, P-C	0.53 min (columna L)
Pirazol-005		P-B	0.48 min (columna L)
Pirazol-006		P-A	0.63 min (columna L)

Pirazol-007		P-A	0.21 min (columna G)
Pirazol-008		P-A	0.81 min (columna L) / EM (M+H)$^+$: Calculado 197.13 Encontrado 197.18
Pirazol-009		P-A	
Pirazol-010		P-A	0.34 min (columna L)
Pirazol-011		P-A	0.47 min (columna L) / EM (M+H)$^+$: Calculado 155.08 Encontrado 155.06
Pirazol-012		P-A	0.38 min (columna G)

Pirazol-013		P-A	
Pirazol-014		P-A	
Pirazol-015		P-A	0.26 min (columna L) / EM (M+Na)$^+$: Calculado 149.07 Encontrado 149.11
Pirazol-016		P-A	0.31 min (columna L) / EM (M+H)$^+$: Calculado 141.10 Encontrado 141.17
Pirazol-017		P-A	0.27 min (columna L) / EM (M+Na)$^+$: Calculado 149.07 Encontrado 149.13

789

Pirazol-018		P-A	0.22 min (columna L)
Pirazol-019		P-A	0.61 min (columna L) / EM $(M+Na)^+$: Calculado 175.08 Encontrado 175.14
Pirazol-020		P-A	0.79 min (columna L) / EM $(M+Na)^+$: Calculado 189.10 Encontrado 189.17
Pirazol-021		P-A	0.59 min (columna L) / EM $(M+H)^+$: Calculado 141.10 Encontrado 141.18
Pirazol-022		P-A	0.22 (columna L)
Pirazol-023		P-A	0.34 min (columna L) / EM $(M+Na)^+$: Calculado 193.10 Encontrado 193.14

Pirazol-024		P-A	1.05 min (columna L) / EM (M+H)+: Calculado 228.08 Encontrado 228.14

Procedimiento general Si-Cu

Procedimiento general para ocultar silicio para enlazar pirazoles, imidazoles y triazoles con puntos de fusión mayores a 160°C hasta C-7 de la posición de azaindoles:

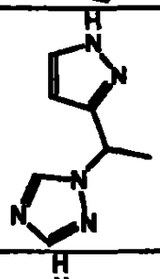
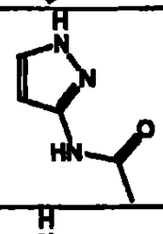
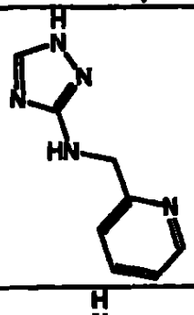
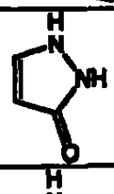
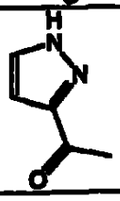
En los casos en donde los puntos de fusión del heterociclo de nitrógeno para ser enlazado al azaindol tiene puntos de fusión mayores que 160°C, un exceso del heterociclo (usualmente mayor de 3 equivalentes) se calentó con un exceso mayor de hexametidisilazano o cloro trimetilsilano (> 10 equivalentes) a temperaturas arriba de 140°C por aproximadamente 12 horas. El reactivo silante en exceso se elimina in vacuo y la mezcla se combina con el haluro de azaindol y la reacción catalizada de cobre se lleva a cabo como a continuación.

Una mezcla de intermediario halo-indol o halo-azaindol, 1-2 equivalentes de polvo de cobre, con 1

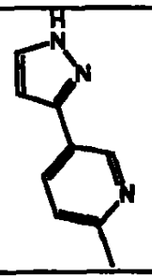
equivalente preferido para la serie de 4-F, 6-azaindol y 2 equivalentes para las series 4-metoxi, 6-azaindol; 1-2 equivalentes de carbonato de potasio, y el reactivo heterocíclico sililado correspondiente como se preparó anteriormente, se calentó a 135-160°C durante 4 hasta 9 horas, con 5 horas a 160°C preferido para las series 4-F, 6-azaindol y 7 horas a 135°C preferido para las series 4-metoxi, 6-azaindol. La mezcla de reacción se enfrió a temperatura ambiente y se filtró a través de papel filtro. El filtrado se diluyó con metanol y se purificó ya sea por CLAR preparativa o gel de sílice. En muchos casos no es necesaria la cromatografía, el producto se puede obtener por cristalización con metanol.

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Tabla I-6 Heterociclos que contienen N aplicados bajo el procedimiento general Si-Cu (condiciones para ocultar silicio)

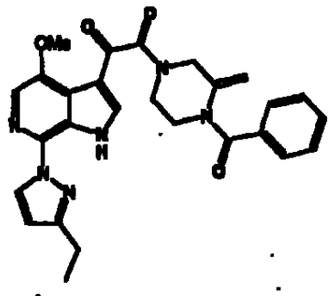
Entrada	Heterociclo que contiene N
HM-01	
HM-02	
HM-03	
HM-04	
HM-05	
HM-06	

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HM-07	

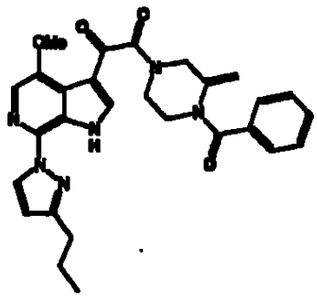
Los Ejemplos 230 hasta el Ejemplo 258, se prepararon usando las mismas condiciones y el método usado para sintetizar el Ejemplo 187:

EJEMPLO 230



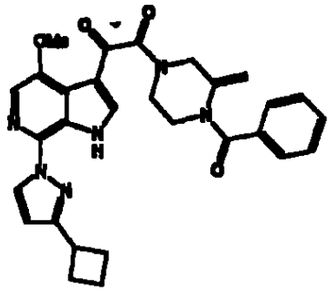
El Ejemplo 230, se preparó de acuerdo con el método general antes descrito a partir del Precursor 5z y Pirazol-001 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-etil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{29}N_6O_4$: 501.23; encontrado 501.17. Tiempo de retención CLAR: 2.30 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

EJEMPLO 231



El Ejemplo 231, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y Pirazol-002 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-propil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{31}N_6O_4$: 515.24; encontrado 515.19. Tiempo de retención CLAR: 2.47 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

EJEMPLO 232

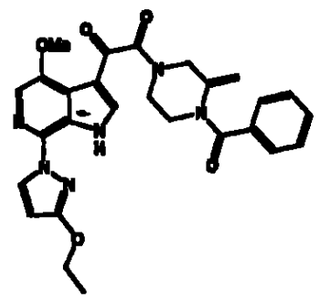


El Ejemplo 232, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y Pirazol-006 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-ciclobutil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{31}N_6O_4$:

795

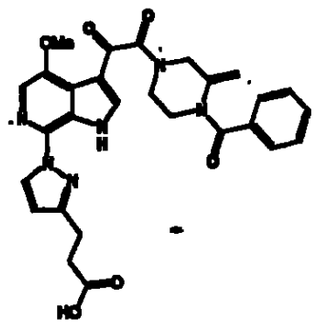
527.24; encontrado 527.16. Tiempo de retención CLAR: 2.53 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

EJEMPLO 233



El Ejemplo 233, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y Pirazol-012 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-etoxi-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{29}N_6O_5$: 517.22; encontrado 517.17. Tiempo de retención CLAR: 2.26 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

EJEMPLO 234

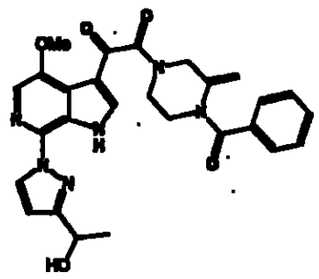


El Ejemplo 234, se preparó de acuerdo con el método

796.

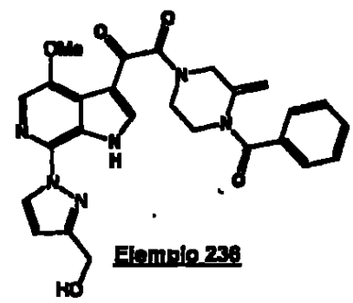
general antes descrito a partir del precursor 5z y pirazol-011 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-(2-hidroxilcarboniletan-1-il)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado de $C_{28}H_{29}N_6O_6$: 545.21; encontrado 545.15. Tiempo de retención CLAR: 2.08 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

EJEMPLO 235



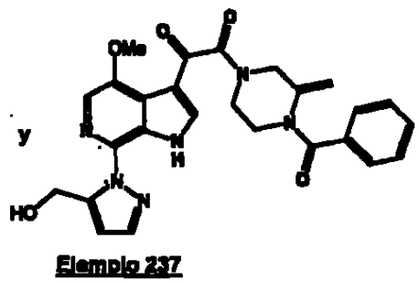
El Ejemplo 235, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y pirazol-009 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-(1-hidroxiletil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{27}H_{29}N_6O_5$: 517.22; encontrado 517.15. Tiempo de retención CLAR: 1.43 minutos (columna G).

EJEMPLOS 236 y 237



Ejemplo 236

y



Ejemplo 237

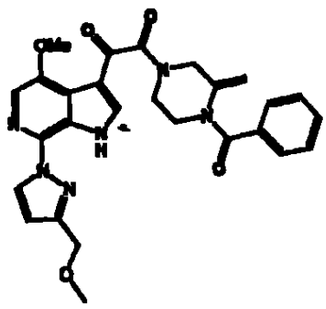
Los ejemplos 236 y 237, se prepararon de acuerdo al método general antes descrito a partir del precursor 5z y Pirazol-007 para suministrar el Ejemplo 236, (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-hidroxilmetil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina y el Ejemplo 237, (R)-1-benzoil-3-metil-4-[(4-metoxi-7-(4-hidroxilmetil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina.

Ejemplo 236, (R)-1-benzoil-3-metil-4-[(4-metoxi-7-(3-hidroxilmetil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina: EM m/z: $(M+H)^+$ calculado por $C_{26}H_{27}N_6O_5$: 503.20; encontrado 503.20. Tiempo de retención CLAR: 1.87 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

Ejemplo 237, (R)-1-benzoil-3-metil-4-[(4-metoxi-7-(4-hidroxilmetil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina: EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{27}N_6O_5$: 503.20; encontrado 503.25. Tiempo de retención CLAR: 1.31 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

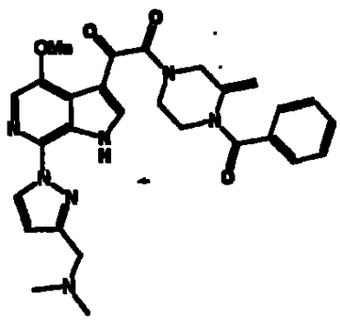
798

EJEMPLO 238



El Ejemplo 238, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y Pirazol-013 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-metoximetil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{29}N_6O_5$: 517.22; encontrado 517.23. Tiempo de retención CLAR: 1.95 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

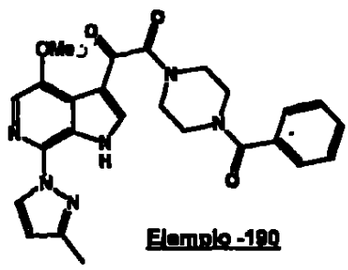
EJEMPLO 239



El Ejemplo 239, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y Pirazol-014 para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-(N,N-dimetilamino)metil-pirazol-1-il)-6-azaindol-3-il)-

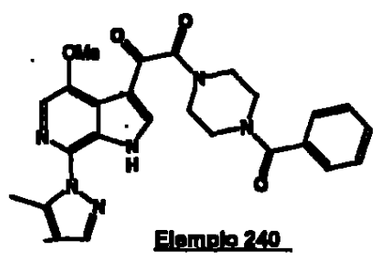
oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{28}H_{32}N_7O_4$: 530.25; encontrado 530.25. Tiempo de retención CLAR: 1.45 minutos (columna G, relación de flujo 4 ml/min, tiempo de gradiente 3 min).

EJEMPLOS 190 Y 240



Ejemplo -190

y



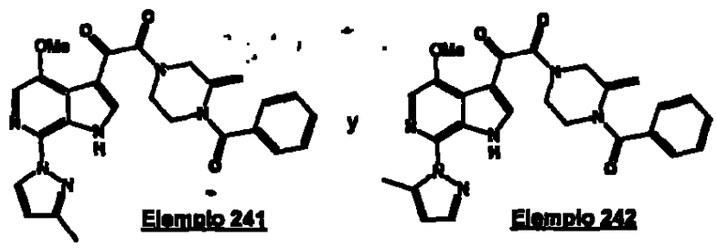
Ejemplo 240

Los Ejemplos 190 y 240, se prepararon de acuerdo al método general antes descrito a partir del precursor 5b y 3-metilpirazol para suministrar el Ejemplo 190 y Ejemplo 240.

El Ejemplo 240, 1-benzoil-4-[(4-metoxi-7-(5-metil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{25}H_{25}N_6O_4$: 473.19; encontrado 473.19. Tiempo de retención CLAR: 1.35 minutos (columna G).

Ejemplo 190, 1-benzoil-4-[(4-metoxi-7-(3-metil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{25}N_6O_4$: 473.19; encontrado 473.17. Tiempo de retención CLAR: 1.50 minutos (columna G).

EJEMPLOS 241 y 242



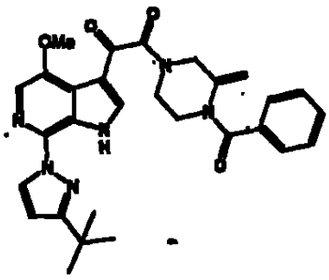
Ejemplo 241 y Ejemplo 242

Los Ejemplos 241 y 242, se prepararon de acuerdo al método general antes descrito a partir del precursor 5z y 3-metilpirazol.

Ejemplo 241, (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-metil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_6O_4$: 487.21; encontrado 486.20. Tiempo de retención CLAR: 1.54 minutos (columna G).

Ejemplo 242, (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(5-metil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{27}N_6O_4$: 487.21; encontrado 486.20. Tiempo de retención CLAR: 1.41 minutos (columna G).

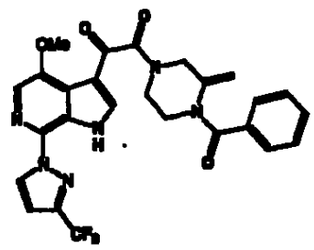
EJEMPLO 243



El Ejemplo 243, se preparó de acuerdo con el método

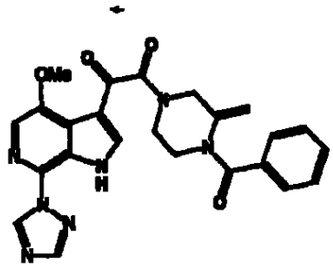
general antes descrito a partir del precursor 5z y 3-t-butilpirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-t-butil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{30}N_6O_4$: 529.26; encontrado 529.29. Tiempo de retención CLAR: 1.86 minutos (columna G).

EJEMPLO 244



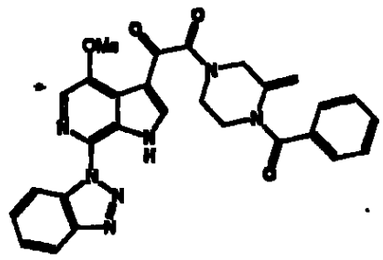
El Ejemplo 244, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y 3-trifluorometilpirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-trifluorometil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{24}F_3N_6O_4$: 541.18; encontrado 541.25. Tiempo de retención CLAR: 1.71 minutos (columna G).

EJEMPLO 245



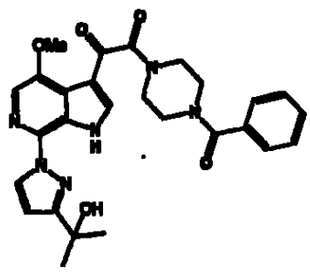
El Ejemplo 245, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y 1,2,4-triazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(1,2,4-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{24}H_{24}N_7O_4$: 474.19; encontrado 474.23. Tiempo de retención CLAR: 1.29 minutos (columna G).

EJEMPLO 246



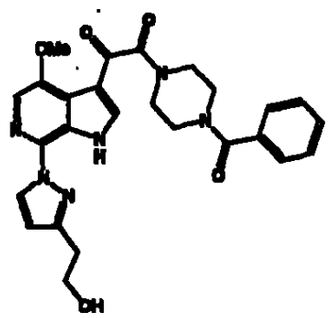
El Ejemplo 246, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y 1,2,3-benzotriazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(1,2,3-benzotriazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{28}H_{26}N_7O_4$: 524.20; encontrado 524.27. Tiempo de retención CLAR: 1.68 minutos (columna G).

EJEMPLO 247



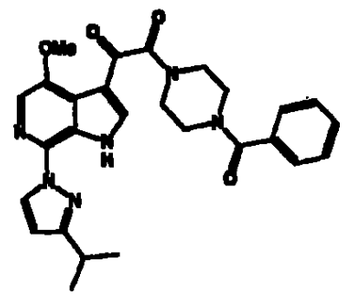
El Ejemplo 247, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y pirazol-010 para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(1-hidroxil-1-metiletil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{29}N_6O_5$: 517.22; encontrado 517.37. Tiempo de retención CLAR: 1.38 minutos (columna L).

EJEMPLO 248



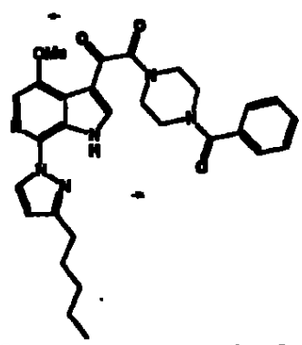
El Ejemplo 248, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y Pirazol-008 para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(3-hidroxiletil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{27}N_6O_5$: 503.20; encontrado 503.27. Tiempo de retención CLAR: 1.16 minutos (columna L).

EJEMPLO 249



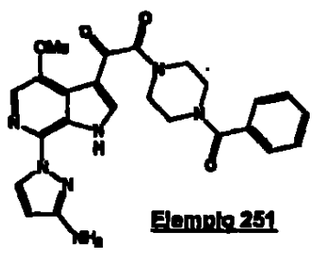
El Ejemplo 249, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y Pirazol-004 para suministrar 1-benzoil-4-[(4-metoxi-7-(3-iso-propil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{29}N_6O_4$: 501.23; encontrado 501.34. Tiempo de retención CLAR: 1.74 minutos (columna L).

EJEMPLO 250



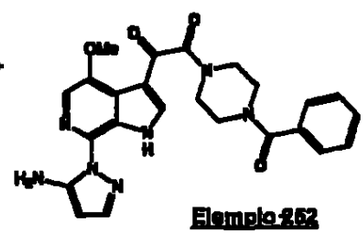
El Ejemplo 250, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y Pirazol-003 para suministrar 1-benzoil-4-[(4-metoxi-7-(3-n-pentil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{33}N_6O_4$: 529.26; encontrado 529.34. Tiempo de retención CLAR: 1.96 minutos (columna L).

EJEMPLOS 251 y APP 252



Ejemplo 251

y



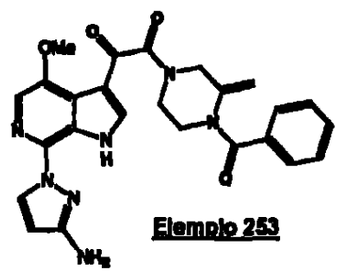
Ejemplo 252

Los Ejemplos 251 y 252, se prepararon de acuerdo al método general antes descrito a partir del precursor 5b y 3-aminopirazol.

Ejemplo 251, 1-benzoil-4-[(4-metoxi-7-(3-amino-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{24}N_7O_4$: 474.29; encontrado 474.24. Tiempo de retención CLAR: 1.58 minutos (columna G).

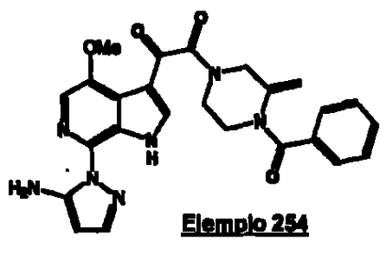
Ejemplo 252, 1-benzoil-4-[(4-metoxi-7-(5-amino-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{24}N_7O_4$: 474.29; encontrado 474.22. Tiempo de retención CLAR: 1.59 minutos (columna G).

EJEMPLOS 253 y 254



Ejemplo 253

y



Ejemplo 254

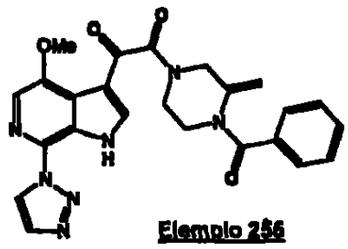
Los Ejemplos 253 y 254, se prepararon de acuerdo al

método general antes descrito a partir del precursor 5z y 3-aminopirazol.

Ejemplo 253, (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-amino-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{26}N_7O_4$: 488.20; encontrado 488.25. Tiempo de retención CLAR: 1.65 minutos (columna G, relación de flujo = 4 ml/min, tiempo de gradiente = 3 min).

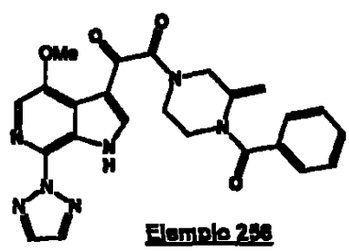
Ejemplo 254, (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(5-amino-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{26}N_7O_4$: 488.20; encontrado 488.25. Tiempo de retención CLAR: 1.74 minutos (columna G, relación de flujo = 4 ml/min, tiempo de gradiente = 3 min).

EJEMPLOS 255 y 256



Ejemplo 256

y



Ejemplo 256

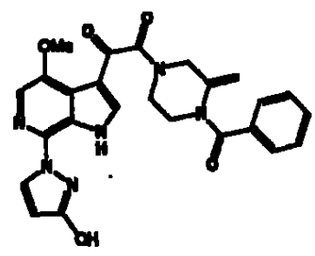
Los Ejemplos 255 y 256, se prepararon de acuerdo al método general antes descrito a partir del precursor 5z y 1,2,3-triazol. El Precursor 5z (0.056 g), 0.056 g polvo Cu, 0.025 g K_2CO_3 y 10 equivalentes de 1,2,3 triazol se calentaron a 155-170 C durante 4 horas. La reacción se dejó enfriar a temperatura ambiente y el residuo se disolvió en MeOH y

purificó por CLAR Preparativa, como se describe arriba en los métodos generales para suministrar el Ejemplo 255 (0.020 g) como un sólido café, 34% de rendimiento y el otro isómero del Ejemplo 256.

Ejemplo 255, (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(1,2,3-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{24}N_7O_4$: 474.19; encontrado 474.21. Tiempo de retención CLAR: 1.84 minutos (columna G, relación de flujo = 4 ml/min, tiempo de gradiente = 3 min). ^1H RMN (500 MHz, CD_3OD) δ 8.85 (s, 1H), 8.32 (ss, 1H), 7.94 (m, 2H), 7.48 (m, 5H), 4.07 (ss, 3H), 4.00-3.00 (m, 7H), 1.33 (m, 3H).

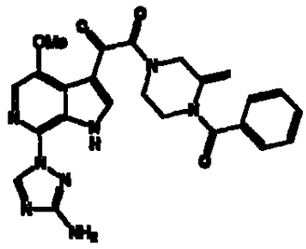
Ejemplo 256, (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(1,2,3-triazol-2-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{24}N_7O_4$: 474.19; encontrado 474.21. Tiempo de retención CLAR: 1.66 minutos (columna G, relación de flujo = 4 ml/min, tiempo de gradiente = 3 min). ^1H RMN (500 MHz, CD_3OD) δ 8.33 (ss, 1H), 8.13 (s, 1H), 7.46 (m, 7H), 4.07 (ss, 3H), 4.00-3.00 (m, 7H), 1.32 (m, 3H).

EJEMPLO 257



El Ejemplo 257, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y 3-hidroxilpirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-hidroxilpirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{25}H_{25}N_6O_5$: 489.19; encontrado 489.15. Tiempo de retención CLAR: 1.38 minutos (columna G).

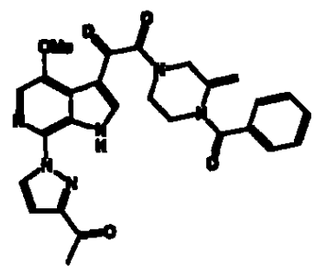
EJEMPLO 258



El Ejemplo 258, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y 3-amino-1,2,4-triazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-amino-1,2,4-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{25}N_8O_4$: 489.20; encontrado 489.24. Tiempo de retención CLAR: 1.69 minutos (columna G).

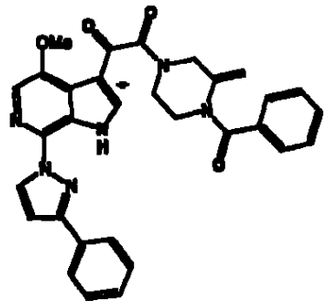
Los Ejemplos 259 hasta 265, se prepararon de acuerdo al procedimiento general Si-Cu (condiciones para ocultar silicio) descritas anteriormente:

EJEMPLO 259



El Ejemplo 259, se preparó de acuerdo con el método general Si-Cu (silicio oculto) descrito anteriormente a partir del precursor 5z y 3-metilcarbonilpirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-metilcarbonil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{27}N_6O_5$: 515.20; encontrado 515.15. Tiempo de retención CLAR: 1.51 minutos (columna G).

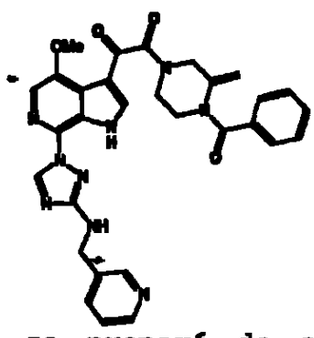
EJEMPLO 260



El Ejemplo 260, se preparó de acuerdo con el método general Si-Cu (silicio oculto) antes descrito a partir del precursor 5z y 3-fenilpirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-fenil-pirazol-1-il)-6-

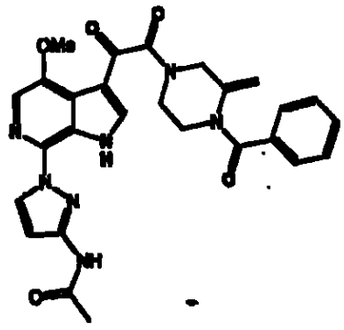
azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{31}H_{29}N_6O_4$: 549.23; encontrado 549.18. Tiempo de retención CLAR: 1.82 minutos (columna G).

EJEMPLO 261



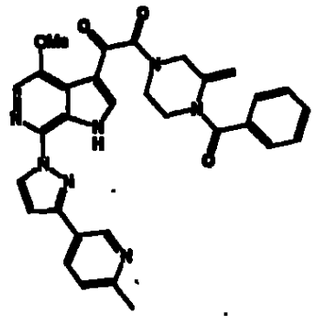
El Ejemplo 261, se preparó de acuerdo con el método general Si-Cu (silicio oculto) antes descrito a partir del precursor 5z y 3-(3-piridinmetilamino)-1,2,4-triazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-(3-piridinmetilamino)-1,2,4-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{30}H_{30}N_9O_4$: 580.24; encontrado 580.14. Tiempo de retención CLAR: 1.15 minutos (columna G).

EJEMPLO 262



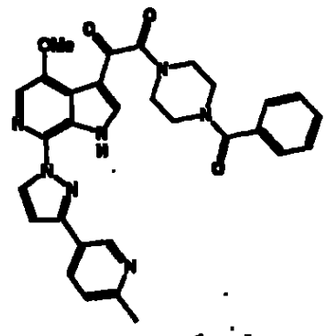
El Ejemplo 262, se preparó de acuerdo con el método general Si-Cu (silicio oculto) antes descrito a partir del precursor 5z y 3-acetilaminopirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-acetilamino-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{28}N_7O_5$: 530.22; encontrado 530.15. Tiempo de retención CLAR: 1.41 minutos (columna G).

EJEMPLO 263



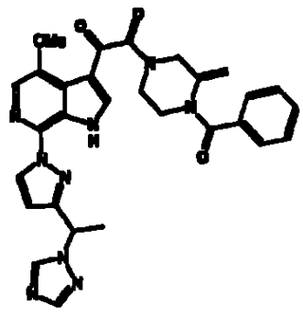
El Ejemplo 263 se preparó de acuerdo con el método general Si-Cu (silicio oculto) antes descrito a partir del precursor 5z y 3-(2-metilpiridin-5-il)pirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-(2-metilpiridin-5-il)pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{31}H_{30}N_7O_4$: 564.24; encontrado 564.26. Tiempo de retención CLAR: 1.22 minutos (columna C).

EJEMPLO 264



El Ejemplo 264 se preparó de acuerdo con el método general Si-Cu (silicio oculto) antes descrito a partir del precursor 5b y 3-(2-metilpiridin-5-il)pirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(2-metilpiridin-5-il)pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{30}H_{28}N_7O_4$: 550.22; encontrado 550.26. Tiempo de retención CLAR: 1.20 minutos (columna C).

EJEMPLO 265



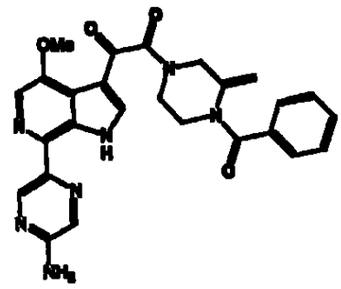
El Ejemplo 265 se preparó de acuerdo con el método general Si-Cu (para ocultar silicio) antes descrito a partir del precursor 5z y 3-(1,2,4-triazol-1-il)etil-pirazol para suministrar (R)-1-benzoil-2-metil-4-[(4-metoxi-7-(3-(1,2,4-triazol-1-

813

il)etil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{30}N_9O_4$: 568.24; encontrado 568.13. Tiempo de retención CLAR: 1.44 minutos (columna G).

Los ejemplos 266 hasta 270, se prepararon de acuerd a un procedimiento análogo al procedimiento usado para sintetizar el Ejemplo 15:

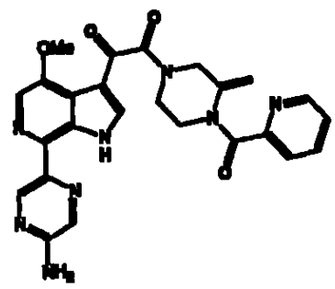
EJEMPLO 266



El Ejemplo 266, se preparó de acuerdo con el método general antes descrito a partir del precursor 5z y 2-amino-pirazin-5-il tributilestaño, para suministrar (R)-1-benzoil-2-metil-4-[(7-(2-amino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_7O_4$: 500.20; encontrado 500.26. Tiempo de retención CLAR: 1.11 minutos (columna G).

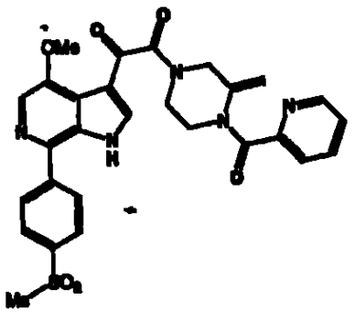
814

EJEMPLO 267



El Ejemplo 267, se preparó de acuerdo con el método general antes descrito a partir del precursor 5za y 2-amino-pirazin-5-il tributilestaño, para suministrar (R)-1-picolinoil-2-metil-4-[(7-(2-amino-pirazin-5-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{25}N_8O_4$: 501.20; encontrado 501.30. Tiempo de retención CLAR: 1.04 minutos (columna J).

EJEMPLO 268

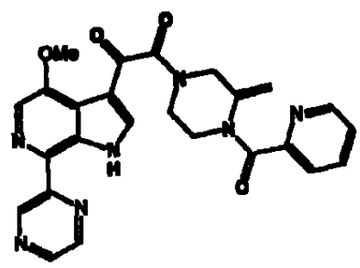


El Ejemplo 268, se preparó de acuerdo con el método general antes descrito a partir del precursor 5xa y ácido 4-metilsulfonilfenil borónico, para suministrar (R)-1-picolinoil-2-metil-4-[(7-(4-metilsulfonil-fenil-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado

815

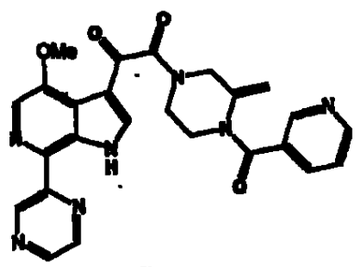
para $C_{28}H_{28}N_5O_6S$: 562.18; encontrado 562.19. Tiempo de retención CLAR: 0.86 minutos (columna G).

EJEMPLO 269



El Ejemplo 269, se preparó de acuerdo con el método general antes descrito a partir del precursor 5xa y tri-butilestanilo pirazina, para suministrar (R)-1-picolinoil-2-metil-4-[(7-pirazinil-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 486.32. Tiempo de retención CLAR: 1.07 minutos (columna G).

EJEMPLO 270



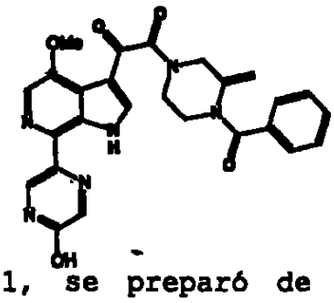
El Ejemplo 270, se preparó de acuerdo con el método general antes descrito a partir del precursor 5y y tri-butilestanilo pirazina, para suministrar (R)-1-nicotinoil-2-

816

metil-4-[(7-pirazinil-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{25}H_{24}N_7O_4$: 486.19; encontrado 486.10. Tiempo de retención CLAR: 0.96 minutos (columna L).

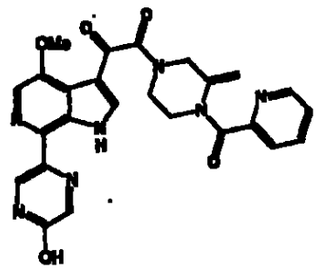
Los Ejemplos 271 hasta 272, se prepararon al usar el "Procedimiento general de conversión del grupo $-NH_2$ al grupo -OH", ejemplificado por la preparación del ejemplo 97:

EJEMPLO 271



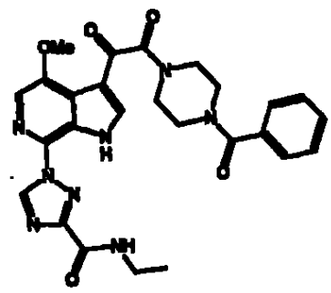
El Ejemplo 271, se preparó de acuerdo con el método general antes descrito a partir del Ejemplo 266 para suministrar (R)-1-benzoil-2-metil-4-[(7-(5-hidroxil-pirazin-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{25}N_6O_5$: 501.19; encontrado 501.21. Tiempo de retención CLAR: 1.08 minutos (columna G).

EJEMPLO 272



El Ejemplo 272, se preparó de acuerdo con el método general antes descrito a partir del Ejemplo 267 para suministrar (R)-1-picolinoil-2-metil-4-[(7-(5-hidroxil-pirazin-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{25}H_{24}N_7O_5$: 502.18; encontrado 502.19. Tiempo de retención CLAR: 0.88 minutos (columna G).

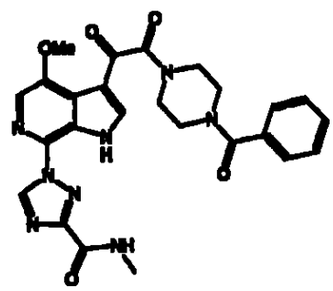
EJEMPLO 273



El Ejemplo 273, se preparó a partir del Precursor 5b y etilamida del -ácido 1H-[1,2,4]-triazol-3-carboxílico para suministrar 1-benzoil-4-[(4-metoxi-7-(3-etilaminocarbonil-1,2,4-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{27}N_8O_5$: 531.21; encontrado 531.21. Tiempo de retención CLAR: 1.75 minutos (columna G). ^1H RMN (500 MHz, CD_3OD) δ 9.35 (s, 1H), 8.34 (s, 1H), 7.86 (s, 1H), 7.48 (b, 5H), 4.06 (s, 3H), 4.00-3.49 (m, 10H), 1.30 (t, 3H, J = 7.5 Hz).

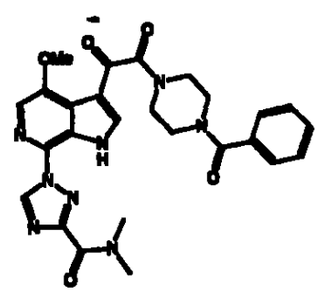
818

EJEMPLO 274



El Ejemplo 274, se preparó a partir del Precursor 5b y metilamida del ácido 1H-[1,2,4]-triazol-3-carboxílico para suministrar 1-benzoil-4-[(4-metoxi-7-(3-metilaminocarbonil-1,2,4-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{25}H_{25}N_8O_5$: 517.19; encontrado 517.18. Tiempo de retención CLAR: 1.67 minutos (columna G). ^1H RMN (500 MHz, CD_3OD) δ 9.36 (s, 1H), 8.35 (s, 1H), 7.88 (s, 1H), 7.48 (b, 5H), 4.06 (s, 3H), 3.80-3.60 (m, 8H), 3.02 (s, 3H).

EJEMPLO 275

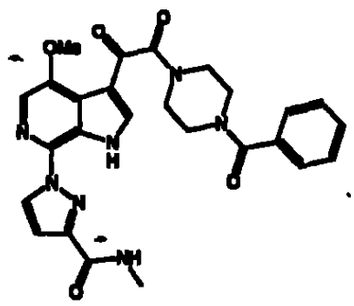


El Ejemplo 275, se preparó a partir del Precursor 5b y dimetilamida del ácido 1H-[1,2,4]-triazol-3-carboxílico para suministrar 1-benzoil-4-[(4-metoxi-7-(3-dimetilaminocarbonil-

019

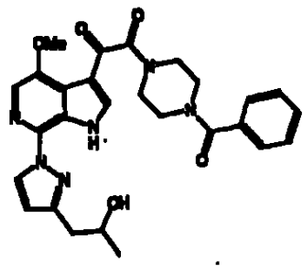
1,2,4-triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{27}N_8O_5$: 531.21; encontrado 531.28. Tiempo de retención CLAR: 1.71 minutos (columna G).

EJEMPLO 276



El Ejemplo 276, se preparó a partir del Precursor 5b y metilamida del ácido 1H-pirazol-3-carboxílico para suministrar 1-benzoil-4-[(4-metoxi-7-(3-metilaminocarbonil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{26}N_7O_5$: 516.20; encontrado 516.27. Tiempo de retención CLAR: 1. 86 minutos (columna G).

EJEMPLO 277

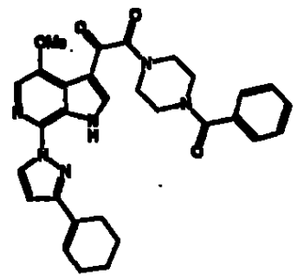


El Ejemplo 277, se preparó a partir del Precursor 5b y 1-(1H-pirazol-3-il)-propan-2-ol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(2-hidroxilpropil)-pirazol-1-il)-6-azaindol-

820

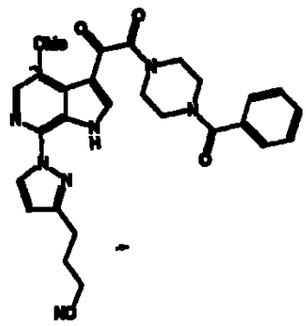
3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{27}H_{29}N_6O_5$: 517.22; encontrado 517.38. Tiempo de retención CLAR: 1.42 minutos (columna L).

EJEMPLO 278



El Ejemplo-278, se preparó a partir del Precursor 5b y 3-ciclohex-1-enil-1H-pirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(ciclohexen-1-il)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{30}H_{31}N_6O_4$: 539.24; encontrado 539.26. Tiempo de retención CLAR: 1.96 minutos (columna L).

EJEMPLO 279

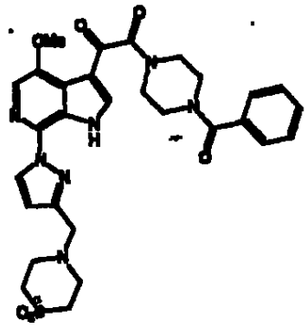


El Ejemplo 279, se preparó a partir del Precursor 5b y 4-(1H-pirazol-3-il)-butironitrilo para suministrar 1-benzoil-

821

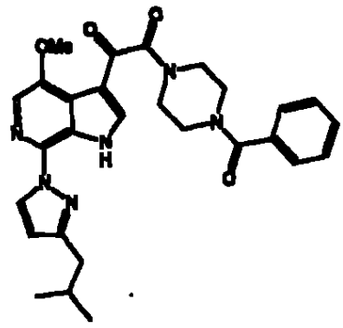
4-[(4-metoxi-7-(3-(3-ciano-propan-1-il)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{28}H_{28}N_7O_4$: 526.22; encontrado 526.35. Tiempo de retención CLAR: 1.51 minutos (columna L).

EJEMPLO 280



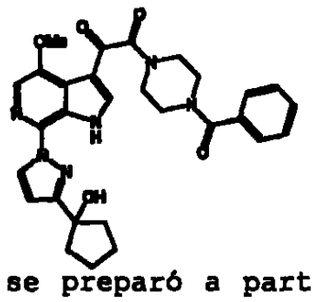
El Ejemplo 280, se preparó a partir del Precursor 5b y 4-(1H-pirazol-3-ilmetil)-tiomorfolina 1,1-dióxido para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(1,1-dioxo-tiomorfolin-4-il)metil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{32}N_7O_6S$: 606.21; encontrado 606.34. Tiempo de retención CLAR: 1.01 minutos (columna L).

EJEMPLO 281



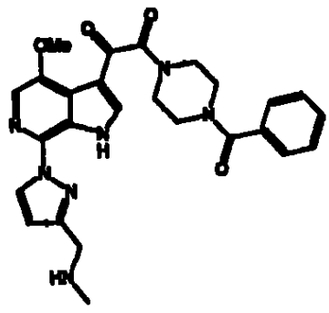
El Ejemplo 281, se preparó a partir del Precursor 5b y 3-isobutil-1H-pirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-isobutil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{31}N_6O_4$: 515.24; encontrado 515.35. Tiempo de retención CLAR: 1.90 minutos (columna L).

EJEMPLO 282



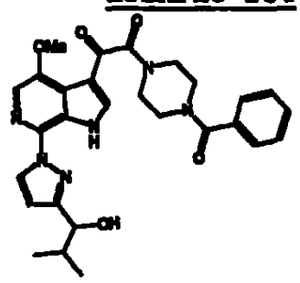
El Ejemplo 282, se preparó a partir del Precursor 5b y 1-(1H-pirazol-3-il)-ciclopentanol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(1-hidroxi-ciclopentil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{31}N_6O_5$: 543.24; encontrado 543.43. Tiempo de retención CLAR: 1.51 minutos (columna L).

EJEMPLO 283



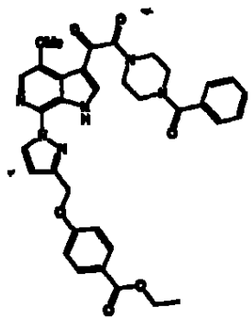
El Ejemplo 283, se preparó a partir del Precursor 5b y metil-(1H-pirazol-3-ilmetil)-amina para suministrar 1-benzoil-4-[(4-metoxi-7-(3-metilaminometil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ calculado para $C_{26}H_{28}N_7O_4$: 502.22; encontrado 502.31. Tiempo de retención CLAR: 1.51 minutos (columna L).

EJEMPLO 284



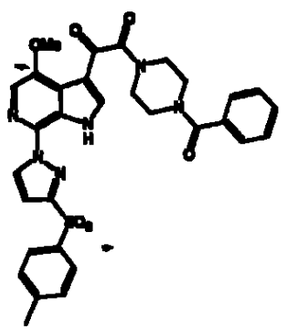
El Ejemplo 284, se preparó a partir del Precursor 5b y 2-metil-1-(1H-pirazol-3-il)-propan-1-ol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(1-hidroxi-2-metil-propil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina. EM m/z: $(M+H)^+$ Calculado para $C_{28}H_{31}N_6O_5$: 531.24; encontrado 531.43. Tiempo de retención CLAR: 1.63 minutos (columna L).

EJEMPLO 285



El Ejemplo 285, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y Pirazol-025 para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(4-etoxicarbonil-fenil)oximetil-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{34}H_{33}N_6O_7$: 637.24; encontrado 637.34. Tiempo de retención CLAR: 1.87 minutos (columna G). ^1H RMN (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.16 (s, 1H), 8.02 (d, 2H, J = 15 Hz), 7.76 (s, 1H), 7.43 (b, 5H), 7.05 (d, 2H, J = 14.5 Hz), 6.60 (s, 1H), 5.29 (s, 2H), 4.33 (q, 2H, J = 12 Hz), 4.03 (s, 3H), 3.80-3.57 (m, 8H), 1.38 (t, 3H, J = 12.0 Hz).

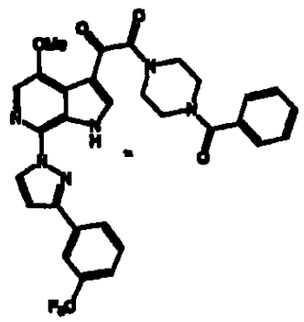
EJEMPLO 286



El Ejemplo 286, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y 3-(toluen-4-sulfonil)-1H-pirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(toluen-4-sulfonil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{31}H_{29}N_6O_6S$: 613.19; encontrado 613.28. Tiempo de retención

CLAR: 1.69 minutos (columna G). ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.21 (s, 1H), 7.94 (d, 2H, J = 8.00 Hz), 7.74 (s, 1H), 7.43 (b, 5H), 7.34 (d, 2H, J = 8.00 Hz), 6.94 (s, 1H), 4.04 (s, 3H), 4.00-3.40 (m, 8H), 2.42 (s, 3H).

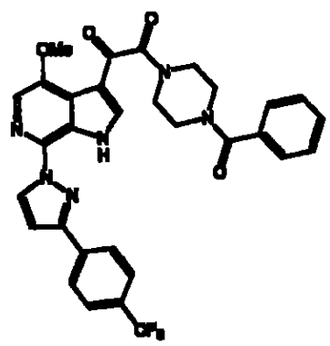
EJEMPLO 287



El Ejemplo 287, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y 3-(3-trifluorometil-fenil)-1H-pirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(3-trifluorometil-fenil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{31}H_{26}F_3N_6O_4$: 603.20; encontrado 603.32. Tiempo de retención CLAR: 1.94 minutos (columna G). ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.26 (s, 1H), 8.09-7.42 (m, 10H), 6.87 (s, 1H), 4.01 (s, 3H), 4.00-3.62 (m, 8H).

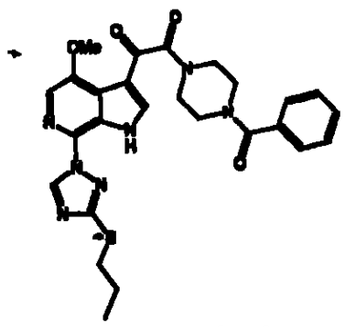
826

EJEMPLO 288



El Ejemplo 288, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y 3-(4-trifluorometil-fenil)-1H-pirazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-(4-trifluorometil-fenil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{31}H_{26}F_3N_6O_4$: 603.20; encontrado 603.32. Tiempo de retención CLAR: 1.96 minutos (columna G). ^1H RMN (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.26 (s, 1H), 8.09-7.43 (m, 10H), 6.87 (s, 1H), 4.01 (s, 3H), 4.00-3.62 (m, 8H).

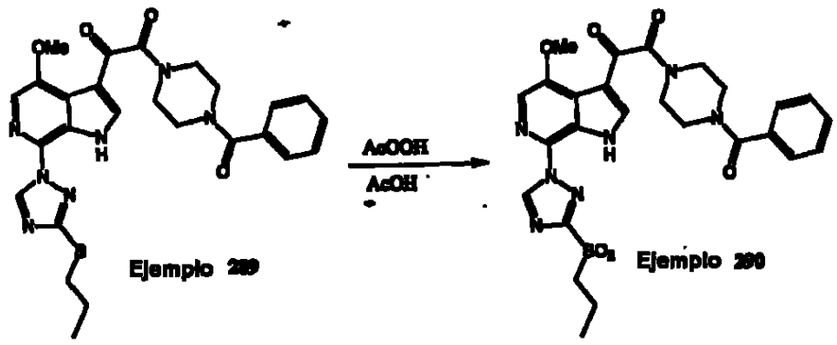
EJEMPLO 289



El Ejemplo 289, se preparó de acuerdo con el método general antes descrito a partir del precursor 5b y 3-

propilsulfanil-1H-[1,2,4]triazol para suministrar 1-benzoil-4-[(4-metoxi-7-(3-propilsulfanil-[1,2,4]triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{28}N_7O_4S$: 534.19; encontrado 534.32. Tiempo de retención CLAR: 1.65 minutos (columna G). ^1H RMN (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.18 (s, 1H), 7.70 (s, 1H), 7.37 (m, 5H), 4.05 (s, 3H), 3.90-3.30 (m, 8H), 3.18 (t, 2H, J = 11.5 Hz), 1.74 (m, 2H), 1.02 (t, 3H, J = 12.5 Hz).

EJEMPLO 290

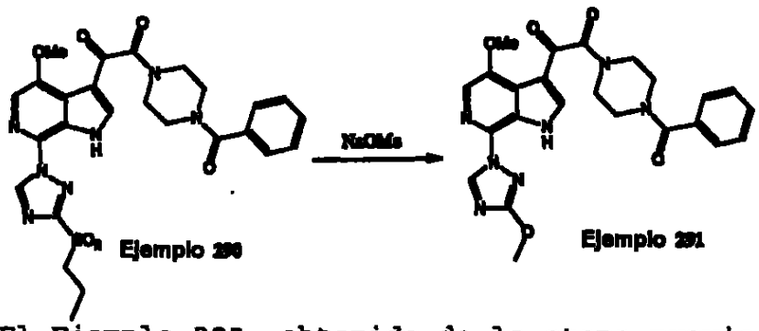


El Ejemplo 290 (18 mg) se disolvió en 1 ml de AcOOH (37% en AcOH) a temperatura ambiente y la mezcla se mantuvo en agitación durante 10 horas. La eliminación de los solventes bajo vacío proporcionó un residuo, el cual se purificó al usar un sistema CLAR preparativa automatizado Shimadzu para suministrar Ejemplo 290, 1-benzoil-4-[(4-metoxi-7-(3-(propan-1-sulfonil)-[1,2,4]triazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{26}H_{28}N_7O_6S$: 566.18; encontrado 566.30. Tiempo de retención

828

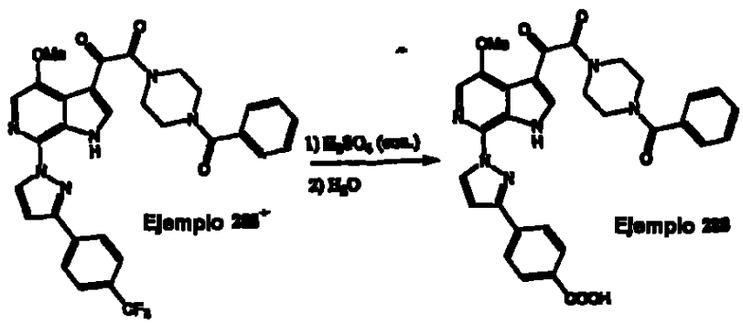
CLAR: 1.44 minutos (columna G). ^{1}H RMN (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.24 (s, 1H), 7.80 (s, 1H), 7.43 (m, 5H), 4.08 (s, 3H), 3.90-3.50 (m, 8H), 3.42 (t, 2H, J = 8.00 Hz), 1.90 (m, 2H), 1.09 (t, 3H, J = 7.50 Hz).

EJEMPLO 291



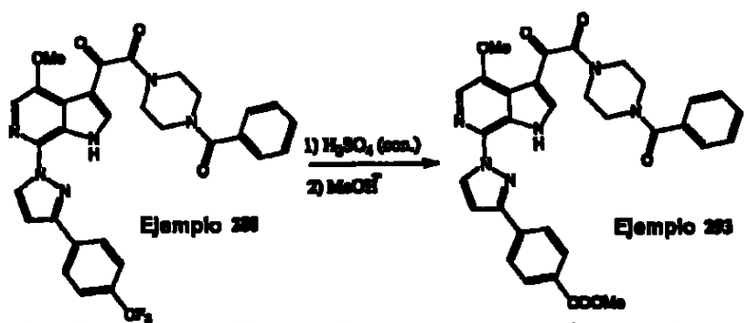
El Ejemplo 290, obtenido de la etapa previa, se disolvió en 5 ml de MeONa (8% en peso en MeOH) a temperatura ambiente y la mezcla se calentó a 90°C durante 10 horas para formar 291, 1-benzoil-4-[(4-metoxi-7-(3-metoxi-[1,2,4]triazol-1-il)--6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{24}H_{24}N_7O_5$: 490.18; encontrado 490.29. Tiempo de retención CLAR: 1.36 minutos (columna G).

EJEMPLO 292



El Ejemplo 288 (8 mg) se disolvió en 0.2 ml de concentrado a temperatura ambiente y la mezcla se calentó a 70°C durante 6 horas. Luego la mezcla se apagó con agua (2 ml) para formar el Ejemplo 292, el cual se purificó usando Sistema CLAR preparativa automatizado Shimadzu (2.1 mg de obtenido Ejemplo 292). Ejemplo 292, 1-benzoil-4-[(4-metoxi-7-(3-(4-hidroxilcarbonilfenil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ calculado para $C_{31}H_{27}N_6O_6$: 579.20; encontrado 579.28. Tiempo de retención CLAR: 1.72 minutos (columna G). ^1H RMN (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.29 (s, 1H), 8.15 (d, 2H, J = 8.00 Hz), 7.97 (d, 2H, J = 8.00 Hz), 7.80 (s, 1H), 7.45 (m, 5H), 6.90 (s, 1H), 4.05 (s, 3H), 4.02-3.49 (m, 8H).

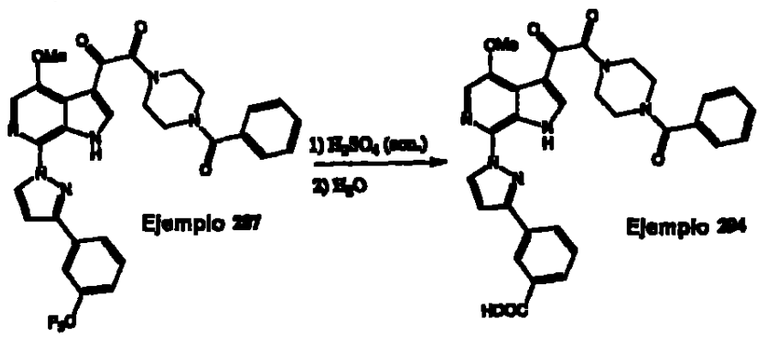
EJEMPLO 293



El Ejemplo 288 (8 mg) se disolvió en 0.2 ml de concentrado a temperatura ambiente y la mezcla se calentó a 70°C durante 6 horas. Luego la mezcla se apagó con MeOH (2 ml) para formar el Ejemplo 293, el cual se purificó usando Sistema de CLAR preparativa automatizado Shimadzu (1.1 mg del

Ejemplo 293 obtenido). Ejemplo 293, 1-benzoil-4-[(4-metoxi-7-(3-(4-metoxicarbonilfenil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{32}H_{29}N_6O_6$: 593.21; encontrado 593.32. Tiempo de retención CLAR: 1.84 minutos (columna G). ^1H RMN (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.29 (s, 1H), 8.16 (d, 2H, J = 8.00 Hz), 7.94 (d, 2H, J = 8.00 Hz), 7.79 (s, 1H), 7.44 (m, 5H), 6.89 (s, 1H), 4.05 (s, 3H), 3.96 (s, 3H), 3.90-3.40 (m, 8H).

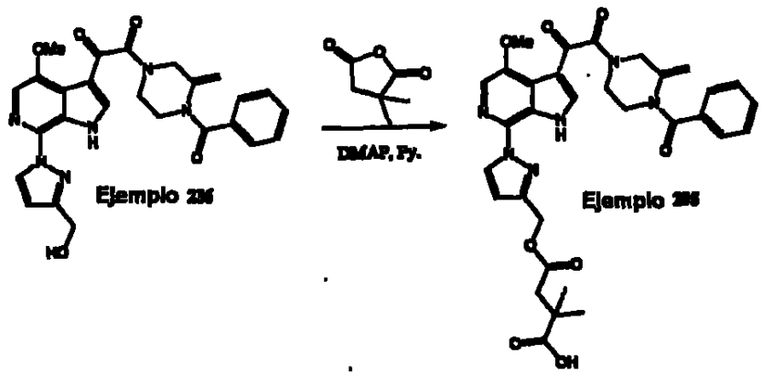
EJEMPLO 294



El Ejemplo 287 (6 mg) se disolvió en 0.2 ml de concentrado a temperatura ambiente y la mezcla se calentó a 70°C durante 6 horas. Luego la mezcla se apagó con agua (2 ml) para formar el Ejemplo 294, el cual se purificó usando Sistema CLAR preparativa automatizado Shimadzu (2.7 mg del Ejemplo 294 obtenido). Ejemplo 294, 1-benzoil-4-[(4-metoxi-7-(3-(3-hidroxilcarbonilfenil)-pirazol-1-il)-6-azaindol-3-il)-oxoacetil]piperazina; EM m/z: $(M+H)^+$ Calculado para $C_{31}H_{27}N_6O_6$:

579.20; encontrado 579.28. Tiempo de retención CLAR: 1.74 minutos (columna G). ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.56 (s, 1H), 8.30 (s, 1H), 8.10 (m, 2H), 7.77 (m, 1H), 7.80 (s, 1H), 7.45 (m, 5H), 6.87 (s, 1H), 4.04 (s, 3H), 4.00-3.40 (m, 8H).

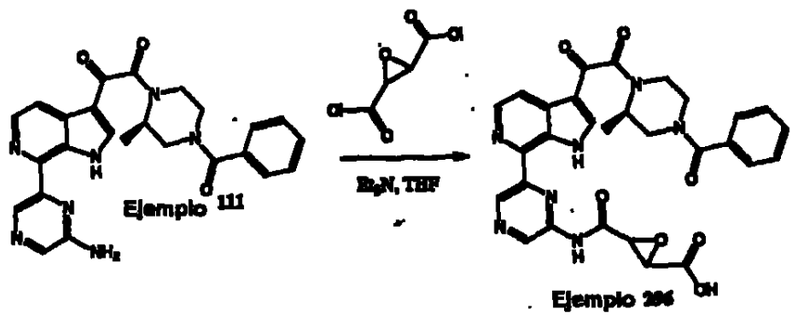
EJEMPLO 295



El Ejemplo 136 (6 mg), anhídrido succínico (20 mg) y DMAP (5 ml) se disolvieron en 5 ml de piridina anhidra a temperatura ambiente y la mezcla se calentó a reflujo durante 10 horas. Luego la mezcla se apagó con MeOH y se retiraron los solventes bajo vacío para suministrar un residuo, el cual se purificó usando Sistema CLAR preparativa automatizado Shimadzu para dar el Ejemplo 295 (2.4 mg), éster 4-(1-{3-[2-(4-benzoil-3-metil-piperazin-1-il)-2-oxo-acetil]-4-metoxi-1H-pirrolo[2,3-c]piridin-7-il}-1H-pirazol-3-ilmetil) del ácido 2,2-Dimetil-succínico; EM m/z: $(M+H)^+$ calculado para $C_{32}H_{35}N_6O_8$:

631.25; encontrado 631.34. Tiempo de retención CLAR: 1.61 minutos (columna G).

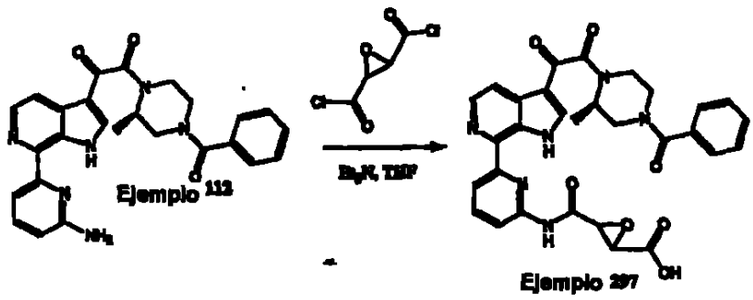
EJEMPLO 296



El Ejemplo 111 (10 mg), cloruro trans-epoxisuccinilo (20 mg) y Et_3N (0.2 ml) se disolvieron en 2 ml de THF anhidro a temperatura ambiente y la mezcla se mantuvo en agitación durante 10 horas. Luego la mezcla se apagó con agua y se retiraron los solventes bajo vacío para suministrar un residuo, el cual se purificó usando Sistema CLAR preparativa automatizado Shimadzu para dar Ejemplo 296 (2 mg), ácido 3-(6-{3-[2-(4-benzoil-2-metil-piperazin-1-il)-2-oxo-acetil]-1H-pirrolo[2,3-c]piridin-7-il}-pirazin-2-ilcarbamoil)-oxiran-2-carboxílico; EM m/z: $(M+H)^+$ Calculado para $C_{29}H_{26}N_7O_7$: 584.19; encontrado 584.36. Tiempo de retención CLAR: 1.44 minutos (columna G).

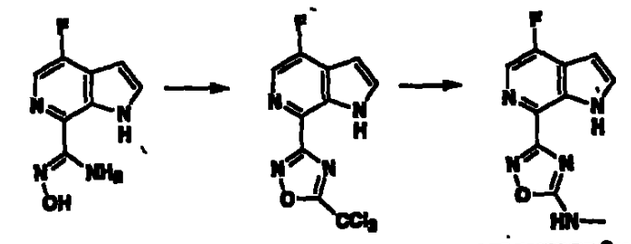
833

EJEMPLO 297



El Ejemplo 112 (10 mg), cloruro trans-epoxisuccinilo (20 mg) y Et_3N (0.2 ml) se disolvieron en 2 ml de THF anhidro a temperatura ambiente y la mezcla se mantuvo en agitación durante 10 horas. Luego la mezcla se apagó con agua y se retiraron los solventes bajo vacío para suministrar un residuo, el cual se purificó usando Sistema CLAR preparativa automatizado Shimadzu para dar el Ejemplo 297 (5 mg), ácido 3-(6-{3-[2-(4-Benzoil-2-metil-piperazin-1-il)-2-oxo-acetil]-1H-pirrolo[2,3-c]piridin-7-il}-piridin-2-ilcarbamoil)-oxiran-2-carboxílico; EM m/z: $(M+H)^+$ Calculado para $C_{30}H_{27}N_6O_7$: 583.19; encontrado 583.34. Tiempo de retención CLAR: 1.31 minutos (columna G).

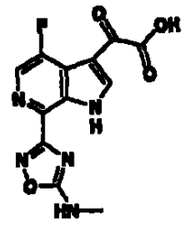
PRECURSOR 4P



precursor 2p precursor 2u

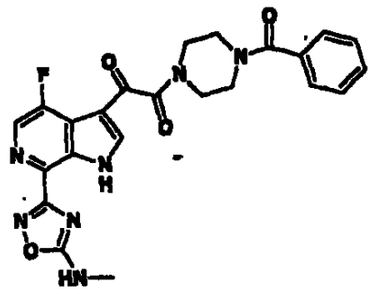
El Precursor 2p (200 mg, 1.0 mmol) se disolvió en anhídrido tricloroacético (1.2 ml) y se calentó a 80°C durante 3 horas se agregó MeOH (10 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Los volátiles se removieron in vacuo. El residuo se diluyó con AcOEt (25 mL) y se lavó con agua (2 x 25 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró. El aceite crudo resultante se disolvió en DMF (1 mL) y se trató con una solución 2M de $MeNH_2$ en MeOH (2 mL). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. CL/EM: (ES+) m/z $(M+H)^+$ = 234. Los volátiles se eliminaron in vacuo y el crudo (134 mg) se tomó en la etapa siguiente sin purificación adicional.

PRECURSOR 4P



El Precursor 4p se preparó a partir del Precursor 2u siguiendo el procedimiento descrito para preparar el precursor 4m. CL/EM: (ES+) m/z $(M+H)^+$ = 306. Tomado para la etapa siguiente sin purificación adicional.

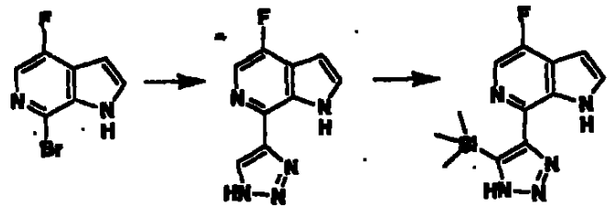
EJEMPLO 298



El Ejemplo 298 se preparó a partir del Precursor 4p por tratamiento con EDC (434 mg, 2.3 mmol), HOBt (308 mg, 2.3 mmol) y benzoilpiperazina (304 mg, 1.36 mmol) en DMF (2 mL). La mezcla se agitó a temperatura ambiente durante 18 horas y luego se concentró in vacuo y se purificó al usar CLAR de fase inversa para resultar el compuesto del título. CL/EM: (ES+) m/z $(M+H)^+$ = 478; temperatura ambiente = 1.25 min.

836

Precursores 2V y 2VV

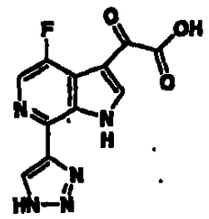


Precursor 2v Precursor 2vv

A una solución dietiléter (10 mL) de trimetilsilildiazometano (2 M en hexano, 5.3 ML) se le agregó n-BuLi (2.5 M en hexano, 4.2 mL) a 0°C. Después de agitarse durante 20 minutos, la mezcla resultante se agregó en una solución de dietiléter (5 ml) de 4-fluoro-7-bromo-6-azaindol (340 mg, 2.1 mmol). La reacción se agitó a 0°C durante 60 minutos y luego, se apagó con agua (20 mL). La mezcla de reacción se extrajo con acetato de etilo (2 x 40 mL). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se trituró con acetato de etilo. El sólido se filtró y se secó al aire para dar el precursor 2v como un sólido blanco (35 mg). ^1H RMN (300 MHz, CD_3OD): 8.43 (bs, 1H); 8.09-8.08 (m, 1H); 7.64-7.63 (m, 1H); 6.72-6.71 (m, 1H). CL/EM: (ES^+) m/z $(M+H)^+$ = 204. tiempo de retención = 0.50 min. El filtrado se concentró y se purificó sobre columna de gel de sílice eluyendo con 5-10% de acetato de etilo/hexano para resultar el precursor 2vv como un sólido amarillo (422 mg). ^1H RMN (300 MHz, $CDCl_3$): 8.09-8.08 (m, 1H); 7.47-7.45 (m, 1H); 6.69-6.67 (m, 1H); 0.45 (s,

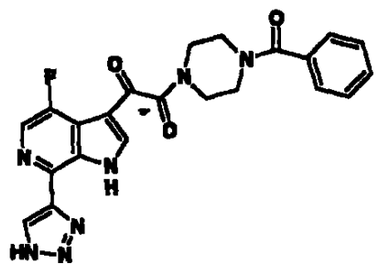
9H). CL/EM: (ES^+) m/z $(M+H)^+$ = 276. tiempo de retención = 1.39 min.

Precursor 4q



El Precursor 4q se preparó siguiendo el procedimiento descrito antes por el compuesto 4m. CL/EM: (ES^+) m/z $(M+H)^+$ = 276. tiempo de retención = 0.42 min.

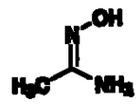
Ejemplo 299



El compuesto del título se preparó siguiendo el proceso de acoplamiento previo descrito antes del precursor 5a. ^1H RMN (300 MHz, DMSO): 8.44 (m, 1H); 8.33-8.31 (m, 2H); 7.44 (m, 5H); 3.87-3.40 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 448. tiempo de retención = 1.04 min.

838

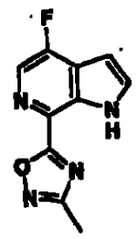
N-HIDROXI-ACETAMIDINA



N-hidroxi-acetamidina

Se agregó una solución de etóxido de sodio (32.5 ml, 21% p/v) se agregó durante 1 h a una solución de clorohidrato (3.5 g, 0.05 mol) y fenolftaleina (5 mg) en etanol (20 mL). Después de agitarse durante 3 horas a temperatura ambiente, se agregó acetonitrilo (1.4 g). La reacción se agitó durante 2 horas y luego se calentó a 40°C durante 48 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró bajo vacío. El residuo se mantuvo a temperatura ambiente durante 48 horas, se purificó sobre columna de gel de sílice eluyendo con 9:1 diclorometano:metanol para dar N-Hidroxi-acetamidina (1.8 g, 73%). ^{1}H RMN (300MHz, DMSO): 8.60 (s, 1H); 5.51 (bs, 2H); 1.60 (s, 3H).

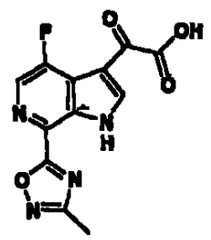
PRECURSOR 2Y



Una solución de 4-fluoro-7-bromo-6-azaindol (100 mg, 0.46 mmol), N-Hidroxi-acetamidina (170 mg, 2.3 mmol),

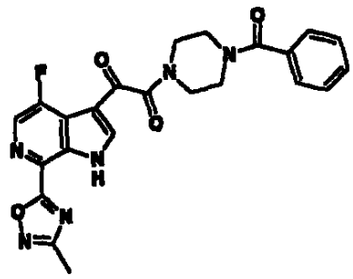
tetraquis(trifenilfosfina)paladio (200 mg, 0.17 mmol) y trietilamina (0.2 mL, 1.4 mmol) en tolueno (2.5 mL) se calentó a reflujo bajo una atmósfera de monóxido de carbono durante 18 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró bajo vacío. El residuo se diluyó con acetato de etilo (10 mL) y se lavó con agua (2 x 25 mL). La capa orgánica se concentró y se purificó en CLAR preparativa para dar el precursor 2y (5 mg, 5%). ^{1}H RMN (300MHz, $CDCl_3$): 10.22 (bs, 1H); 8.32-8.31 (m, 1H); 7.55-7.53 (m, 1H); 6.81-6.79 (m, 1H); 2.55 (s, 3H). CL/EM: (ES+) m/z $(M+H)^+$ = 219. tiempo de retención = 1.15 min.

PRECURSOR 4R



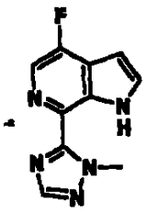
El precursor 4r se preparó siguiendo el procedimiento previo descrito por el compuesto 4k CL/EM: (ES+) m/z $(M+H)^+$ = 291. tiempo de retención = 0.87 min.

EJEMPLO 300



El compuesto del título se preparó siguiendo el procedimiento de acoplamiento descrito antes por el precursor 5a y al usar el precursor 4k y benzoil piperazina como la alimentación. ^{1}H RMN (300 MHz, $CDCl_3$): 10.92 (bs, 1H); 8.51-8.50 (m, 1H); 8.41-8.40 (m, 1H); 7.43 (m, 5H); 3.97-3.50 (m, 8H); 2.58 (s, 3H). CL/EM: (ES+) m/z $(M+H)^+$ = 463. Rt = 1.24 minutos.

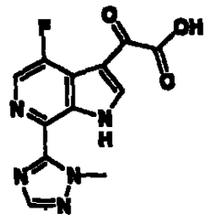
PRECURSOR 2Z



El 1-Metil-1,2,4-triazol (249 mg, 3 mmol) se disolvió en THF anhidro (3 mL) y se enfrió a -78°C. Se agregó n-BuLi (2.5 M en hexano, 1.2 ml) por medio de una jeringa. Después de agitarse durante 10 minutos, se agregó $ZnCl_2$ (0.5 M en hexano, 6 mL). La mezcla de reacción se agitó a -78°C durante 20 minutos, luego se calentó hasta temperatura ambiente. La mezcla resultante se transfirió por medio de una jeringa en un matraz de presión el cual contiene una mezcla de 4-fluoro-7-bromo-6-azaindol (215 mg, 1.0 mmol), tetraquis (trifenilfosfina)paladio (127 mg, 0.11 mmol) y dioxano (6mL). La mezcla de reacción se calentó a 120°C en el matraz sellado durante 15 h, y luego se enfrió hasta temperatura ambiente.

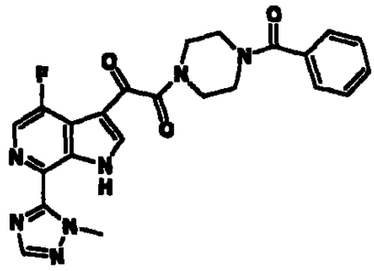
Se agregó acetato de etilo (100 mL) para apagar la reacción. La mezcla resultante se lavó con agua (2 X 20 mL). La capa orgánica se concentró y se purificó en CLAR preparativa. La cristalización final en metanol/agua dio el precursor 2z (80 mg, 37%). ^{1}H RMN (300 MHz, $CDCl_3$): 11.10 (bs, 1H); 8.18-8.17 (m, 1H); 8.02-8.01 (m, 1H); 7.50-7.48 (m, 1H); 6.74-6.72 (m, 1H); 4.52 (s, 3H). CL/EM: (ES+) m/z $(M+H)^+$ = 218. tiempo de retención = 1.23 min.

PRECURSOR 4S



El Precursor 4s se preparó siguiendo el procedimiento descrito antes por el precursor 4m. CL/EM: (ES^+) m/z $(M+H)^+$ = 293. tiempo de retención = 0.92 min.

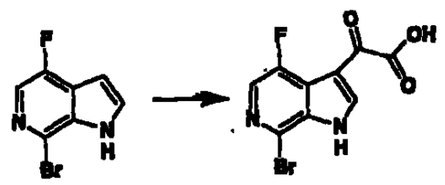
EJEMPLO 301



El compuesto del título se preparó siguiendo el

procedimiento de acoplamiento del ejemplo descrito antes del precursor 5a y al usar el precursor 4s y (benzoil piperazina como la alimentación. ^{1}H RMN (300MHZ, $CDCl_3$): 11.86 (bs, 1H); 8.37-8.36 (m, 1H); 8.32-8.31 (m, 1H); 8.02-8.01 (m, 1H); 7.42 (m, 5H); 4.51 (s, 3H); 3.95-3.51 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 462 temperatura ambiente = 1.32 min.

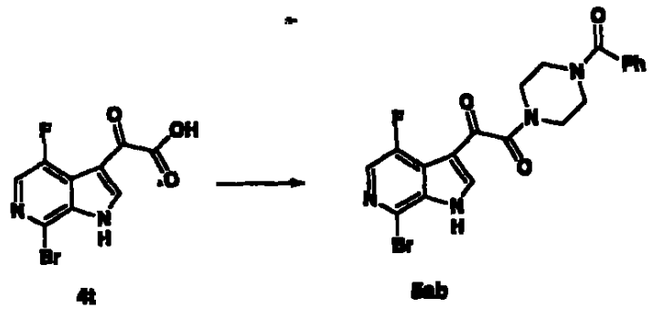
PREPARACIÓN DEL PRECURSOR 4T



Precursor 2i precursor 4t

A una solución del cloruro de 1-etil-3-metil imidazolio (2.7g, 18.6 mmol) y cloruro de aluminio (7.5g, 55.8mmol) se agregó el precursor 2i (2.0g, 9.3mmol) seguido por la adición lenta de etiloxalilacetato (2.1 ml, 18.6 mmol) a temperatura ambiente. La reacción luego se agitó a temperatura ambiente durante 20 horas, y luego se apagó por de adición lenta de agua con hielo (20mL). Un sólido café claro se precipitó y se recolectó por filtración y se secó al aire para suministrar el compuesto precursor 4t (2.2g, 82%). CL/EM: (ES^+) m/z $(M+H)^+$ = 289. tiempo de retención = 0.85 min.

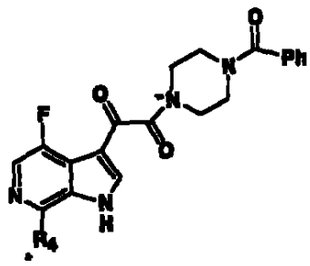
PREPARACIÓN DEL PRECURSOR 5AB



4t 5ab

Una mezcla del compuesto precursor 4t (500mg, 1.74 mmol), clorohidrato de bencilpiperazina (395mg, 1.74 mmol), DEBPT (520mg, 1.74 mg) y diisopropiletilamina (0.61 ml, 3.48 mmol) en 3 ml de DMF se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se diluyó con EtOAc (50ml) y se lavó con agua (50 ml). La capa acuosa se extrajo con EtOAc (3 x 50ml). Los extractos orgánicos se combinaron y se secaron sobre Mg_2SO_4, se filtraron y se concentraron hasta secarse. El residuo se volvió a disolver en EtOAc y el precursor 5ab se cristalizó como un sólido café pálido y se recolectó por filtración (221mg, 27%). ^1H RMN (d, MeOD): 8.4 (s, 1H), 8.1 (s, 1H), 7.5 (bs, 5H), 3.82-3.53 (m, 8H); EM m/z 461 (MH); tiempo de retención = 1. 24 min.

PROCEDIMIENTO GENERAL PARA LA PREPARACIÓN DE LOS EJEMPLOS 302-315

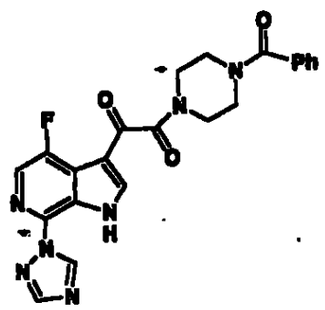


344

Procedimiento general para la preparación de los heterociclos 7-N enlazados

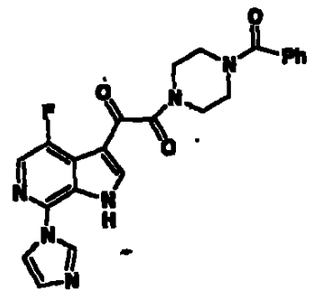
Una mezcla del precursor 5ab para los ejemplos 302-313 ó 5ac para los ejemplos 314-315, los equivalentes 15-30 de la amina correspondiente, preferiblemente 30 equivalentes se usaron, 1 equivalente de polvo de cobre y 1 equivalente de carbonato de potasio se calentaron a 160°C durante 4-7 horas en un tubo sellado. La reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc y se filtró a través de papel filtro. El solvente se removió en vacuo y el residuo se diluyó con metanol y se purificó por CLAR preparativa.

EJEMPLO 303



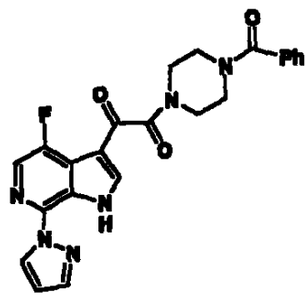
El Ejemplo 303 se preparó a partir del precursor 5ab y 1,2,4-triazol siguiendo el procedimiento antes descrito. ^{1}H RMN (500 MHz, $CDCl_3$): 11.15 (bs, 1H); 9.28 (s, 1H); 8.33-8.34 (m, 1H); 8.22 (s, 1H); 8.10 (s, 1H); 7.46-7.42 (m, 5H); 3.90-3.48 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 448. tiempo de retención = 1.21 min.

EJEMPLO 304



El ejemplo 304 se preparó a partir del precursor 5ab e imidazol siguiendo el procedimiento antes descrito. ^{1}H RMN (500 MHz, $CDCl_3$): 13.35 (bs, 1H); 9.49 (s, 1H); 8.35-8.30 (m, 1H); 8.20 (s, 1H); 7.97 (s, 1H); 7.56-7.53 (m, 1H); 7.46-7.41 (m, 5H); 3.98-3.40 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 447. tiempo de retención = 1.25 min.

EJEMPLO 305

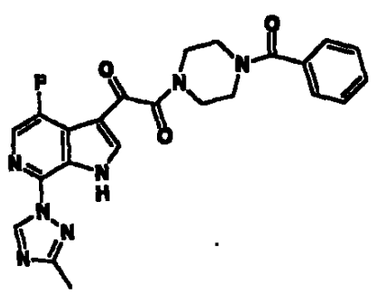


El Ejemplo 305 se preparó a partir del precursor 5ab y pirazol siguiendo el procedimiento antes descrito. ^{1}H RMN (500 MHz, $CDCl_3$): 11.52 (bs, 1H); 8.65-8.64 (m, 1H); 8.27-8.26 (m, 1H); 8.05-8.04 (m, 1H); 7.81-7.80 (m, 1H); 7.50-7.35 (m, 5H); 6.54-6.53 (m, 1H); 4.01-3.47 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 447. tiempo de retención = 1.25 min. El

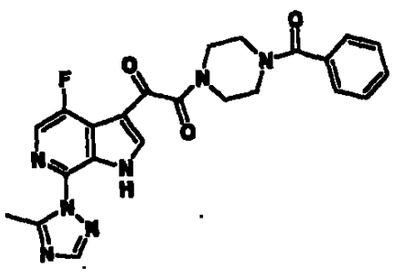
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compuesto del Ejemplo 222 se preparó a partir del precursor 5i y morfolina siguiendo el procedimiento antes descrito. ^{1}H RMN (300 MHz, CD_3OD_3): 8.38 (s, 1H); 7.86-7.84 (m, 1H); 4.14-3.25 (m, 16H). CL/EM: (ES^+) m/z $(M+H)^+$ = 466. tiempo de retención = 0.988 min.

EJEMPLOS 306 y 307



Ejemplo 306

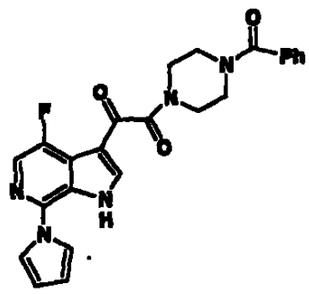


Ejemplo 307

Los ejemplos 306 y 307 se prepararon del precursor 5ab al usar el procedimiento general previamente descrito antes de usar 3-metiltriazol. Ejemplo 306: ^{1}H RMN (500MHz, $CDCl_3$): 9.14 (s, 1H); 8.32 (s, 1H); 8.06 (s, 1H); 7.42 (m, 5H); 3.75-3.85 (m, 4H); 3.55-3.70 (m, 4H); 2.57 (s, 3H). CL/EM: (ES^+) m/z $(M+H)^+$ = 462; tiempo de retención = 1.27 min. Ejemplo 307: ^{1}H RMN (500 MHz, $CDCl_3$): 8.29 (s, 1H); 8.17 (s, 1H); 8.05 (s, 1H); 7.42 (m, 5H); 4.75-4.85 (m, 4H); 4.55-5.70 (m, 4H); 3.02 (s, 3H). CL/EM: (ES^+) m/z $(M+H)^+$ = 462; tiempo de retención = 1.27 min.

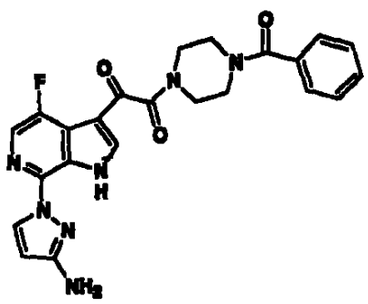
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EJEMPLO 308



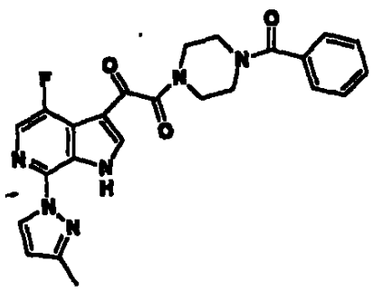
El ejemplo 308 se preparó a partir del precursor 5ab y pirrol siguiendo el procedimiento antes descrito. ^{1}H RMN (300 MHz, CD_3OD_3): 8.33-8.29 (m, 2H); 7.49-7.40 (m, 5H); 7.38-7.37 (m, 2H); 6.42-6.41 (m, 2H); 3.91-3.40 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 446. tiempo de retención = 1.34 min.

EJEMPLO 309



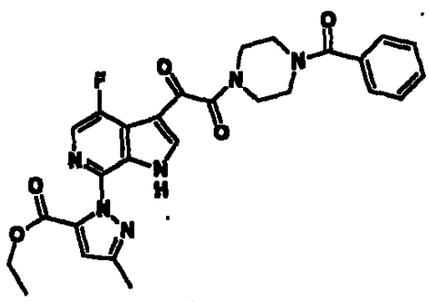
El compuesto del título se preparó a partir del precursor 5ab al usar el procedimiento general previamente descrito al usar 3-aminopirazol. ^{1}H RMN (300 MHz, DMSO): 12.42 (bs, 1H); 8.34-8.33 (m, 1H); 8.31-8.30 (m, 1H); 8.04-8.03 (m, 1H); 7.44 (bs, 5H); 5.93-5.92 (m, 1H); 3.80-3.16 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 462. tiempo de retención = 1.26 minutos.

EJEMPLO 310



El compuesto del título se preparó a partir del precursor 5ab de conformidad con el procedimiento general previamente descrito al usar 3-metilpirazol. ^{1}H RMN (500 MHz, $CDCl_3$): 11.59 (bs, 1H); 8.53-8.52 (m, 1H); 8.27-8.26 (m, 1H); 8.02-8.01 (m, 1H); 7.46-7.42 (m, 5H); 6.32-6.31 (m, 1H); 3.82-3.48 (m, 8H); 2.43 (s, 3H). CL/EM: (ES^+) m/z $(M+H)^+$ = 461. tiempo de retención = 1.50 minutos.

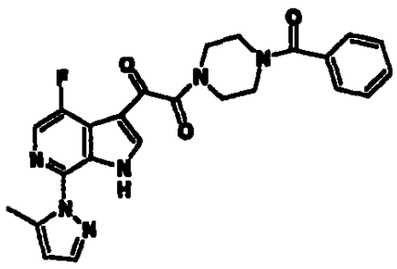
EJEMPLO 311



El compuesto del título se preparó a partir del precursor 5ab de conformidad con el procedimiento general previamente descrito. ^{1}H RMN (500MHZ, $CDCl_3$): 11.92 (bs, 1H); 8.28-8.27 (m, 1H); 8.08-8.07 (m, 1H); 7.47-7.42 (m, 5H); 6.73-6.72 (m, 1H); 4.45-4.38 (m, 2H); 4.0-3.49 (m, 8H); 2.84

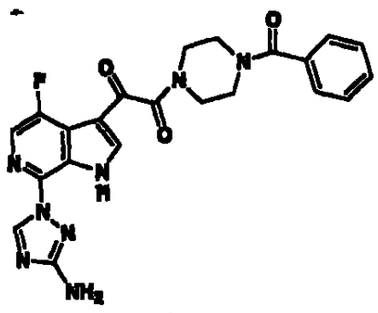
(s, 3H); 1.44-1.37 (m, 3H). CL/EM: (ES^+) m/z $(M+H)^+$ = 583. tiempo de retención = 1.67 min.

EJEMPLO 312



El ejemplo 312 se preparó a partir del precursor 5ab de conformidad con el procedimiento general previamente descrito al usar 3-metilpirazol. ^1H RMN (300 MHz, $CDCl_3$): 11.61 (bs, 1H); 8.23-8.22 (m, 1H); 8.06-8.05 (m, 1H); 7.67-7.66 (m, 1H); 7.42 (m, 5H); 6.25 (m, 1H); 3.89-3.48 (m, 8H); 2.82 (s, 3H). CL/EM: (ES^+) m/z $(M+H)^+$ = 461. tiempo de retención = 1.41 min.

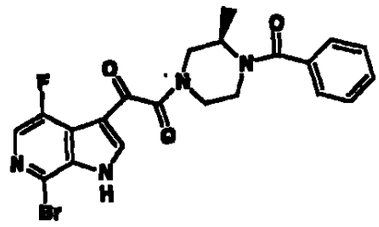
EJEMPLO 313



El ejemplo 313 se preparó a partir del precursor 5ab de conformidad con el procedimiento general previamente descrito al usar 3-amino-1,2,4-triazol. ^1H RMN (500 MHz, $CDCl_3$): 11.12

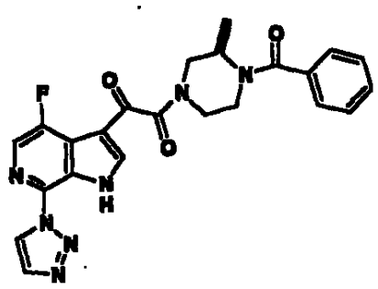
(bs, 1H); 8.89-8.88 (m, 1H); 8.29-8.28 (m, 1H); 8.03-8.02 (m, 1H); 7.58-7.51 (m, 5H), 3.87-3.50 (m, 8H). CL/EM: (ES^+) m/z $(M+H)^+$ = 463. tiempo de retención = 1.16 min.

PRECURSOR 5AC



El precursor 5ac se preparó a partir del precursor 4t siguiendo el procedimiento descrito por el precursor 5ab al usar 1-benzoil-3-(R)-metilpiperazina en lugar de bencilpiperazina. CL/EM: (ES^+) m/z $(M+H)^+$ = 474-475. tiempo de retención = 1.20 min.

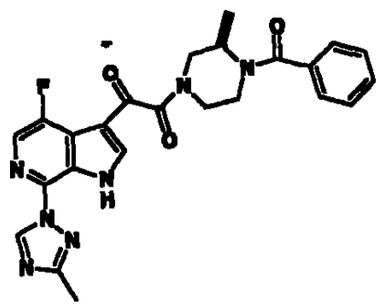
EJEMPLO 314



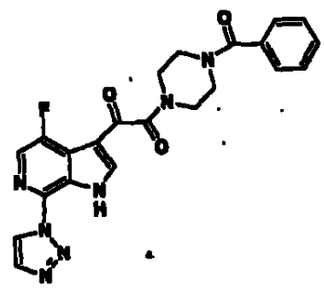
El ejemplo 314 se preparó a partir del Precursor 5ac siguiendo el procedimiento general descrito antes por los heterociclos enlazados a 7-N. ^1H RMN (500 MHz, $CDCl_3$): 8.75 (s, 1H); 8.36 (m, 1H); 8.08 (m, 1H); 7.45-7.38 (m, 5H); 4.75-

2.947 (series de múltiplos, 7H); 1.37-1.30 (m, 3H).

EJEMPLO 315



El ejemplo 315 se preparó a partir del Precursor 5ac siguiendo el procedimiento general descrito antes por heterociclos enlazados a 7-N. ^{1}H RMN (500 MHz, $CDCl_3$): 9.15 (s, 1H); 8.32 (d, J = 3.0 Hz, 1H); 8.16 (m, 1H); 7.92 (s, 1H); 7.45-7.38 (m, 5H); 4.72-2.94 (series de múltiplos, 7H); 2.57 (s, 3H); 1.37-1.30 (m, 3H); CL/EM: (ES^+) m/z $(M+H)^+$ = 476. tiempo de retención = 1.29 min.



Procedimientos experimentales sintéticos para la mejor preparación del ejemplo 216 (Esquema de reacción 80)



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Se agregó 5-Amino 2 metoxipiridina (50g, 0.4 mol) a una mezcla agitada de etanol absoluto (280 ml) y HBF_4 (48% en agua, 172 ml) y se enfrió a 0°C. Se disolvió nitrato de sodio (129g) en agua (52 ml) y se agregó en porciones durante 1 hora). La agitación continuó a 0°C durante 2 horas. La mezcla de reacción se diluyó con éter (1L). El producto sólido se recolectó por filtración y se lavó con 500 ml de 50:50 EtOH/éter y posteriormente varias veces con éter hasta que el producto se volvió ligeramente rosado en color. El sólido rosa pálido 90g (~100% de rendimiento) se mantuvo en un deshidratador sobre P_2O_5.

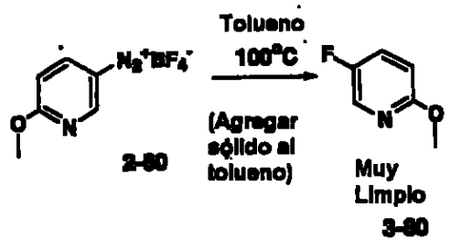
El mismo procedimiento se siguió para llevar a cabo la reacción a una escala mayor:

-- (1) (200g, 1.6 mol); HBF_4 (688 ml); $NaNO_2$ (116 g); EtOH (1.12 L); H_2O (208 ml).

La reacción se corrió 4 veces (total 800 gramos (1-80)). El producto se secó sobre P_2O_5 durante 48 horas (solamente 24 horas por el primer lote).

Un total de 1,293 g de (2-80) se obtuvieron, (91% de rendimiento).

Ref: J. Heterocyclic Chem., 10,779,1973 (para las reacciones de arriba, incluyendo datos analíticos)



La descomposición de la sal de diazonio se corrió en 3 lotes de:

206 g, 219 g y 231 g al usar 1.3L, 1.4L y 1.6L de tolueno anhidro respectivamente.

El tolueno se precalentó bajo nitrógeno hasta 100°C (temperatura interna) en un matraz de 2L de fondo redondo de 3 cuellos con un agitador mecánico. El sólido se agregó en porciones por medio de una cuchara a través de un embudo de polvo el cual se colocó a un adaptador con un flujo de nitrógeno positivo externo ligero. Durante la adición, la temperatura se mantuvo entre 99-102°C (fijada a 100°C) y se agitó vigorosamente. El tiempo de adición total fue de 60 minutos para los dos lotes más pequeños y 70 minutos para el último. Después de que la adición finalizó, cada reacción de agitación se calentó a 110°C durante 1 hora. La cubierta de calentamiento se removió y se agitó hasta detenerse. Las reacciones se permitieron reposar durante 2 horas (alcanzado temperatura ambiente). Nota de seguridad: la reacción contiene BF3 de manera que quien trabaja con los vapores calientes se expone a vapores que causan irritación en la piel con algunas personas. No se notan incidentes a

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temperatura ambiente (6 personas diferentes). El tolueno caliente de la reacción se vació en un Erlenmeyer de 4L (queda en el matraz un aceite café oscuro y el residuo). El residuo se lavó con 50 ml de tolueno y se vació en los extractos de tolueno originales.

Se agregó 1.5L de NaOH 1N a la capa de tolueno, se extrajo y se lavó con ~100 ml de NaCl acuoso saturado.

El NaCl se combinó con la capa de NaOH, se volvió a extraer con 150 ml de tolueno, se lavó con 50 ml de NaCl saturado.

Las capas de tolueno se combinaron.

Se agregó 1L de NaOH 1N al residuo en el matraz de reacción y se agitó para disolver tanto residuo como sea posible, luego se agregó 500 ml de Et_2O y se vació en el Erlenmeyer.

Se agregó ~500 ml más de NaOH 1N al matraz de reacción y se revolvió ~500 ml de Et_2O.

El combinado oscuro de Et_2O y NaOH se lavó en el matraz erlenmyer.

La mezcla Et_2O/NaOH se vació a través de un embudo de polvo que contiene un tapón de cristal y lana para colectar el sólido viscoso oscuro. (Se agregó ~500 ml más de éter para lavar) en 6L embudo sep.

Extracto. La capa de éter se lavó con ~200ml de H_2O y luego 100 ml de NaCl saturado.

Se lavaron todos los combinados con la capa acuosa de NaOH original y se volvieron a extraer con 500 ml de éter. Se lavó con 100 ml H_2O y 100 ml de NaCl.

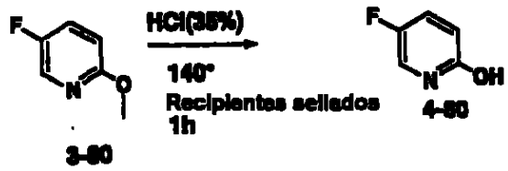
Los extractos de éter se combinaron. Los extractos de tolueno y éter se checaron por un producto limpio CL/EM.

El éter se concentró en un evaporador rotatorio y el residuo se combinó con los extractos de tolueno para hacer una solución homogénea la cual se tomó para la siguiente etapa como es.

Las otras dos corridas se combinaron y se trabajaron de la misma manera.

Todas las capas acuosas se checaron por CL/EM = sin producto.

Ref: J. Heterocyclic Chem., 10, 779, 1973 (para las reacciones de arriba, incluyendo datos analíticos)



3-80 4-80

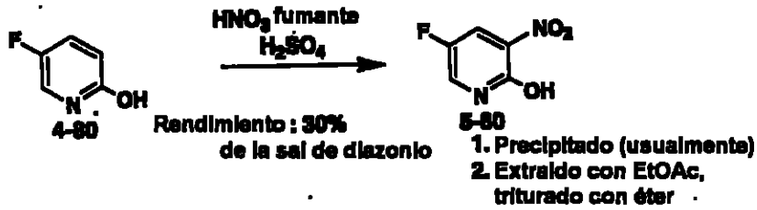
Un total de 4.6L de una solución de tolueno que contiene 3-80 se colocó en varios tubos sellados y se trató con 900ml de HCl al 35% a 145°C durante 2 horas. El CL/EM no mostró material de partida, solamente 4. La solución de tolueno se decantó y se descartó. La fase acuosa se lavó con EtOAc y se concentró para remover los volátiles, para proporcionar un sólido café que

concentró para remover los volátiles, para proporcionar un sólido café que contiene la fluoro-hidroxipiridina 4-80 deseada.

Un total de 244g de este sólido se recolectó y se tomó para la siguiente etapa como es (no está completamente seco).

Nota: Posteriormente se ha corrido al vaciar la primera capa de tolueno antes de calentar para reducir el volumen. La misma reacción se lleva a cabo usando HBr (48% en H_2O) a 100°C durante 6 horas con un resultado similar al procedimiento de la literatura en 49% de rendimiento.

Ref: J. Heterocyclic Chem., 10,779,1973 (para reacciones de arriba, incluyendo datos analíticos)



El sólido de arriba que contiene (4-80) se dividió en 4 lotes y se trató con H_2SO_4 y HNO_3 fumante como se mostró a continuación. Las cantidades usadas fueron:

	Lote 1	Lote 2	Lote 3	Lote 4
(1)	25 g	54 g	75 g	90 g
Fumante HNO_3	20.8 ml	45 ml	62.4 ml	75 ml
H_2SO_4 (para adición)	5.6 ml+	12 ml+	16.8 ml+	20 ml+
(para soln)	56 ml	120 ml	168 ml	200 ml

El compuesto 4-80 se disolvió en ácido sulfúrico (las cantidades más grandes se indican arriba) a temperatura ambiente y luego se calentó a 65°C. Una solución preformada de ácido nítrico fumante y ácido sulfúrico (la cantidad más pequeña indicada arriba) se agregó gota a gota. La temperatura se mantuvo entre 65°C y 80°C (rxn es exotérmico y no obstante que el baño está a 65°C, la temperatura se hace superior, usualmente 75, algunas veces 80°C). Después de que la adición se completó, la mezcla de reacción se calentó a 65°C durante 1 hora adicional. La mezcla de reacción luego se enfrió a temperatura ambiente y se vació en un matraz que contiene hielo) (20g de hielo/gr de compuesto, la evolución del gas se presenta). Un precipitado sólido salió y esto se recolectó por filtración (^{1}HNM" mostró 4-80 y algunas veces otro (se descartó)).

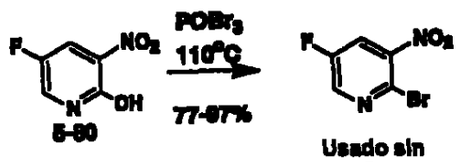
La capa acuosa se extrajo con AcOEt varias veces (3-5) y se concentró en un evaporador rotatorio bajo vacío para proporcionar un sólido que se trituró con éter para resultar 5-80 como un sólido amarillo ligero. Un total de 117g del producto deseado se colectó en el primer cuerpo (27% de rendimiento de sal de diazonio). La porción no se cristalizó: este aceite se trituró con MeOH y Et_2O para resultar 3.6g de 5-80; otra precipitación del líquido madre proporcionó 6.23g adicionales del producto deseado 5-80.

Total: 117.0+3.6+6.23 = 126.83. 30.4%). Rendimiento de 3

etapas (descomposición de sal de diazonio; desprotección y nitración).

Datos analíticos del cuaderno: 53877-115: ^{1}H RMN (δ, MeOD): 8.56-8.27 (dd, J=7.5, 3.3 Hz, 1H), 8.01 (d, J=3.3 Hz, 1H); CL/EM $(M+1)^+$ = 158.9; tiempo de retención = 0.15 min.

Nota: Una porción de la solución ácida acuosa se tomó y se neutralizó con Na_2CO_3 hasta que se detuvo la efervescencia y luego se extrajo con AcOEt ⇒ Un producto diferente se obtuvo. No se desea producto en estos extractos.



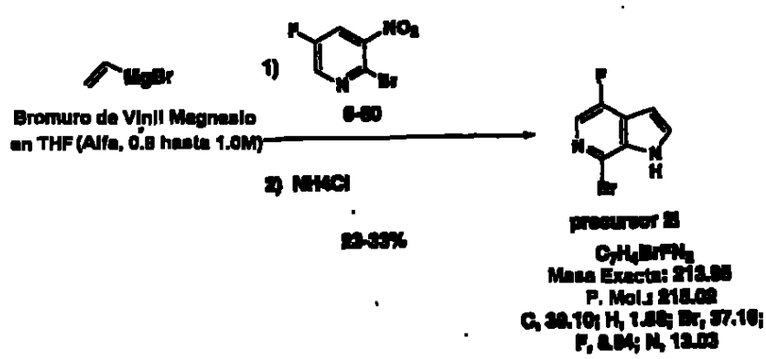
Un total de 117g de 5-80 se dividió en 4 lotes de 30g x 3 y 27g x 1 y se trató con $POBr_3$ (3 equiv.; 163g x 3 y 155 g x 1) y una cantidad catalítica de DMF (15 ml) a temperatura ambiente (DMF se agregó cuidadosamente ⇒ evolución de gas). Después de 5 minutos a temperatura ambiente, las soluciones se calentaron a 110°C durante 3 horas. La CL/EM mostró que el material de partida se consumió. Las mezclas de reacción se permitieron enfriar a temperatura ambiente. Los matraces de reacción se colocaron en un baño de hielo; y luego se agregó hielo muy lentamente y cuidadosamente en porciones en el matraz, la evolución de gas se debe a la formación de HBr; el líquido y el sólido negro que se formó se vació en una cubeta

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con hielo. Se agregó EtOAc y la mezcla luego se extrajo varias veces con EtOAc. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado; H_2O y salmuera; se secó sobre Na_2SO_4 y se filtró. El producto se secó en la bomba durante la noche para suministrar 123g del 6-80 como un sólido café (77% de rendimiento).

Nota: La reacción se completó dentro de 1 hora.

^1H RMN (δ, $CDCl_3$): 8.52 (m, 1H), 7.93 (m, 1H).

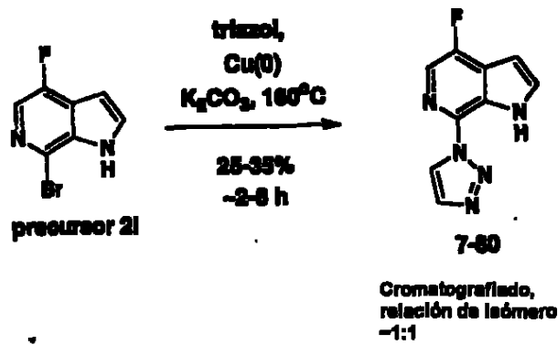


Se enfriaron 800 ml de bromuro de vinil magnesio (1M en THF, Aldrich) debajo de -60°C con agitación vigorosa bajo N_2. La 2-bromo-5-fluoro-3-nitro piridina (43.3g, 0.196 mol) en 200 ml de THF se agregó gota a gota por medio de un embudo de adición a una relación tal que la temperatura se mantuvo debajo de -60°C. Esto tomó ~1.25 hora. La mezcla de reacción se calentó a -40 hasta -50°C y se agitó durante 1 hora más. Luego 1L de NH_4Cl acuoso saturado se agregó lentamente y cuidadosamente. Primero, se presenta un espumado y luego se presenta un sólido considerable, pero esencialmente se

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disolvió cuando la adición se completó y el material se calentó a temperatura ambiente. Las capas se separaron y la capa acuosa se extrajo 3 veces con acetato de etilo. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron para resultar en ~50 g de un sólido gomoso negro. La CLAR indicó 57-58% del producto. A esto se agregó CH_2Cl_2 y el sólido se recolectó por filtración y se lavó con CH_2Cl_2 para resultar 12.5g del producto como un sólido café. La reacción se repitió en exactamente la misma escala y se preparó en la misma manera. De la trituración CH_2Cl_2 se obtuvieron 12.4g del Precursor 2i (CLAR-97% puro). El crudo se recubrió y se permitió estar en diclorometano. Durante el reposo, 3.6 g del producto adicional se separaron y se recubrieron por filtración.

Rendimiento total = 29.5g (35%). ^1H RMN (δ, $CDCl_3$): 8.69 (bs, 1H), 7.92 (d, J=1.8 Hz, 1H), 7.41 (m, 1H), 6.77 (m, 1H); CL/EM $(M+1)^+$ = 216.-217.9; tiempo de retención = 1.43 min.

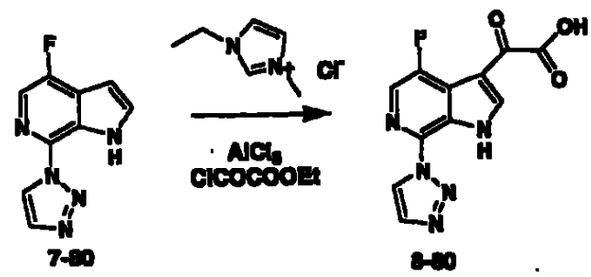


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La reacción se portó en un matraz de 250ml (ocurriendo una espuma durante el calentamiento y el matraz de tamaño más grande es más conveniente). Una mezcla del precursor 2i (3g, 13.95 mmol), 1,2,3-triazol (15g, 217.6 mmol, 15 eq.), K_2CO_3 (1.9 g, 13.95 mmol, 1 eq) y Cu (O)(0.9g, 13.9 mmol, 1eq.) se calentó a 160°C durante 7 horas (desde temperatura ambiente hasta 160°C total 7 horas) bajo N_2 (dependiendo en el lote de Cu(O), el tiempo de reacción puede variar desde 2 horas hasta 7 horas). La mezcla resultante se diluyó con MeOH, se filtró a través de papel filtro (para remover el cobre). Se lavó con MeOH (20 ml) y agua (30 ml).

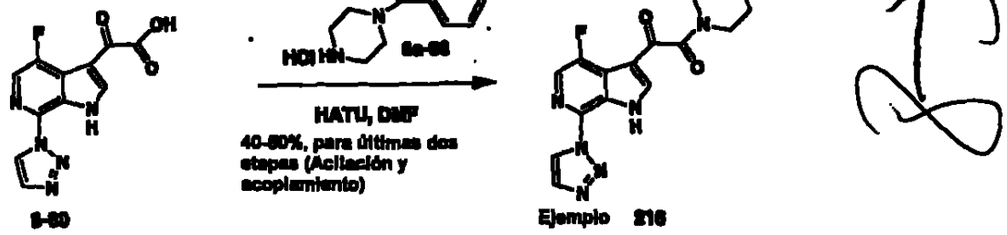
El filtrado se concentró (el solvente se removió en un evaporador rotatorio) y se diluyó con acetato de etilo. La capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se disolvió en MeOH (20 ml), 7-80 (750mg) se cristalizó a partir de metanol como un sólido blanco y se recolectó por filtración. (volumen de gradiente bajo, gel de sílice hex/AcOEt (0→48%) de licores madre usualmente proporciona 5-10% más de 7-80.

^{1}H RMN (δ, $CDCl_3$): 10.47 (bs, 1H), 8.76 (s, 1H), 7.94 (s, 1H), 7.89 (s, 1H), 7.53 (m, 1 H), 6.78 (m, 1H); CLEM $(M+1)^+$ = 204; tiempo de retención = 1.29 min.



Cromatografiado, relación de isómero ~1:1

El cloruro de etil metilimidazolio (4.3g, 29.6 mmol, 3eq) se colocó en un matraz de 250 ml. Se agregó $ACLl_3$ (11.8g, 88.6mmol, 9eq) en el matraz en una porción. Una suspensión líquida se formó (algo de $ACLl_3$ se mantiene como sólido). Después de agitarse durante 5-10 minutos, el compuesto (1) (2.0g, 9.85 mmol) se agregó en una porción seguido por la adición lenta (por medio de una jeringa) de clorooxalacetato de etilo (3.3 mL, 29.6 mmol, 3eq). La reacción se agitó a temperatura ambiente durante 20 horas. La CLEM indicó que el compuesto 8-80:compuesto 7-80 = 6:2. (El compuesto I tiene una absorción de UV fuerte) La reacción se apagó por adición cuidadosa de agua con hielo (~75 ml) a 0°C. Un sólido amarillo se precipitó a este punto. La suspensión resultante se filtró y el sólido se lavó con agua. El MeOH y acetato de etilo (para remover el SM que no reacciona) y el sólido se secaron al aire. (pureza CLEM 70% ~ 80%) 2g del sólido que contiene 8-80 se obtiene y se toma para la siguiente etapa sin purificación adicional. CLEM $(M+1)^+$ = 276; tiempo de retención = 0.97 min.



Una mezcla del compuesto 8-80 (4.9g, 17. 8 mmol) y clorohidrato de N-benzoilpiperazina 8a-80 (sal HCl; 6.0g, 26.7mmol, 1.5eq) en DMF (30 ml) se agitó a temperatura ambiente durante la noche (16 horas). Se formó una solución espesa. Se agregó 20 ml adicionales de DMF en la solución espesa. Luego se agregó HATU (12.2g, 26.7mmol, 1.5eq) seguido por DMAP (4.3g, 35.6 mmol, 2eq). La mezcla de reacción se agitó durante 30 minutos. La CLEM indicó que el material de partida 8-80 se completó convirtiendo al producto (EJEMPLO 216). La mezcla resultante se filtró y el sólido se lavó con agua. El filtrado se concentró en vacuo. Se agregó agua al residuo y el sólido se recolectó por filtración. Los sólidos se combinaron y se lavaron con agua, MeOH y EtOAc. Luego el sólido se secó al aire. La CLEM y CLAR mostró BEM-585248, >99% puro. El producto sólido se purificó además por precipitación y cristalización en 5 ~ 10% $CH_3OH/CHCl_3$.

Purificación del Ejemplo 216

El compuesto crudo del Ejemplo 216 obtenido como arriba (15.3g) se disolvió en MeOH/$CHCl_3$ al 10% (600 ml). Una suspensión café ligera se formó, se filtró a través de papel filtro y se lavó con MeOH dos veces. El sólido café se descartó (~1.2g). El Ejemplo 216 se cristalizó en el filtrado, el sólido se recolectó por filtración y el sólido blanco se secó al aire. El filtrado se usó para repetir la cristalización varias veces. El sólido obtenido de cada filtración se analizó por CLAR. Todas las fracciones puras se combinaron. Las fracciones no puras se volvieron a someter a cristalización con MeOH y $CHCl_3$. Un total de 12.7g del Ejemplo 216 se obtienen de la recristalización y precipitación. El líquido madre se concentró y se purificó sobre columna de gel de sílice (EtOAc, luego $CHCl_3$/MeOH (0-2%)) para suministrar 506mg del producto) como un sólido blanco.

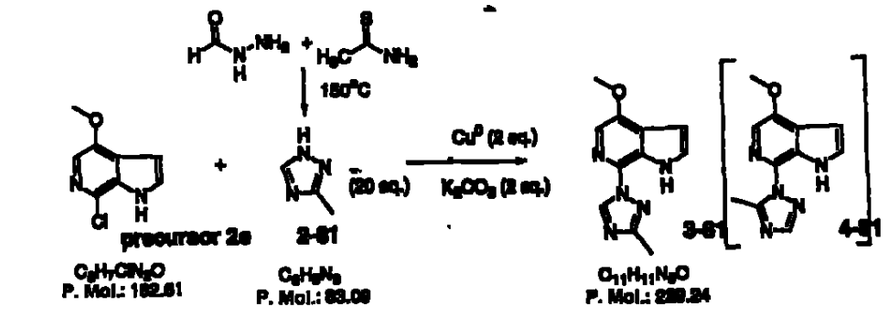
^1H RMN (d, DMSO) 13.1 (bs, 1H), 9.0 (s, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 8.2 (s, 1H), 7.4 (bs, 5H), 3.7 (bs, 4H), 3.5 (bs, 4H); EM m/z 448 (MH). Análisis calculado para $C_{22}H_{18}FN_7O_3$; C 59.05, H 4.05, N 21.91, F 4.24. Encontrado; C 57.28, H 4.14, N 21.22; F 4.07%.

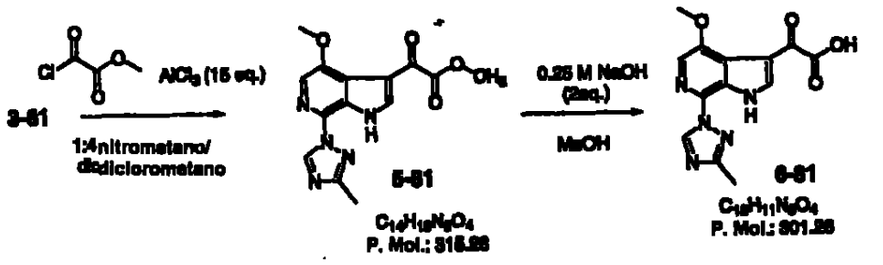
El Esquema de reacción 81 es un método preferido para hacer los compuestos de la fórmula I y Ia en donde R^2 es metoxi. Esto se ejemplifica específicamente para la

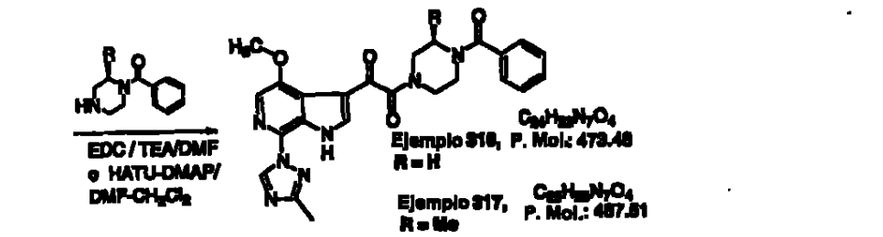
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preparación del compuesto del Ejemplo 316 y 317.

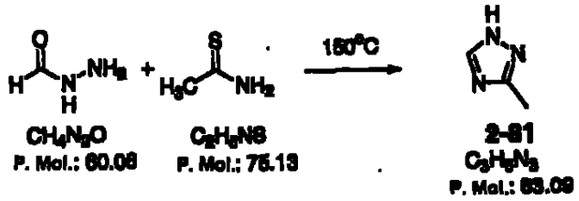
Esquema de reacción 81







Preparación de 3-metil-1,2,4-triazol (2-81)



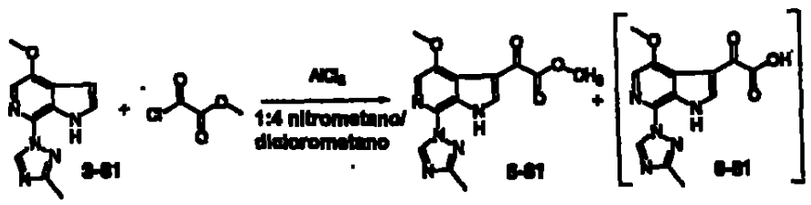
metil-1,2,4-triazol (83 g, 1.0 mol, 20 eq.). La mezcla sólida se calentó hasta fundirse a 170-175°C (temperatura del baño de aceite externo) bajo una corriente suave de nitrógeno anhidro durante 12 horas, por lo cual el análisis CLAR de tiempo indica que la cantidad del pico para el material de partida siendo 5-30% y el pico del producto deseado es de alrededor de 45% con el isomérico con pico de subproducto siendo 15%. Como la mezcla de reacción se enfría, se agregó MeOH (150 mL) lentamente a la mezcla caliente agitada. Durante el enfriamiento, el material insoluble (polvo de cobre) se filtró a través de una almohadilla de Celite, y se enjuagó con metanol. El filtrado se concentró en vacuo para dar una solución espesa la cual se diluyó con agua (1 L) y se extrajo con EtOAc (3x150ml). Los extractos EtOAc se secaron ($MgSO_4$), se filtraron y se concentraron para obtener alrededor de 8 g del residuo crudo, el cual se cristalizó al disolverse en CH_3CN caliente (50 mL), seguido por dilución con agua (100 mL) y se enfrió a 0°C para colectar 1.45 g (12.7%) del compuesto del título como un sólido blanco. El filtrado se purificó por C-18 de gel de sílice de fase inversa (YMC ODS-A 75 μm) se eluyó con 15-30% CH_3CN/H_2O. Las fracciones apropiadas se combinaron y la solución acuosa después de remover el CH_3CN por evaporador rotatorio se liofilizo para dar 1.15 g adicional del compuesto del título 3-81. La capa acuosa cruda además se extrajo con EtOAc varias

veces. Los extractos de acetato de etilo se secaron ($MgSO_4$), se filtraron, se concentraron, y se cristalizaron de MeOH para dar 200 mg adicionales del compuesto del título 3-81. El rendimiento total: 2.8 g (12.2 mmol, R. 24.5%); EM m/z 230 (MH), EMAR (ESI) m/z calculado para $C_{11}H_{12}N_5O$ (M+H), 230.1042, encontrado 230.1038 (Δ-1.7 ppm); ^1H RMN ($CDCl_3$) δ ppm 2.54 (3H, s, CH_3), 4.05 (3H, s, OCH_3), 6.73 (1H, s, H-3), 7.40 (1H, s, H-2), 7.56 (1H, s, H-5), 9.15 (1H, s, triazol-H-5); ^{13}C RMN ($CDCl_3$, 125.7 MHz) δ ppm 14.2 (triazol-Me), 56.3 (OMe), 100.5 (C-3), 116.9 (C-5), 123.5, 127.2, 127.5 (C-2), 129.5 (C-7), 141.2 (C-5'), 149.5 (C-4), 161.8 (C-3'); Análisis Calculado para $C_{11}H_{11}N_5O$: C 57.63, H 4.83, N 30.55, encontrado C 57.37, H 4.64, N 30.68.

La estructura se confirmó por un análisis cristalográfico de rayos X sencillo usando cristales obtenidos de fracciones de columna C-18. Una porción de las fracciones de columna C-18 QUE contiene una mezcla del 3-metil-1,2,4-triazolilo deseado, el 3-81 análogo y el 5-metil-1,2,4-triazolil análogo isomérico 4-81 se purificó además por una columna de fase inversa C-18 eluyendo con 8-10% de CH_3CN/H_2O. Las fracciones apropiadas se extrajeron con CH_2Cl_2, y la evaporación lenta del solvente dio un material cristalino del 7-(5-metil-1,2,4-triazolil)-4-metoxi-6-azaindol isomérico (4-81): EM m/z 230 (MH), ^1H RMN ($CDCl_3$) δ ppm 3.05 (3H, s, CH_3), 4.07 (3H, s, OCH_3), 6.74 (1H, q, J=2.4,

H-2), 7.37 (1H, t, J=2.4, H-3), 7.65 (1H, s, H-5), 8.07 (1H, s, triazol-H-3). La estructura se confirmo por un análisis cristalográfico de rayos X sencillo.

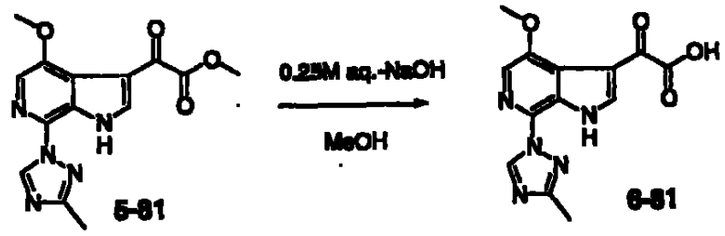
Preparación de 5-81



Procedimiento: Se disolvió $AlCl_3$ (40 g, 0.3 mol, 15 eq.) en una solución de CH_2Cl_2 (100 mL) y nitrometano (20 mL) bajo nitrógeno seco. A esta solución se le agregó el compuesto 3-81 (4.58 g, 0.02 mol) bajo agitación y bajo N_2, seguido por clorooxoacetato de metilo (9.8 g, 0.08 mol, 4 eq.). La mezcla se agitó bajo N_2 a temperatura ambiente durante 1.5 hora. La mezcla se agregó gota a gota a una solución enfriada y agitada de una solución de acetato de amonio acuoso al 20% (750 mL). La mezcla se agitó durante 20 minutos, y el precipitado resultante se filtró, se lavó a fondo con agua y se secó en vacuo para obtener 4.7 g (0.015 mol, R. 75%) del compuesto del título 5-81 como un sólido blanco: EM m/z 316 (MH); EMAR (ESI) m/z calculado para $C_{14}H_{14}N_5O_4$ (M+H), 316.1046; encontrado 316.1041 (Δ-1.6 ppm); ^1H RMN ($CDCl_3$, 500 MHz) δppm 2.58 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.76 (1H, s, H-5), 8.34 (1H, d, J=3Hz, H-2), 9.15 (1H, s,

triazol-H-5), 11.0 (1H, brs, NH). Más compuesto del título 5-81 y ácido hidrolizado 6-81 pueden obtenerse del filtrado por extracción de base ácida con EtOAc.

Preparación de 6-81

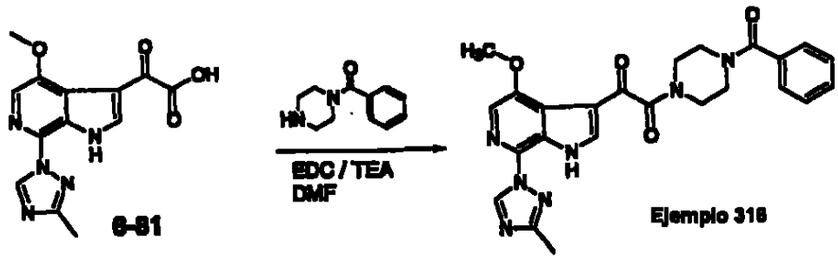


Procedimiento: A una suspensión del éster de metilo 5-81 (2.2 g, 7.0 mmol) en MeOH (50 mL) se le agregó solución de NaOH 0.25M en agua (56 mL, 14 mmol, 2 eq.) a temperatura ambiente y la mezcla se agitó durante 15 minutos tiempo al cual la CLAR indica que la hidrólisis se completó. La mezcla se concentró en vacuo rápidamente para remover el MeOH, y a la solución residual se agregó agua (100 mL) y HCl 1N (14 mL) con agitación para neutralizar la mezcla. El precipitado fino resultante se filtró, se lavó con agua y se secó in vacuo para obtener 1.98 g (6.58 mmol, R. 94%) del compuesto del título 6-81 como un sólido blanco opaco: EM m/z 302 (MH); ^{1}H RMN (DMSO-d_6, 500 MHz) δ ppm 2.50 (3H, s, traslapado con picos de DMSO), 3.98 (3H, s, CH_3O), 7.87 (1H, s, H-5), 8.29 (1H, d, J=3.5Hz, H-2), 9.25 (1H, s, triazol-H-5), 12.37 (1H, s, NH).

Procedimiento alternativo: A una suspensión del éster

de metilo 5-81 (10.7 g, 34 mmol) en MeOH (150 mL) se le agregó solución de NaOH 0.25M en agua (272 mL, 68 mmol, 2 eq.) a temperatura ambiente y la mezcla se agitó durante 20 minutos, tiempo al cual la CLAR indica que la hidrólisis se completó. La mezcla se concentró in vacuo rápidamente para remover el MeOH, y la solución restante se extrajo con EtOAc para remover cualesquiera de las impurezas neutrales. A la fase acuosa se le agregó HCl 1N (68 mL, 68 mmol) para neutralizar el producto. La mezcla resultante se congeló y se liofilizó para obtener 14.1 g (33.7 mmol, R. 99.2%) del compuesto del título 6-81, que contiene 2 equivalentes mol de NaCl como un sólido blanco opaco. Este material se usó en la reacción posterior sin purificación adicional. La sal de sodio del compuesto del título 6-81 se obtiene por cromatografía de columna de fase inversa C-18 después de tratamiento con bicarbonato de sodio: CLAR >97% (AP, uv a 254nm); EMAR (sal de Na, ESI-) m/z calculado para $C_{13}H_{10}N_5O_4$ (M-H), 300.0733; encontrado 300.0724 (Δ -3 ppm); ^{1}H RMN (sal de Na, DMSO-d_6, 500 MHz) δ ppm 2.37 (3H, s, Me), 3.83 (3H, s, CH_3O), 7.56 (1H, s, H-5), 8.03 (1H, s, H-2), 9.32 (1H, s, triazol-H-5); ^{13}C RMN (sal de Na, DMSO-d_6, 125.7 MHz) δ ppm 13.8 (triazol-Me), 57.2 (OMe), 114.8 (C-3), 120.0 (C-5), 125.1, 143.5 (C-5'), 149.8 (C-4), 160.0 (C-3'), 171.7, 191.3.

Preparación del Ejemplo 316



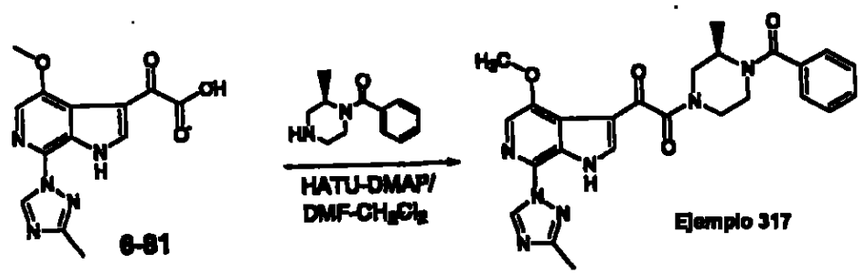
Procedimiento: A una solución del ácido 6-81 (3.01 g, 10 mmol) y clorohidrato de benzoilpiperazina (3.39 g, 15 mmol) en DMF (50 mL) se le agregó trietilamina (10.1 g, 100 mmol, 10 eq.), seguido por clorohidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (EDC; 5.75 g, 30 mmol) bajo N_2 y la mezcla se agitó a temperatura ambiente durante 22 horas después de sonicación y a 40°C durante 2 horas. La mezcla se concentró in vacuo para remover el DMF y TEA, y a la solución residual se le agregó agua (200 mL) bajo agitación y sonicación. Los precipitados formados se colectaron, se lavó con agua y se secó in vacuo para obtener 2.8 g (5.9 mmol, R. 59%) del compuesto del título Ejemplo 316 como un sólido blanco opaco. El filtrado se extrajo con CH_2Cl_2 (x2). Los extractos de CH_2Cl_2 se secaron (Na_2SO_4), se filtraron y se concentraron hasta una goma la cual se trituró con Et_2O para obtener un sólido. Este sólido se suspendió y se trituró con MeOH para obtener 400 mg del compuesto del título Ejemplo 316 como un sólido blanco opaco. Rendimiento total: 3.2 g (6.8 mmol, R. 68%): EM m/z 474 (MH); EMAR (ESI)

m/z calculado para $C_{24}H_{24}N_7O_4$ (M+H) 474.1890, encontrado 474.1884 (Δ - 1.2 ppm); ^1H RMN (DMSO-d_6) δ ppm 2.50 (3H, s, traslapado con picos de DMSO), 3.43 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 3.99 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.88 (1H, s, indol-H-5), 8.25 (1H, s, indol-H-2), 9.25 (1H, s, triazol-H-5), 12.40 (1H, s, NH); ^{13}C-RMN (DMSO-d_6) δ ppm 13.78, 40.58, 45.11; 56.78, 114.11, 120.95, 122.71, 123.60, 126.98, 128.34, 129.6, 135.43, 138.52, 142.10, 149.15, 161.29, 166.17, 169.22, 185.42; UV (MeOH) λmax 233.6 nm (ε $3.43x10^4$), 314.9 nm (ε $1.73x10^4$); Análisis: Calculado para $C_{24}H_{24}N_7O4.1/5H_2O$; C 60.42, H 4.94, N 20.55, Encontrado; C 60.42, H 5.03, N 20.65; KF (H_2O) 0.75%.

Esta reacción también puede realizarse por el uso de HATU y DMAP para suministrar un rendimiento más consistente del compuesto del título: A una suspensión del ácido 6-81 (15.6 mmol) y HATU [hexafluorofosfonato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio] (8.90 g, 23.4 mmol; 1.5 eq.) en DMF (60 mL) y CH_2Cl_2 (60 mL) se le agregó una mezcla de DMAP (5.72 g, 46.8 mmol, 3 eq.) y clorohidrato de benzoilpiperazina (5.30 g, 23.4 mmol; 1.5 eq.) en DMF (60 mL) a temperatura ambiente y la mezcla se agitó bajo atmósfera de nitrógeno por 4 horas. La mezcla se concentró in vacuo para remover el CH_2Cl_2 y la mayoría de DMF, y a la solución residual se le agregó agua bajo agitación y sonicación. Los precipitados formados se colectaron, se

lavaron con agua y se secó in vacuo para obtener 5.38 g (11.4 mmol, R. 72.8%) del compuesto del título Ejemplo 316 como un sólido blanco opaco: CLAR >95% (AP, uv a 254nm).

Preparación de Ejemplo 317

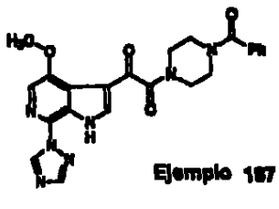


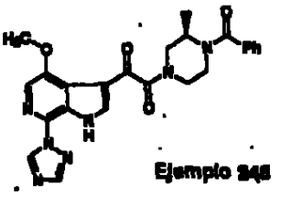
Procedimiento: A una solución del ácido 6-81, que contiene 2 mol equivalente de NaCl (4.1 g, 9.8 mmol) en CH_2Cl_2 (30 mL) y DMF (30 mL) se agregó a -10°C bajo nitrógeno anhidro HATU [hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio] (5.59 g, 14.7 mmol; 1.5 eq.), y se agitó a -10°C por 30 minutos. A esta mezcla se le agregó una solución de trifluoroacetato de 2-(R)-metil-N-benzoilpiperazina (4.7 g, 14.7 mmol; 1.5 eq.) y dimetilaminopiridina (3.5 g, 29 mmol; 3 eq.) en DMF (30 mL) y CH_2Cl_2 (30 mL) y la mezcla se agitó a temperatura ambiente durante la noche, tiempo al cual el análisis CLAR indicó que la reacción está esencialmente completa. La mezcla se concentró in vacuo para remover los volátiles y DMF, y al residuo se le agregó agua (~150 mL) bajo agitación y sonicación. Los precipitados formados se colectaron, se

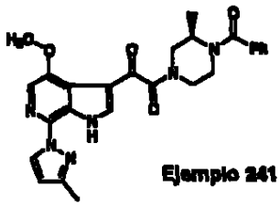
lavaron con agua y se secaron in vacuo para obtener 4.3 g del compuesto del título Ejemplo 317 como un sólido blanco opaco. Esto se disolvió en MeOH al 20% en CH_2Cl_2 (alrededor de 250 mL), removiendo cualquier material insoluble, y el filtrado se concentró in vacuo para remover más CH_2Cl_2 volátil. El precipitado resultante se recolectó, se lavó con MeOH y luego con Et_2O para obtener 3.5 g (7.18 mmol, R. 73.2%; AP >99%) del compuesto del título Ejemplo 317 como un sólido blanco opaco: CL/EM m/z 488 (MH); ^1H RMN (DMSO-d_6) δ ppm 1.15, 1.22 (3H, 2d, J = 7Hz), 2.50 (3H, s, traslapado con picos de DMSO), 3-4.3 (8H, m, CH_2N), 3.98, 4.00 (3H, s, CH_3O), 7.45 (5H, m, Ar-Hs), 7.89 (1H, s, indol-H-5), 8.19, 8.26 (1H, 2s, indol-H-2), 9.24, 9.25 (1H, 2s, triazol-H-5), 12.40 (1H, br. s, NH); Análisis: Calculado para $C_{25}H_{25}N_7O_4$; C 61.59, H 5.16, N 20.11, Encontrado; C 61.69, H 5.27, N 20.10; KF (H_2O) <0.1%.

NOTAS:

Los siguientes compuestos, Ejemplos 187, 245, y 241, también se prepararon por el método descrito arriba al usar azoles apropiados (1,2,4-triazol para el Ejemplo 187, y Ejemplo 245; 3-metilpirazol para el Ejemplo 241.


Ejemplo 187

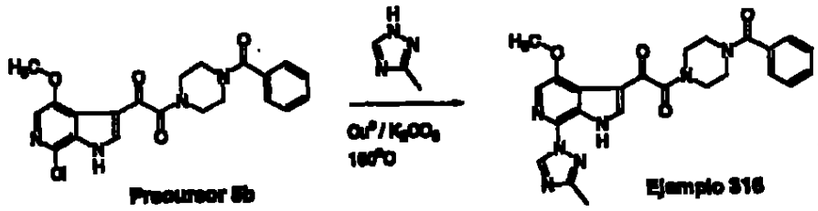

Ejemplo 245


Ejemplo 241

876

Preparación del Ejemplo 316

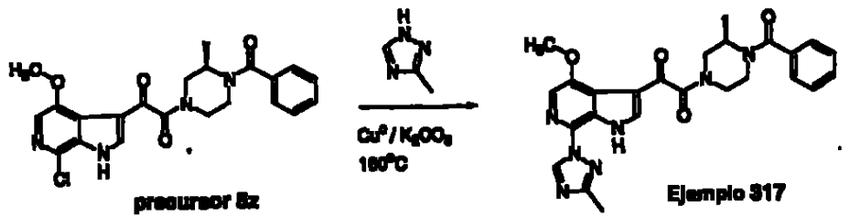
Preparación Alterna del Ejemplo 316



Una mezcla del compuesto precursor 5b (150 mg, 0.35 mmol), 3-metil-1,2,4-triazol (581 mg, 7 mmol; 20 eq.; preparado por el método descrito en Coll. Czech. Chem. Comm. 1985, 49, 2492), polvo de cobre (45 mg, 0.7 mmol; 2 eq.), carbonato de potasio (97 mg, 0.7 mmol; 2 eq.) se limpió con nitrógeno anhidro y se calentó en un tubo sellado a 160°C durante 11 horas. Durante el enfriamiento, a la mezcla se le agregó MeOH, y el material insoluble se filtró. El filtrado se concentró in vacuo y se purificó por columna de fase inversa C-18 (Sistema preparativo eluyendo con MeOH-agua que contiene 0.1% TFA) para obtener 19 mg (0.040 mmol, R. 11%) del compuesto del título Ejemplo 216 como polvo amorfo (sal de TFA): EM m/e 474 (MH); ^{1}H RMN (DMSO-d_6) δ ppm 2.50 (3H, s, traslapado con picos de DMSO), 3.44 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.00 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.89 (1H, s), 8.25 (1H, s), 9.24 (1H, s), 12.41 (1H, s, NH).

317

Preparación Alterna del Ejemplo 317

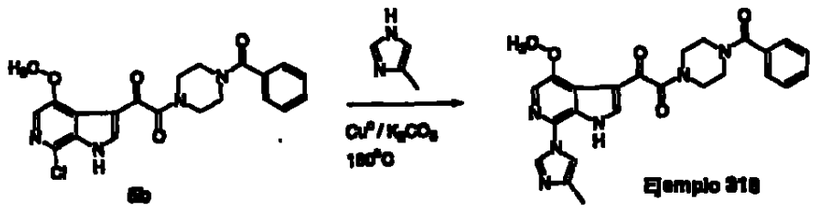


precursor 5z Ejemplo 317

Una mezcla del compuesto 5z (220 mg, 0.5 mmol), 3-metil-1,2,4-triazol (830 mg, 10 mmol; 20 eq.; preparado por el método descrito en Coll. Czech. Chem. Comm. 1985, 49, 2492), polvo de cobre (63.5 mg, 1 mmol; 2 eq.), carbonato de potasio (138 mg, 1 mmol; 2 eq.) se limpió con nitrógeno anhidro y se calentó en un tubo sellado a 160°C durante 11 horas. Durante el enfriamiento, a la mezcla se le agregó MeOH, y el material insoluble se filtró. El filtrado se concentró in vacuo y se purificó por columna de fase inversa C-18 (Sistema preparativo eluyendo con gradiente 0-70% MeOH-agua que contiene 0. 1% TFA) para obtener 24 mg (0.049 mmol, R. 9. 8%) del compuesto del título Ejemplo 317 como polvo amorfo (sal de TFA): EM m/e 488 (MH); ^{1}H RMN (CD_3OD) δ ppm 1.30, 1.35 (3H, 2d, J=7Hz), 2.54 (3H, s, CH_3), 3-4.5 (8H, m, CH_2N), 4.04, 4.05 (3H, 2s, CH_3O), 7.46, 7.47 (5H, 2s, Ar-Hs), 7.85, 7.86 (1H, 2s), 8.28, 8.31 (1H, 2s), 9.22 (1H, s).

318

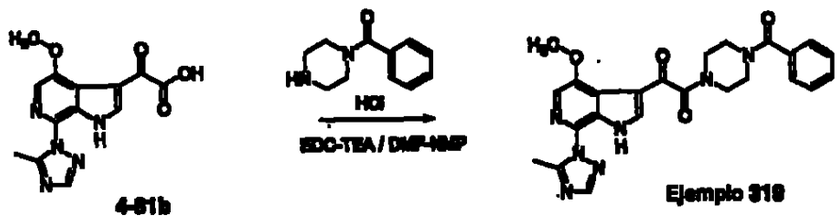
Preparación de Ejemplo 318



5b Ejemplo 318

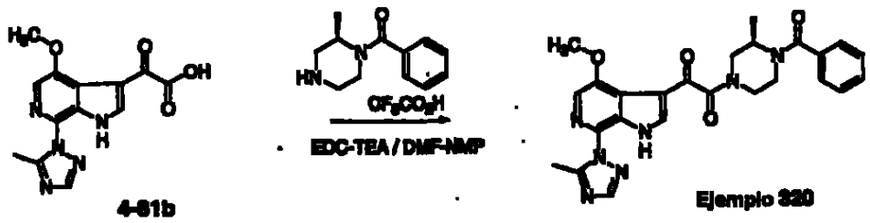
Una mezcla del compuesto 5b (150 mg, 0.35 mmol), 4-metilimidazol (517 mg, 6.2 mmol; 18 eq.; Aldrich), polvo de cobre (26 mg, 0.42 mmol; 1.2 eq.), carbonato de potasio (57 mg, 0.42 mmol; 1.2 eq.) se limpió con nitrógeno anhidro y se calentó en un tubo sellado a 160°C por 6 horas. Durante el enfriamiento, a la mezcla se le agregó MeOH, y el material insoluble se filtró. El filtrado se concentró in vacuo y se purificó por columna de fase inversa C-18 eluyendo con 15% CH_3CN-agua que contiene 0.1% TFA para obtener 32 mg (0.068 mmol, R. 19%) del compuesto del título Ejemplo 318 como polvo amorfo (sal de TFA). La H-RMN indica contaminación de alrededor de 30% del producto isomérico, análogo de 5-metilimidazolil: EM (ES) m/e 473 (MH); ^1H RMN (CD_3OD) δ ppm 2.25 (s), 2.51 (3H, s, CH3), 3.63 (4H, br, CH_2N), 3.9 (4H, br, CH_2N), 4.13 (3H, s, CH_3O), 4.15 (s), 7.50 (5H, br. s, Ar-Hs), 7.60 (s), 7.89 (1H, s), 8.03 (1H, s), 8.11 (s), 8.43 (1H, s), 9.35 (s), 9.42 (1H, s).

Preparación de Ejemplo 319



Una mezcla del precursor 4-81b (30 mg, 0.11 mmol; preparado a partir de 7-(5-metil-1,2,4-triazolil)-4-metoxi-6-azaindol por el método usado para el mejor modo de preparación del Ejemplo 316), clorohidrato de benzoilpiperazina (39 mg, 0.17 mmol), trietilamina (200 mg, 1.9 mmol; 18 eq.), clorohidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (EDC; 77 mg, 0.45 mmol) en 1:1 DMF-NMP (1 mL) se agitó bajo N_2 a temperatura ambiente durante 20 horas. La mezcla se concentró in vacuo para remover el DMF y al residuo se le agregó agua y la mezcla se agitó para formar precipitados los cuales se colectaron y se secaron para obtener 14 mg (0.030 mmol, R. 27%) del compuesto del título Ejemplo 319 como polvo amorfo: EM m/e 474 (MH); ^{1}H RMN (DMSO-d_6) δ ppm 2.67 (3H, s, CH_3), 3.44 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.02 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.98 (1H, s), 8.21 (1H, s), 8.24 (1H, s), 12.57 (1H, s, NH).

Preparación de Ejemplo 320

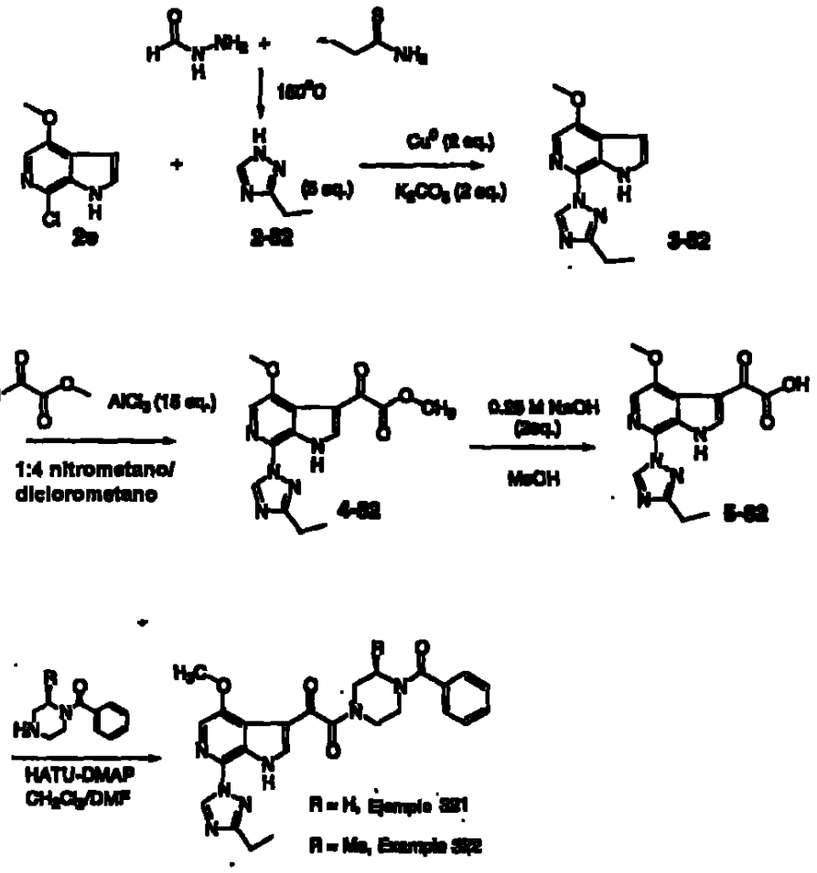


4-81b Ejemplo 320

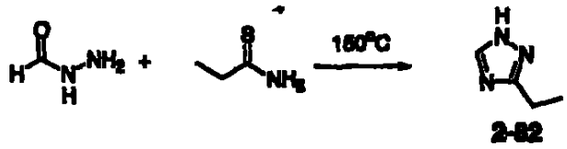
Una mezcla del compuesto 4-81b (30 mg, 0.11 mmol; preparado a partir de 7-(5-metil-1,2,4-triazolil)-4-metoxi-6-azaindol por el método usado para el mejor modo de preparación del Ejemplo 316), trifluoroacetato de 2R-metil-1-benzoilpiperazina (54 mg, 0.17 mmol), trietilamina (200 mg, 1.9 mmol; 18 eq.), clorohidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (EDC; 77 mg, 0.45 mmol) en 1:1 DMF-NMP (1 mL) se agitó bajo N_2 a temperatura ambiente durante 20 horas. Más EDC (20 mg) se agregó a la mezcla y se agitó por 6 horas adicionales. La mezcla se concentró in vacuo para remover DMF y al residuo se le agregó agua y el producto se extrajo con EtOAc dos veces. Los extractos de EtOAc se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó por cromatografía de columna en gel de sílice eluyendo con 5% MeOH-CH_2Cl_2 para obtener 10 mg (0.021 mmol, R. 19%) del compuesto del título Ejemplo 320 como polvo amorfo: EM m/e 488 (MH); ^1H RMN ($CDCl_3$) δ ppm 1.33, 1.36 (3H, 2d, J=7Hz), 3.00 (3H, s, CH_3), 3-4.6 (8H, m, CH_2N), 4.05 (3H, s, CH_3O), 7.38-7.44 (5H, m, Ar-Hs), 7.81 (1H, s), 8.02 (1H, s), 8.16, 8.17, 8.18, 8.19 (1H, 4s), 11.10 (1H, s, NH).

Preparación del Ejemplo 321 y Ejemplo 322

Esquema de reacción 82



Preparación de 3-metil-1,2,4-triazol (2-82)

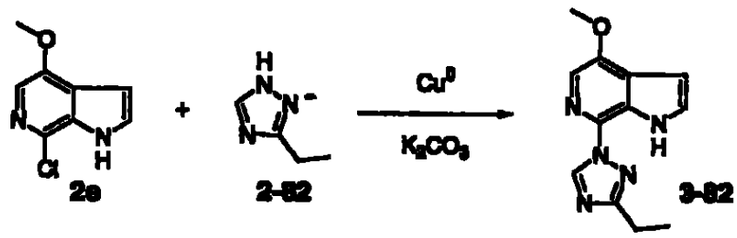


Procedimiento: Una mezcla sólida de hidrazida fórmica (6.0 g, 0.1 mol; Aldrich) y tiopropionamida (8.92 g, 0.1 mol; TCI) se calentó con agitación a 150°C (temperatura del baño de aceite) durante 2 horas con una corriente suave de

nitrógeno. Se enfrió y se almacenó a temperatura ambiente durante la noche. La mezcla de reacción sólida se suspendió en 20% EtOAc/CH_2Cl_2, se removió el sólido insoluble y el filtrado se concentró. El residuo se purificó por cromatografía de columna, eluyendo primero con 50-80% EtOAc/CH_2Cl_2, remover los subproductos, y luego con 10% MeOH/CH_2Cl_2, colectando 5.4 g (0.056 mol, R. 56 %) del compuesto del título como un sólido: EM (ESI-) m/z 96 (M-H); ^{1}H RMN ($CDCl_3$) δppm 1.37 (3H, t, J=7.5 Hz), 2.88 (2H, q, J=7.5 Hz), 8.06 (1H, s, 5-H), 9.4 (1H, br, NH).

Referencia: Vanek, T.; Velkova, V.; Gut, Jiri Coll. Czech. Chem. Comm. 1985, 49, 2492.

Preparación de 3-82

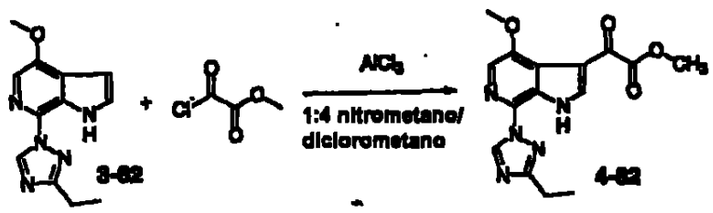


2e 2-82 3-82

Procedimiento: Una mezcla de 4-metoxi-7-cloro-6-azaindol 2e (910 mg, 5.0 mmol), carbonato de potasio (1.38 g, 10 mmol, 2 eq.), polvo de cobre (635 mg, 10 mmol, 2 eq.), y 3-etil-1,2,4-triazol (2.4 g, 25 mmol, 5 eq.) en un tubo sellado se calentó a 145-150°C (temperatura del baño de aceite externo) por 52 horas, tiempo al cual el análisis CLAR indica que no hay más progreso de la reacción. Después del enfriamiento,

MeOH se agregó, el material insoluble (polvo de cobre) se filtró a través de una almohadilla de Celite, y se enjuagó con metanol. El filtrado se concentró in vacuo. El residuo se purificó por cromatografía de columna en gel de sílice (50% EtOAc/CH_2Cl_2) para obtener 450 mg de los productos como una mezcla de alrededor de 4:1 de dos regioisómeros. Esto se separó además por gel de sílice de fase inversa C-18 (YMC, ODS-A 75 μm) eluyendo con 15% CH_3CN/H_2O que contiene 0.1% TFA. Las fracciones que contienen el isómero mayor se concentraron in vacuo para remover el acetonitrilo y la solución acuosa se extrajo con CH_2Cl_2 después de neutralizar con bicarbonato de sodio acuoso para obtener el compuesto del título 3-82 (305 mg, 1.25 mmol; Y. 25%): CLAR >97% (AP en 254nm); EM (CL/EM) m/z 244 (M+H); ^1H RMN ($CDCl_3$) δppm 1.43 (3H, t, J=7.5 Hz; CH_3), 2.91 (2H, q, J=7.5 Hz; CH_2), 4.05 (3H, s, OCH_3), 6.71 (1H, dd, J=6, 2.4 Hz, H-3), 7.57 (1H, t, J=3 Hz, H-2), 7.57 (1H, s, H-5), 9.16 (1H, s, triazol-H-5), 10.3 (1H, br, NH).

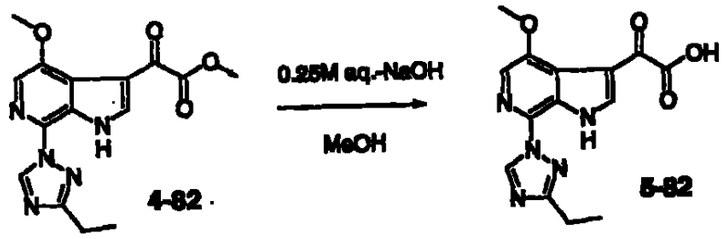
Preparación de 4-82



Procedimiento: El $AlCl_3$ (2.50 g, 18.8 mmol, 15 eq.) se disolvió en una solución de CH_2Cl_2 (8 mL) y nitrometano (2 mL)

bajo nitrógeno seco. A esta solución se le agregó el compuesto 3-82 (305 mg, 1.26 mmol) bajo agitación y bajo N_2, seguido por clorooxoacetato de metilo (612 mg, 5.0 mol, 4 eq.). La mezcla se agitó bajo N_2 a temperatura ambiente durante 1.5 hora. La mezcla se agregó gota a gota a una solución fría y agitada de solución de acetato de amonio acuoso al 20% (120 mL). La mezcla se agitó por 30 minutos y el precipitado resultante se filtró, se lavó a fondo con agua y se secó in vacuo para obtener 320 mg (0.97 mmol, R. 77%) del compuesto del título 5-82 como un sólido: pureza CLAR 97% (AP en 254nm); CL/EM m/z 330 (M+H); ^{1}H RMN (DMSO-d_6) δppm 1.35 (3H, t, J=7.5 Hz, CH_3), 2.85 (2H, q, J=7.5 Hz, CH_2), 3.89 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 7.90 (1H, s, H-5), 8.35 (1H, s, H- 2), 9.25 (1H, s, triazol-H-5), 12.4 (1H, brs, NH).

Preparación de 5-82

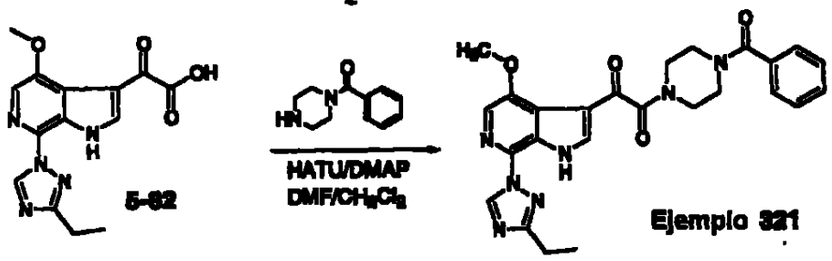


4-82 5-82

Procedimiento: A una suspensión del éster de metilo 4-82 (315 mg, 0.957 mmol) en MeOH (8 mL) se agregó solución de NaOH 0.25M en agua (7.6 mL, 1.9 mmol, 2 eq.) a temperatura ambiente y la mezcla se agitó durante 15 minutos, tiempo al cual la CLAR indica que la hidrólisis se completó. La mezcla

se concentró in vacuo rápidamente para remover el MeOH, y a la solución residual se le agregó agua (~10 mL) y HCl 1N (2 mL) con agitación para neutralizar la mezcla. El precipitado fino resultante se filtró, se lavó con agua y se secó in vacuo para obtener 285 mg (0.904 mmol, R. 94%) del compuesto del título 5-82 como un sólido blanco opaco: pureza CLAR >96% (AP en 254nm); CL/EM m/z 316 (M+H); 1H RMN (DMSO-d6) 8 ppm 1.35 (3H, t, J=7.5 Hz, Me), 2.85 (2H, q, J=7.5 Hz, CH2), 3.97 (3H, s, CH3O), 7.88 (1H, s, H-5), 8.30 (1H, d, J=3 Hz, H-2), 9.24 (1H, s, triazol-H-5), 12.28 (1H, s, NH).

Preparación de Ejemplo 321

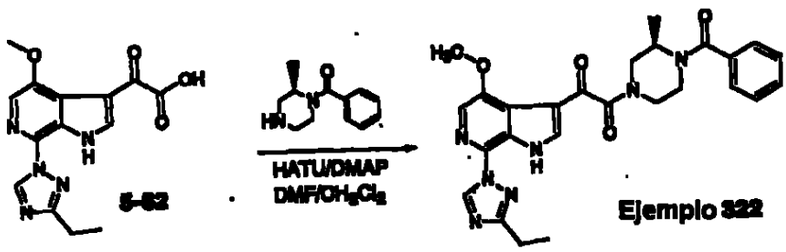


5-82 Ejemplo 321

Procedimiento: Una mezcla del ácido 5-82 (126 mg, 0.4 mmol) y HATU (O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfonato, 228 mg, 0.6 mmol; 1.5 eq.) en una mezcla de CH_2Cl_2 (2 mL) y DMF (2 mL) se agitó durante 30 min bajo N_2. A esta mezcla se agregó una mezcla de clorohidrato de benzoilpiperazina (136 mg, 0.60 mmol; 1.5 eq.) y DMAP (dimetilaminipiridina, 147 mg, 1. 2 mmol; 3 eq.) en DMF (2 mL), y la mezcla se agitó a temperatura ambiente bajo N_2 durante 15 min, tiempo al cual la CLAR indica que la

reacción estuvo completa. La mezcla se concentró rápidamente in vacuo para remover DMF y todos los materiales volátiles, y al residuo se agregó agua (50 mL) bajo agitación y sonicación. Los precipitados formados se colectaron, se lavó con agua y se secó in vacuo para obtener 160 mg (0.328 mmol, R. 82%) del compuesto del título Ejemplo 321 como un sólido blanco opaco: pureza CLAR 100% (AP, en 254 nm); CL/EM m/z 488 (M+H); 1H RMN (DMSO-d6 δ ppm 1.35 (3H, t, J=7.5 Hz, Me), 2.85 (2H, q, J=7.5 HZ, CH_2), 3.43 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.00 (3H, s, CH_3O), 7.46 (5H, br. s, Ar-Hs), 7.89 (1H, s, indol-H-5), 8.26 (1H, s, indol-H-2), 9.25 (1H, s, triazol-H-5), 12.32 (1H, br. s, NH).

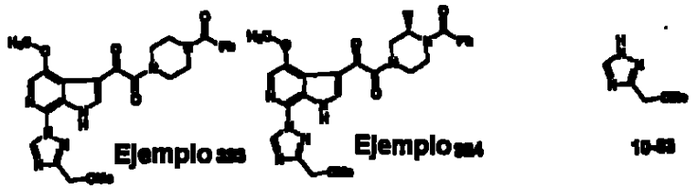
Preparación de Ejemplo 322



Procedimiento: Una mezcla del ácido 5-82 (79 mg, 0.25 mmol) y HATU (O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfonato, 142 mg, 0.375 mmol; 1.5 eq.) en una mezcla de CH_2Cl_2 (1 mL) y DMF (1 mL) se agitó durante 30 min bajo N_2. A esta mezcla se agregó una mezcla de clorohidrato de benzoilpiperazina (136 mg, 0.60 mmol ; 1. 5 eq.) y DMAP (dimetilaminipiridina, 92 mg, 0.75 mmol; 3 eq.)

en DMF (1 mL), y la mezcla se agitó a temperatura ambiente bajo N_2 durante 15 min, tiempo al cual la CLAR indica que la reacción estuvo completa. La mezcla se concentró rápidamente in vacuo para remover todos los solventes, CH_2Cl_2 y DMF, y al residuo se agregó agua (-25 mL) bajo agitación y sonicación. La goma resultante se lavó además con agua y recolectó por decantación. La goma residual se secó in vacuo. La solución de esta goma en isopropanol se concentró in vacuo para remover cualquier agua residual. La adición de dietil éter anhidro y trituración dio 90 mg (0.18 mmol, R. 72%) del compuesto del título Ejemplo 322 como un sólido blanco opaco: pureza CLAR ~95% (AP, en 254 nm); CL/EM m/z 502 (M+H); ^{1}H RMN (DMSO-d_6) δ ppm 1.15, 1.22 (3H, 2d, J=6.6 Hz, Me), 1.35 (3H, t, J=7.5 Hz, Me), 2.85 (2H, q, J=7.5 Hz, CH_2), 2.9-4.4 (7H, m, CH_2N, CHN), 3.99, 4.00 (3H, 2S, CH_3O), 7.45 (5H; br. s, Ph-Hs), 7.89 (1H, s, indol-H-5), 8.20, 8.25 (1H, 2s, indol-H-2), 9.24, 9.25 (1H, 2s, triazol-H-5), 12.29, 12.32 (1H, 2br. s, NH).

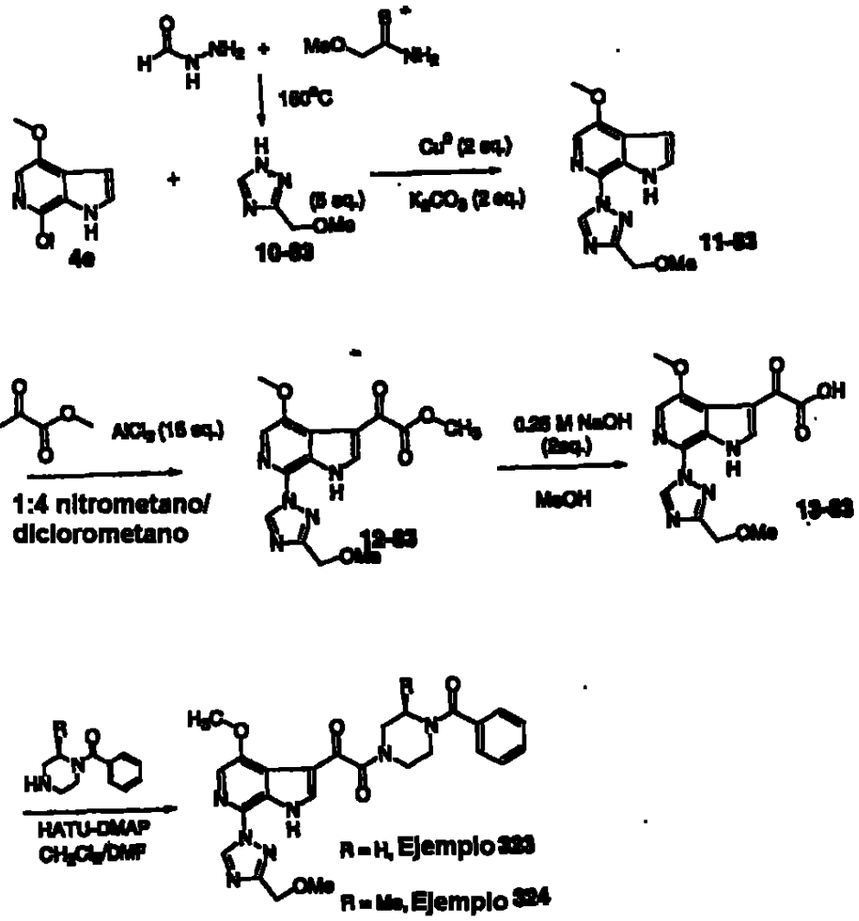
Los siguientes compuestos, Ejemplo 323, y Ejemplo 324, se prepararon por el método descrito arriba al usar 3-(metoximetil)-1,2,4-triazol (10-83).



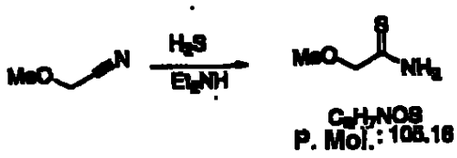
388

Esquema de reacción sintético

Esquema de reacción 83



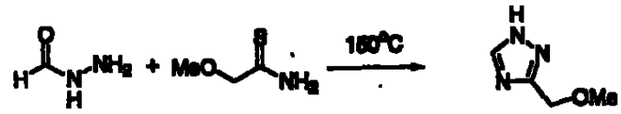
Preparación de 3-metoximetil-1,2,4-triazol (10-83)



Procedimiento: A una mezcla de metoxiacetonitrilo (25 g, 0.35 mol: Aldrich) y dietilamina (1 g, 8.6 mmol) se condensó H_2S (50 mL), y la mezcla se selló, y se calentó a 50°C

durante 14 horas. Después de enfriamiento se evaporaron los materiales volátiles y el residuo se disolvió en agua, se extrajo con EtOAc varias veces. Los extractos orgánicos combinados se lavaron con salmuera, secaron sobre Na_2SO_4 anhidro y se concentró in vacuo. El residuo se purificó por cromatografía de columna (EtOAc:CH_2Cl_2=1:10) para obtener 13 g (0.12 mol, R. 35%) del compuesto del título como un aceite obscuro: GC/EM m/z 105 (M); ^{1}H RMN ($CDCl_3$) δppm 3.43 (3H, s, CH_3), 4.26 (2H, s, CH_2).

Preparación de 3-metoximetil-1,2,4-triazol (10-83)

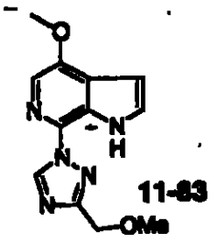


CH_4N_2O P. Mol.: 60.06 — C_3H_7NOS P. Mol.: 105.16 — 10-83 $C_4H_7N_3O$ P. Mol.: 113.12

Procedimiento: Una mezcla sólida de hidrazida fórmica (4.58 g, 0.0763 mol) y metoxitioacetamida (8.92 g, 0.1 mol) se calentó con agitación a 150°C (temperatura del baño de aceite) durante 2 horas con una corriente suave de nitrógeno. Se enfrió y se almacenó a temperatura ambiente durante la noche. La mezcla de reacción sólida se suspendió en 20% ETOAc/CH_2Cl_2, se removió el sólido insoluble y el filtrado se concentró. El residuo se purificó por cromatografía de columna, eluyendo primero con 50-80% EtOAc/CH_2Cl_2, removiendo los subproductos, y luego con 10% MeOH/CH_2Cl_2, colectando 3.8

g (0.034 mol, R. 44 %) del compuesto del título 10-83 como un sólido: ^{1}H RMN ($CDCl_3$) δ ppm 3.48 (3H, s, MeO), 4.67 (2H, s, CH_2), 8.10 (1H, s, 5-H).

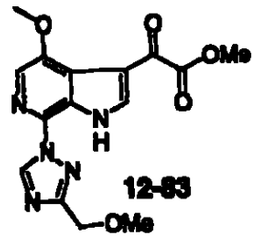
Compuesto 11-83



11-83

Y. 9%: CLAR >98% (AP en 254nm); EM (CL/EM) m/z 260 (M+H); ^{1}H RMN ($CDCl_3$) δ ppm 3.53 (3H, s, MeO), 4.06 (3H, s, 4-OCH_3), 4.69 (2H, s, CH_2), 6.73 (1H, dd, J=3, 2.4 Hz, H-3), 7.40 (1H, t, J=2.7 Hz, H-2), 7.58 (1H, s, H-5), 9.16 (1H, s, triazol-H-5), 10.2 (1H, br, NH).

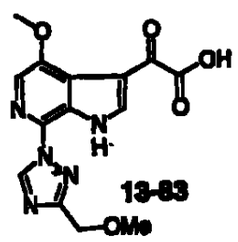
Compuesto 12-83



12-83

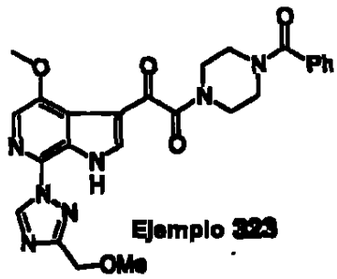
Y. 78%: CLAR 100% (AP en 254 nm); EM (CL/EM) m/z 346 (M+H); ^{1}H RMN (CD_3OD) δ ppm 3.51 (3H, s, MeO), 3.94 (3H, s, MeO), 4.05 (3H, s, MeO), 4.71 (2H, s, CH_2), 7.87 (1H, s), 8.35 (1H, s), 9.33 (1H, s, triazol-H-5).

Compuesto 13-83



Y. 97%: CLAR 98% (AP en 254 nm); EM (CL/EM) m/z 332 (M+H); ^{1}H RMN ($CDCl_3$) δ ppm 3.49 (1H, s, OH), 3.55 (3H, s, MeO), 4.10 (3H, s, MeO), 4.72 (2H, s, CH_2), 7.84 (1H, s, H-5), 9.13 (1H, d, J=3.3 Hz), 9.21 (1H, s, triazol-H-5), 11.15 (1H, br, NH).

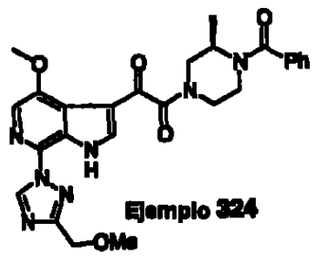
Ejemplo 323



Y. 79%: CLAR 100% (AP en 254 nm); EM (CL/EM) m/z 504 (M+H); ^{1}H RMN (DMSO-d_6) δ ppm 3.39 (3H, s, MeO), 3.42 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.01 (3H, s, 4-MeO), 4.61 (2H, s, CH_2), 7.46 (5H, s, Ph-Hs), 7.92 (1H, s), 8.27 (1H, s), 9.36 (1H, s, triazol-H-5), 12.42 (1H, br. s, NH).

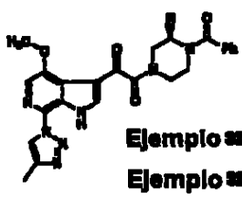
892

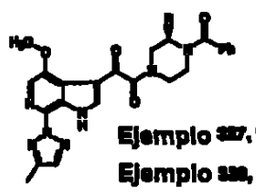
Ejemplo 324



Y. 69%: CLAR >97% (AP en 254nm); EM (CL/EM) m/z 518 (M+H); ^{1}H RMN (DMSO-d_6) δ ppm 1.15, 1.22 (3H, 2d, J=7 Hz, Me), 2.9-4.4 (7H, m, CH_2N, CHN), 3.39 (3H, s, MeO), 4.00, 4.01 (3H, 2s, CH_3O), 4.61 (2H, s, CH_2), 7.4-7.5 (5H, m, Ph-Hs), 7.92 (1H, s, indol-H-5), 8.21, 8.29 (1H, 2s, indol-H-2), 9.35, 9.36 (1H, 2s, triazol-H-5), 12.4 (1H, br, NH).

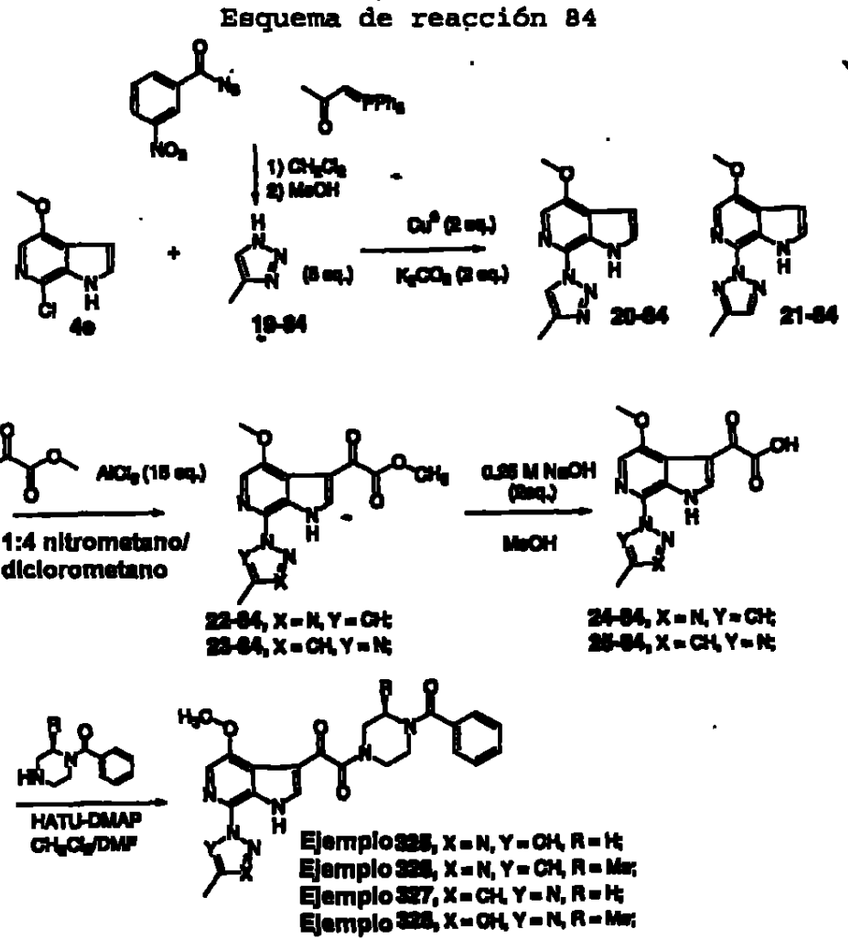
Los siguientes compuestos, Ejemplos 325, 326, 327, y 328, se prepararon por el método descrito arriba al usar 4-metil-1,2,3-triazol (19-84).



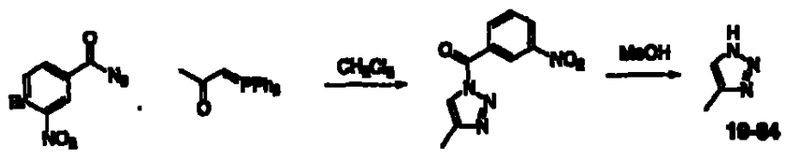




Esquema de reacción 84



Preparación de 4-metil-1,2,3-triazol (19-84)



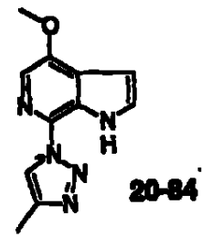
Procedimiento:

Este compuesto 19-84 se preparó por el método descrito en M. Begtrup J. Chem Soc., Perkin Transactions IL, 1976,736.

Una mezcla de m-nitrobenzoil azida (38.4 g, 0.200 mol; preparado a partir de cloruro de m-nitrobenzoilo y azida de

sodio, siguiendo el procedimiento descrito en Org. Syn. Coll. Vol. IV, 1963, p. 715) y 1-trifenilfosforanilideno-2-propanona (63.6 g, 0.200 mol: Aldrich) en CH_2Cl_2 (300 mL) se agitó a temperatura ambiente durante 2 horas. La mezcla se concentró in vacuo para obtener un sólido. Este sólido se disolvió en MeOH, y la solución se agitó a temperatura ambiente durante 30 minutos, y los precipitados formados se eliminaron. El filtrado se concentró in vacuo, y el residuo se extrajo con agua (500 mL) que contiene TFA (17 mL). Esta solución se lavó una vez con una pequeña cantidad de CH_2Cl_2 para remover la mayoría de trifenilfosfina, y la fase acuosa se neutralizó con $NaHCO_3$ hasta pH 7 y se extrajo cinco veces con CH_2Cl_2 (total de 500 mL). Los extractos combinados se secaron sobre Na_2SO_4, se concentraron para obtener 7.6 g (0.091 mol, R. 46%) del compuesto del título 19-84 como un aceite amarillo: ^1H RMN ($CDCl_3$) δ ppm 2.37 (3H, s, Me), 7.50 (1H, s, 5-H), 10.41 (1H, br, NH).

Compuesto 20-84



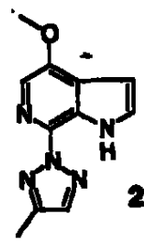
20-84

Rendimiento 5-9%: pureza CLAR 100% (TR 1.89 min, AP en 254 nm); EM (CL/EM) m/z 230 (M+H); ^1H RMN ($CDCl_3$) δ ppm 2.47

(3H, s, Me), 4.07 (3H, s, 4-OCH_3), 6.74 (1H, t, J=2.7 Hz, H-3), 7.42 (1H, t, J=2.7 Hz, H-2), 7.62 (1H, s, H-5), 8.41 (1H, s, triazol-H-5), 10.3 (1H, br, NH).

La estructura se confirmó por análisis cristalográfico de rayos X sencillos.

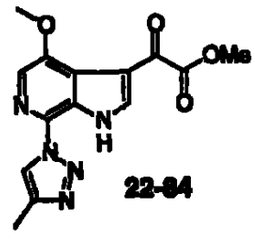
Compuesto 21-84



21-84

Rendimiento 11-14%: pureza CLAR 100% (TR 1.36 min, AP en 254nm); EM (CL/EM) m/z 230 (M+H); ^{1}H RMN ($CDCl_3$) δppm 2.48 (3H, s, Me), 4.06 (3H, s, 4-OCH_3), 6.74 (1H, dd, J=3, 2.4 Hz, H-3), 7.39 (1H, t, J=3 Hz, H-2), 7.68 (1H, s, H-5), 7.72 (1H, br, triazol-H-5), 10.25 (1H, br, NH).

Compuesto 22-84

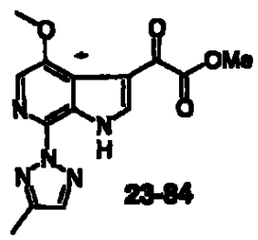


22-84

Rendimiento 79%: pureza CLAR 94% (AP en 254 nm); EM (CL/EM) m/z 316 (M+H); ^{1}H RMN ($CDCl_3$) δ ppm 2.49 (3H, s, Me), 3.96 (3H, s, OMe), 4.07 (3H, s, OMe), 7.81 (1H, s, H-5), 8.38

(1H, d, J=3.3 Hz, H-2), 8.42 (1H, s, triazol-H-5), 11.07 (1H, br, NH).

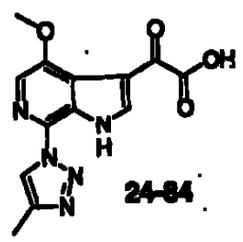
Compuesto 23-84



23-84

Rendimiento 81%: pureza CLAR >95% (AP en 254 nm); EM (CL/EM) m/z 316 (M+H); ^{1}H RMN ($CDCl_3$) δ ppm 2.49 (3H, S, Me), 4.00 (3H, s, OMe), 4.05 (3H, s, OMe), 7.72 (1H, s, H-5), 7.89 (1H, br. s, triazol-H-5), 8.33 (1H, d, J=3 Hz, H-2), 11 (1H, br, NH).

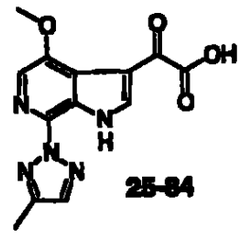
Compuesto 24-84



24-84

Rendimiento 83%: pureza CLAR 98% (AP en 254 nm); EM (CL/EM) m/z 302 (M+H); ^{1}H RMN (CD_3OD) δppm 2.46 (3H, s, Me), 4.06 (3H, s, OMe), 7.89 (1H, s, H-5), 8.39 (1H, d, J=3.3 Hz, H-2), 8.58 (1H, s, triazol-H-5).

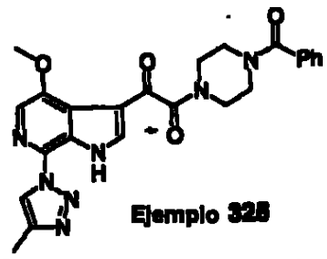
Compuesto 25-84



25-84

Rendimiento 74%: pureza CLAR 100% (AP en 254 nm); EM (CL/EM) m/z 302 (M+H); ^{1}H RMN (CD_3OD) δppm 2.50 (3H, s, Me), 4.05 (3H, s, OMe), 7.84 (1H, s), 7.90 (1H, s), 8.39 (1H, s).

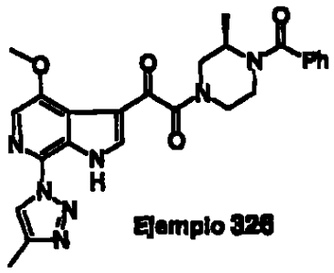
Ejemplo 325



Ejemplo 325

R. 76%: CLAR 98% (AP en 254 nm); EM (CL/EM) m/z 474 (M+H); ^{1}H RMN (DMSO-d_6) δppm 2.40 (3H, s, Me), 3.44 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.02 (3H, s, 4-MeO), 7.46 (5H, s, Ph-Hs), 7.96 (1H, s), 8.21 (1H, s), 8.68 (1H, s, triazol-H-5), 12.72 (1H, br. s, NH).

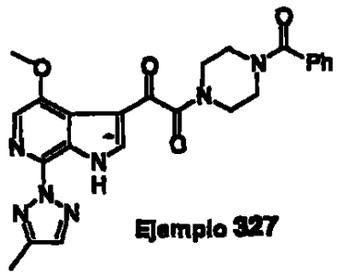
Ejemplo 326



Ejemplo 326

R. 62%: CLAR 97% (AP en 254 nm); EM (CL/EM) m/z 488 (M+H); ^{1}H RMN (DMSO-d_6) δ ppm 1.14; 1.21 (3H, 2d, J=7 Hz, Me), 2.40 (3H, s, Me), 2.9-4.4 (7H, m, CH_2N, CHN), 4.01, 4.02 (3H, 2s, CH_3O), 7.46 (5H, s, Ph-Hs), 7.96 (1H, s), 8.16, 8.23 (1H, 2s), 8.675, 8.68 (1H, 2d, J=2.5 Hz), 12.72 (1H, br. s, NH).

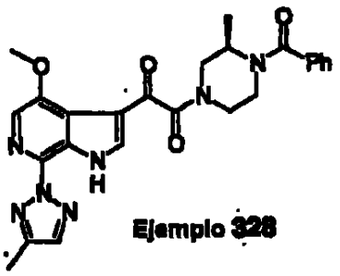
Compuesto Ejemplo 327



Ejemplo 327

R. 73%: CLAR 96% (AP en 254nm); EM (CL/EM) m/z 474 (M+H); ^{1}H RMN (DMSO-d_6) δppm 2.45 (3H, s, Me), 3.44 (4H, br, CH_2N), 3.68 (4H, br, CH_2N), 4.01 (3H, s, 4-MeO), 7.46 (5H, s, Ph-Hs), 7.93 (1H, s), 8.04 (1H, s), 8.24 (1H, d, J=3Hz, H-2), 12.51 (1H, br. s, NH).

Ejemplo 328

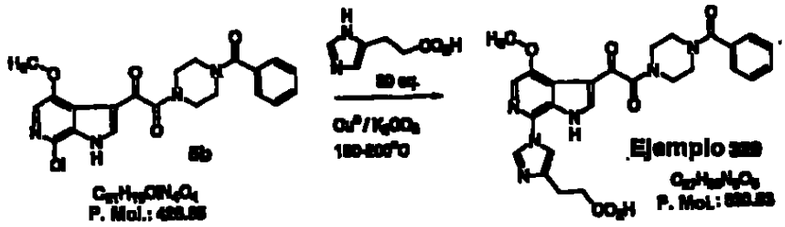


Ejemplo 328

R. 74%: CLAR 99% (AP en 254 nm); EM (CL/EM) m/z 488

(M+H); ^{1}H RMN (DMSO-d_6) δ ppm 1.15, 1.22 (3H, 2d, J=7 Hz, Me), 2.45 (3H, s, Me), 2.9-4.4 (7H, m, CH_2N, CHN), 4.00, 4.01 (3H, 2s, CH_3O), 7.45 (5H, s, Ph-Hs), 7.92 (1H, s), 8.03 (1H, s), 8.18, 8.26 (1H, 2s), 12.5 (1H, br. s, NH).

Preparación de Ejemplo 329

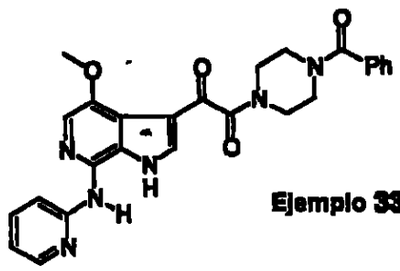


Una mezcla del compuesto 5b (128 mg, 0.3 mmol), ácido imidazol-4-propionico (1.26 g, 9 mmol ; 30 eq.; preparado a partir de ácido urocánico por hidrogenación catalítica al usar Pd-C al 10% en ácido acético, siguiendo el procedimiento descrito en J. Altman, N. Shoef, M. Wichek, y A. Warshawsky J. Chem. Soc., Perkin Trans. I, 1984, 59), polvo de cobre (38 mg, 0.6 mmol; 2 eq.), carbonato de potasio (83 mg, 0.6 mmol; 2 eq.) se limpió con nitrógeno anhidro y se calentó en un tubo sellado en 190°-200°C (temperatura del baño de aceite) durante 2 horas. Durante el enfriamiento, a la mezcla se le agregó MeOH, y el material insoluble se filtró. El filtrado se concentró in vacuo y se purificó por columna de fase inversa C-18 (YMC, eluyendo con 15% CH_3CN-agua que contiene 0.1% TFA) para obtener 12 mg (0.023 mmol, R. 7.5%) del compuesto del título Ejemplo 329 como un polvo amorfo

(alrededor de 1:1 de mezcla de dos regioisómeros): pureza CLAR 96% (AP, en 254nm); EM (CL/EM) m/z 531 (M+H); ^{1}H RMN (CD_3OD) δ ppm 2.74, 3.00 (2H, 2t, J=7 Hz), 2.82, 3.11 (2H, 2t, J=7 Hz), 3.59 (4H, br, CH_2N), 3.79 (4H, br, CH_2N), 3.79, 4.10 (3H, 2s, CH_3O), 6.73 (s), 7.33 (s), 7.48 (5H, br. s, Ar-Hs), 7.93 (br. s), 8.00 (s), 8.10 (s), 8.40 (s), 8.77 (s), 9.43 (br. s).

Los siguientes compuestos, Ejemplos 330 y 331 se prepararon similarmente siguiendo el procedimiento anterior.

Ejemplo 330

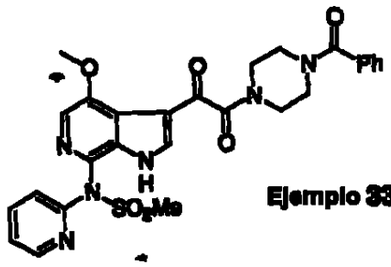


Ejemplo 330

R. 10 % (150°C, 7h): CLAR 93 % (AP en 254nm); EM (CL/EM) m/z 485 (M+H); ^{1}H RMN (CD_3OD, 500 MHz) δppm 3.63 (4H, br, CH_2N), 3.84 (4H, br, CH_2N), 4.05 (3H, s, 4-MeO), 7.32 (2H, m, pyr-Hs), 7.52 (5H, s, Ph-Hs), 7.71 (1H, s), 8.06 (1H, t, J=7.5 Hz, pyr-H), 8.48 (1H, d, J=4.5 Hz), 8.60 (1H, s).

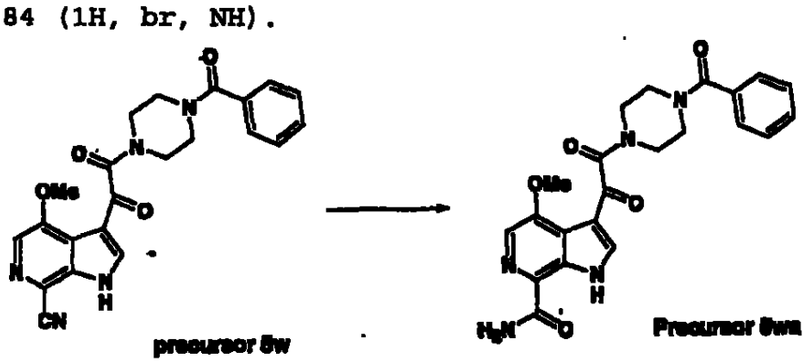
401

Ejemplo 331



Ejemplo 331

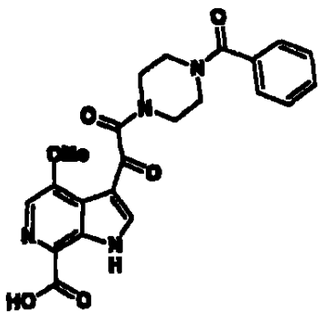
R. 10 % (150°C, 7h): CLAR 93% (AP en 254nm); EM (CL/EM) m/z 563 (M+H); ^{1}H RMN ($CDCl_3$) δppm 2.76 (3h. s, Me), 3.55 (4H, br, CH_2N), 3.78 (4H, br, CH_2N), 4.09 (3H, s, 4-MeO), 6.71 (1H, t, J=7 Hz, pyr-H), 7.43 (5H, s, Ph-Hs), 7.68 (1H, t, J=7 Hz, pyr-H), 7.82 (1H, t, J=7 Hz, pyr-H), 7.91 (1H, S), 8.15 (1H, s), 10.84 (1H, br, NH).



precursor 5w

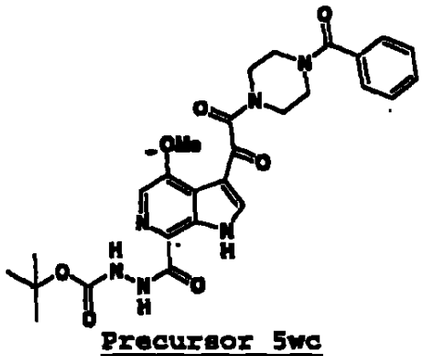
Precursor 5wa

Una mezcla del precursor 5w (71.5 mg, 0.17 mmol) en MeOH (1.5 mL) se enfrió hasta 0°C, y se saturó con gas de cloruro de hidrógeno durante el curso de 10 minutos. Luego se evaporaron los volátiles por medio del soplado con N_2 durante la noche para suministrar el precursor 5wa. ^{1}H RMN: (DMSO-d_6) δ 12.45 (s, 1H), 8.12 (s, 2H), 8.07 (s, 1H), 7.65 (s, 1H), 7.45 (s, 5H), 4.04 (s, 3H), 3.80-3.30 (b m, 8H); CL/EM: (ES+) m/z (M+H) + = 436, CLAR tiempo de retención = 1.357 (columna G).



Precursor 5wb

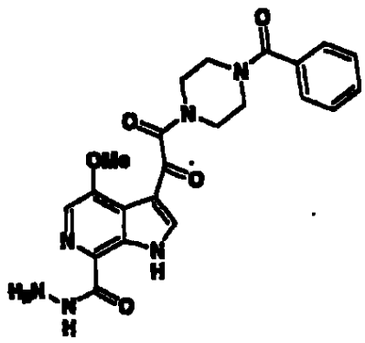
A una mezcla del precursor 5wa (10 mg, 23 µmol) en ácido acético (0-4 mL) y anhídrido acético (0.75 mL) en 0°C, se agregó $NaNO_2$ (30 mg, 0.43 mmol). La mezcla de reacción se agitó a 0°C por 30 minutos, y se permitió entibiar a temperatura ambiente. Después de agitar durante 1.5 hora adicional, la mezcla se filtró y el residuo se secó bajo vacío para dar el compuesto deseado 5wb un sólido blanco opaco. ^1H RMN: (CD_3OD) δ 8.44 (s, 1H), 8.08 (s, 1H), 7.48 (b s, 5H), 4. 14-3.27 (m, 8H), 4.14 (s, 3H); CL/EM: (ES+) m/z (M+H) + = 437, CLAR tiempo de retención = 0.750 (columna G).



Precursor 5wc

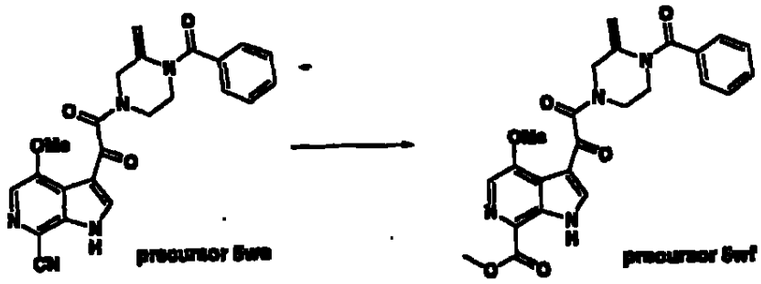
Se cargó un matraz con el precursor 5wb (2.6 mg, 6.0 µmol), DMF (0.5 mL), tert-butil carbazato (1.2 mg, 8.9 µmol), DEPBT (5.4 mg, 18 µmol), y N,N-diisopropiletilamina (10 µL,

30 µmol). La mezcla de reacción se permitió agitar a temperatura ambiente durante la noche. El producto 5wc se separó al usar el siguiente método de CLAR preparativa de fase inversa: Inicio % B = 0, Final % B = 100, Tiempo de gradiente = 6 minutos, Relación de flujo = 30ml/min, Columna: Xerra Prep EM C18 5µm19x50mm, Colección de Fracción: 4.38-4.59 minutos. ^{1}H RMN: (CD_3OD) δ 8.29 (s, 1H), 8.11 (s, 1H), 7.47 (b s, 5H), 4.11-3.28 (m, 8H), 4.10 (s, 3H), 1.50 (b s, 9H); CL/EM: (ES+) m/z (M+H) + = 551, CLAR tiempo de retención = 1.203 (columna G).



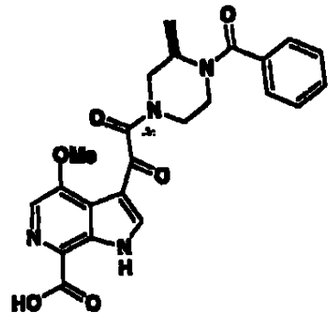
Precursor 5wd

Al precursor 5wc (57 mg, 0.104 mmol) se le agregó una solución de HCl en 1,4-dioxano (4 M, 0.25 mL), y la mezcla de reacción se agitó durante la noche a temperatura ambiente. La desprotección produjo el producto deseado precursor 5wd limpiamente. El reactivo en exceso y el solvente se evaporaron por medio de soplado de N_2, y el producto secó bajo vacío. CL/EM: (ES+) m/z (M+H) + = 451, CLAR tiempo de retención = 0.803 (columna G).



precursor 5we precursor 5wf

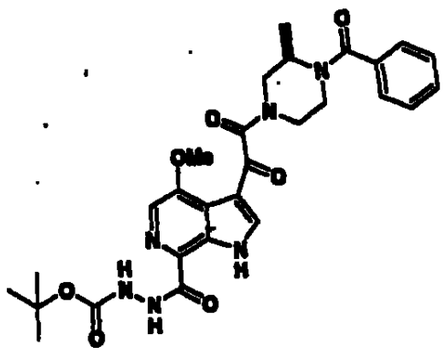
Una solución del precursor 5we (106 mg, 0.25 mmol) en MeOH (2.5 mL) en un tubo sellado a 0°C se limpió con N_2, y saturó con HCl gas durante 10 minutos. Se cerró el tubo y la mezcla de reacción se agitó a 70°C durante 50 minutos. Después del enfriamiento a temperatura ambiente, se evaporaron los volátiles in vacuo para dar el precursor 5wf. ^{1}H RMN: (CD_3OD) δ 8.33, 8.30 (s, 1H), 8.13, 8.12 (s, 1H), 7.48-7.44 (m, 5H), 4.60-3.10 (b m, 7H), 4.12, 4.11 (s, 3H) 4.06 (s, 3H), 1.35, 1.29 (d, J = 6.5, 7.0, 3H); CL/EM: (ES+) m/z (M+H) + = 465, CLAR tiempo de retención = 0.993 (columna G).



Precursor 5wg

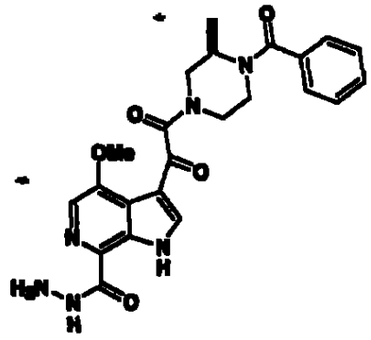
A una solución de precursor 5wf (65 mg, 0.14 mmol) en MeOH (1 mL) se le agregó NaOH (1.5 mL, 1 N AQ.). La mezcla se agitó durante 2 horas, y durante cuyo tiempo el HCl (1.5 mL, 1 N ac.) se agregó para apagar la reacción. Se evaporaron los

volátiles in vacuo para dar el precursor 5wg. ^{1}H RMN: (solvato TFA, CD_3OD) δ 8.54, 8.51 (s, 1H), 8.11 (b s, 1H), 7.57-7.48 (b s, 5H), 4.60-3.10 (b m, 7H), 4.17, 4.16 (s, 3H), 1.37, 1.33 (d, J = 6.5, 6.0, 3H); CL/EM: (ES+) m/z (M+H) + = 451, CLAR tiempo de retención = 0.837 (columna G).



Precursor 5wh

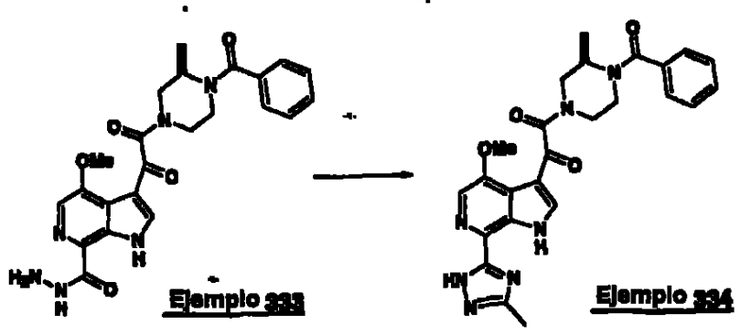
A una mezcla del precursor 5wg (22 mg, 0.048 mmol) en DMF (1 mL) se le agregó tert-butil carbazato (14 mg, 0.11 mmol), DEPBT (53 mg, 0.18 mmol), y N,N-diisopropiletilamina (40 µL, 0.23 mmol). La mezcla de reacción se agitó durante la noche, y el compuesto deseado precursor 5wh se aisló por medio de CLAR preparativa de fase inversa al usar las siguientes condiciones: Inicio % B = 0, Final % B = 100, Tiempo de gradiente = 6 minutos, Relación de flujo = 30mL/min, Columna: Xerra Prep EM C18 5µm19x50mm, Colección de Fracción: 4.37-4.98 minutos. ^{1}H RMN: (CD_3OD) δ 8.28, 8.26 (s, 1H), 8.08 (b s, 1H), 7.47-7.43 (m, 5H), 4.75-3.26 (m, 7H), 4.10 (s, 3H), 1.50 (b s, 9H), 1.36-1.27 (m, 3H); CL/EM: (ES+) m/z (M+H) + = 565, CLAR tiempo de retención = 1.207 (columna G).



Precursor 5wi

Una mezcla de precursor 5wh en una solución de HCl en 1,4-dioxano (0.2 mL, 4 M) se agitó por 3.5 horas a temperatura ambiente. Se evaporaron los volátiles in vacuo, y la mezcla cruda se purificó por medio de CLAR preparativa de fase inversa al usar el siguiente método: Inicio % B = 0, Final % B = 100, Tiempo de gradiente = 6 minutos, Relación de flujo = 30mL/minuto, Columna: Xerra Prep EM C18 5µm19x50mm, Colección de Fracción: 3.20-3.80 minutos. ^{1}H RMN: (CD_3OD) δ 8.74, 8.71 (s, 1H), 8.31, 8.28 (s, 1H), 7.47-7.44 (m, 5H), 4.46-3.35 (m, 7H), 4.18, 4.10 (s, 3H), 1.38-1.22 (m, 3H); CL/EM: (ES+) m/z (M+H) + = 465, CLAR tiempo de retención = 0.850 (columna G).

Ejemplo 333 y Ejemplo 334

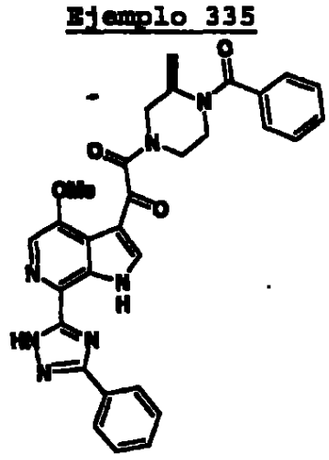


Ejemplo 333 Ejemplo 334

La tioacetamida (2 mg, 22 µmol) se agregó al Ejemplo 333 (10 mg, 20 µmol, sal de HCl) en un matraz de fondo redondo. La mezcla se calentó hasta 150°C durante 20 minutos, después de lo cual se enfrió hasta temperatura ambiente, y se diluyó con MeOH. La purificación del compuesto deseado Ejemplo 334 se realizó por medio de CLAR preparativa de fase inversa al usar el siguiente método: Inicio % B = 0, Final % B = 100, Tiempo de gradiente = 6 minutos, Relación de flujo = 30ml/minuto, Columna: Xerra Prep EM C18 5µm19x50mm, Colección de Fracción: 3.47-3.86 minutos. ^{1}H RMN: (CD_3OD) δ 8.64, 8.62 (s, 1H), 8.04 (b s, 1H), 7.49-7.44 (m, 5H), 4.37-3.44 (m, 7H), 4.16, 4.14 (s, 3H), 2.63 (s, 3H), 1.36-1.32 (m, 3H); CL/EM: (ES+) m/z (M+H) + = 488, CLAR tiempo de retención = 0.973 (columna G).

Los siguientes ejemplos se prepararon en una manera similar como arriba.

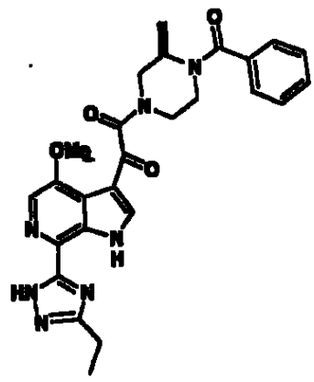
Ejemplo 335



Preparación de Ejemplo 335

^{1}H RMN: (CD_3OD) δ 8.60, 8.58 (s, 1H), 8.12 (d, J= 3,1H), 7.71-7.67 (m, 1H), 7.59-7.54 (m, 4H), 7.50-7.46 (m, 5H), 4.37-3.44 (m, 7H), 4.16, 4.14 (s, 3H), 1.37, 1.33 (d, J = 6.5, 3H); CL/EM: (ES+) m/z (M+H) + = 550, CLAR tiempo de retención = 1.283 (columna G).

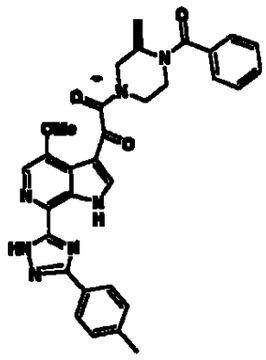
Ejemplo 336



Ejemplo 336

^{1}H RMN: (CD_3OD) δ 8.66, 8.64 (s, 1H), 8.04 (d, J= 3,1H), 7.49-7.40 (m, 5H), 4.41-3.44 (m, 7H), 4.16, 4.14 (s, 3H), 3.00 (q, J = 7.5, 2H), 1.46 (t, J = 7.5, 3H), 1.36-1.32 (m, 3H); CL/EM: (ES+) m/z (M+H) + = 502, CLAR tiempo de retención = 1.007 (columna G).

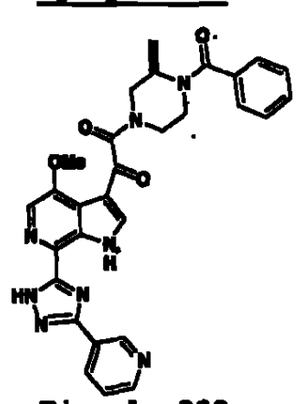
Ejemplo 337



Ejemplo 337

^{1}H RMN: (CD_3OD) δ 8.59, 8.57 (s, 1H), 8.11 (b d, 1H), 7.48-7.40 (m, 9H), 4.46-3.39 (m, 7H), 4.16, 4.14 (s, 3H), 2.45 (s, 3H), 1.40-1.29 (m, 3H); CL/EM: (ES+) m/z (M+H) + = 564, CLAR tiempo de retención = 1.363 (columna G).

Ejemplo 338



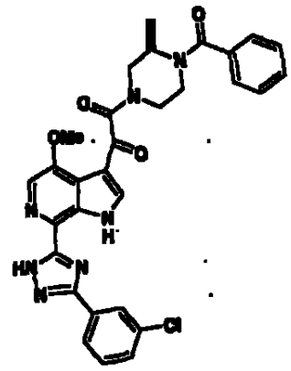
Ejemplo 338

^{1}H RMN: (CD_3OD) δ 9.62 (s, 1H), 9.11 (s, 1H), 8.82 (d, J = 5.5, 1H), 8.47 (d, J = 8.5, 1H), 8.19 (s, 1H), 7.98 (s, 1H), 7.49-7.46 (m, 5H), 4.64-3.35 (m, 7H), 4.14, 4.13 (s, 3H), 1.37, 1.32 (d, J = 7,3H); CL/EM: (ES+) m/z (M+H) + =

910

551, CLAR tiempo de retención = 1.090 (columna G).

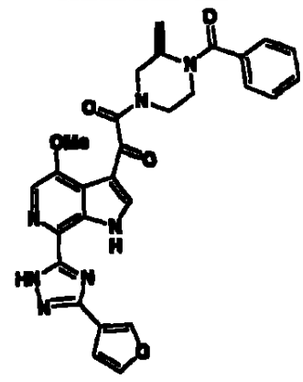
Ejemplo 339



Ejemplo 339

^{1}H RMN: (CD_3OD) δ 8.50 (s, 1H), 8.17 (b d, 1H), 7.53-7.45 (m, 9H), 4.64-3.35 (m, 7H), 4.14, 4.13 (s, 3H), 1.37, 1.32 (d, J = 6.5, 7,3H); CL/EM: (ES+) m/z (M+H) + = 584, CLAR tiempo de retención = 1.427 (columna G).

Ejemplo 340

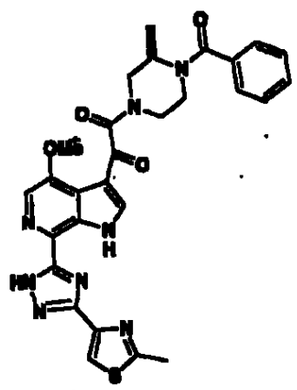


Ejemplo 340

^{1}H RMN: (CD_3OD) δ 8.56, 8.55 (s, 1H), 8.36 (s, 1H), 8.10 (s, 1H), 7.72 (s, 1H), 7.48-7.45 (m, 5H), 7.09 (s, 1H), 4.64-

3.44 (m, 7H), 4.15, 4.14 (s, 3H), 1.36-1.32 (m, 3H); CL/EM: (ES+) m/z (M+H) + = 540, CLAR tiempo de retención = 1.139 (columna G).

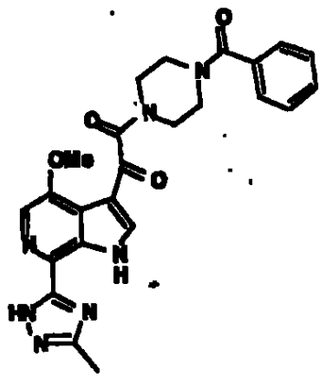
Ejemplo 341



Ejemplo 341

^{1}H RMN: (CD_3OD) δ 8.54, 8.51 (s, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 7.48-7.39 (m, 5H), 4.71-3.44 (m, 7H), 4.14, 4.13 (s, 3H), 2.85 (s, 3H), 1.37-1.29 (m, 3H); CL/EM: (ES+) m/z (M+H) + = 571, CLAR tiempo de retención = 1.450 (columna G).

Ejemplo 342

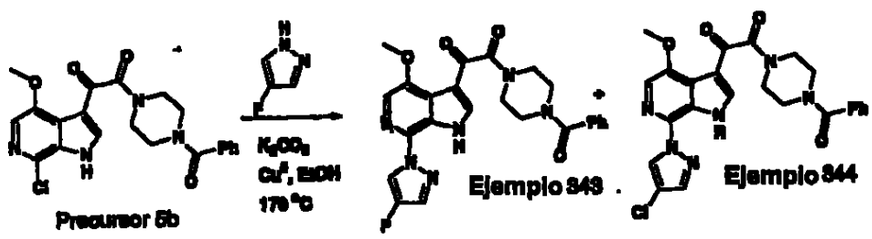


912

Ejemplo 342

^{1}H RMN: (CD_3OD) δ 8.64 (s, 1H), 8.04 (s, 1H), 7.48 (s, 5H), 4.16 (s, 3H), 3.92-3.39 (m, 8H), 2.64 (s, 3H); CL/EM: (ES+) m/z (M+H) + = 474, CLAR tiempo de retención = 0.903 (columna G).

Ejemplos 343 y 344



El Precursor 5b (60 mg, 0.14 mmol), 4-fluoropirazol (0.30 mL) (preparado como se describe en Molines, H.; Wakselman, C. J. Org. Chem. 1989, 54, 5618-5620), cobre (0) (8.0 mg, 0.13 mmol), K_2CO_3 (15 mg, 0.11 mmol) y ETOH (0.30 mL) se combinaron en un tubo sellado se limpió con nitrógeno y calentó a 170°C con irradiación por microondas durante 1.5 hora. La reacción se enfrió, se filtró y se concentró. El residuo se purificó por CLAR preparativa bajo las condiciones estándar antes descritas para suministrar (6.6 mg, 0.014 mmol) del Ejemplo 343 como un sólido amarillo y Ejemplo 344 (3.1 mg. 0.006 mmol) como un sólido verdoso.

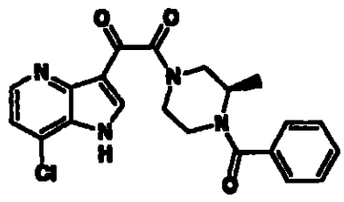
Ejemplo 343: ^{1}H RMN (500 MHz, CD_3OD) δ 8.56 (d, J = 4.3 Hz, 1H), 8.27 (s, 1H), 7.82-7.79 (m, 2H), 7.47 (br s, 5H), 4.03

913

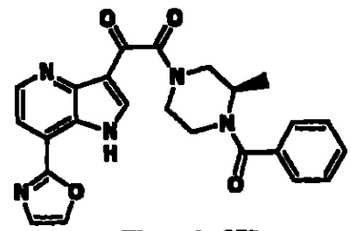
(s, 3H), 3.97-3.45 (m, 8H). EM m/z: $(M+H)^+$ calculado para $C_{24}H_{21}FN_6O_2$: 477.16; encontrado 477.16. Tiempo de retención CLAR: 1.45 minutos (columna G).

Ejemplo 344: ^1H RMN (500 MHz, $CDCl_3$) δ 11. 16 (br s, 1H), 8.59 (s 1H), 8.19 (s, 1H), 7.78-7.62 (m, 2H), 7.43 (br s, 5H), 4.04 (s, 3H), 3.987-3.40 (m, 8H). EM m/z: (M+H) + calculado para $C_{24}H_{21}ClN_6O_2$: 493.13; encontrado 493.12. Tiempo de retención CLAR: 1.59 minutos (columna G).

Ejemplo 353



Precursor 5mn



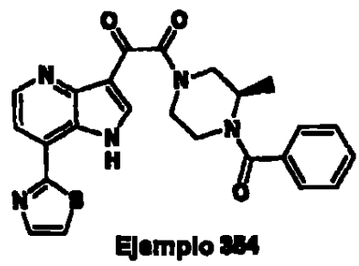
Ejemplo 353

El Ejemplo 353 se preparó a partir del correspondiente precursor 7-cloro 5mn y 2-tributil estanil oxazol por medio de las condiciones de acoplamiento Stille estándar descritas arriba. El precursor 7-cloro se preparó similarmente al precursor 5d excepto que 2-(R)metil piperazina benzamida (precursor 17b) se utilizó. El Ejemplo 353, 4-azaindol-7-(2'-oxazol): ^1H RMN (500 MHz, CD_3OD) δ 8.68 (s, 0.5H), 8.67 (s, 0.5H), 8.45 (s, 0.5H), 8.43 (s, 0.5H), 8.18 (s, 1H), 7.86 (d, J = 4.9 Hz, 0.5H), 7.85 (d, J = 4.9 Hz, 0.5H), 7.55 (s, 1H), 7.50-7.40 (m, 5H), 4.45-3.06 (m, 7H), 1.48 (d, J = 6.7 Hz, 1.5H) 1.24 (d, J = 6.7 Hz, 1.5H). EM m/z: $(M+H)^+$ Calculado

414

para $C_{24}H_{22}N_5O_4$: 444.16; encontrado 444.23. Tiempo de retención CLAR: 0.90 minutos (columna G).

Ejemplo 354

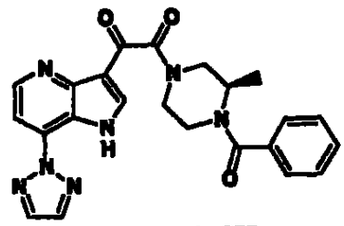


Ejemplo 354

El Ejemplo 354 se preparó a partir del correspondiente precursor 7-cloro 5mn y 2-tributil estanil tiazol por medio de las condiciones de acoplamiento Stille descritas arriba. El precursor 7-cloro se preparó similarmente al precursor 5d excepto que se utilizó 2-(R) metil piperazina benzamida (precursor 17b). Ejemplo 354: 4-azaindol-7-(2'-tiazol): ^{1}H-RMN (500 MHz, CD_3OD) δ 8.80 (s, 0.5H), 8.74-8. 71 (m, 1.5H), 8.35 (d, J = 3.5 Hz, 0.5H), 8.35 (d, J = 3.5 Hz, 0.5H), 8.26 (d, J = 3.5 Hz, 0.5H), 8.25 (d, J = 3.5 Hz, 0.5H), 8.14 (d, J = 3.1 Hz, 0.5H), 8.14 (d, J = 3.1 Hz, 0.5H), 7.50-7.42 (m, 5H), 4.48-3.08 (m, 7H), 1.36 (d, J = 6.7 Hz, 1.5H) 1.32 (d, J = 6.7 Hz, 1.5H). EM m/z: $(M+H)^+$ calculado para $C_{24}H_{22}N_5O_3S$: 460.14; encontrado 460.20. Tiempo de retención CLAR: 0.94 minutos (columna G).

915

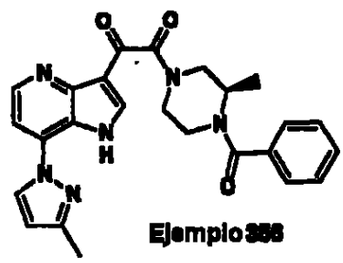
Ejemplo 355



Ejemplo 355

El Ejemplo 355 se preparó por medio del procedimiento usado por el Ejemplo 205 a partir del correspondiente precursor 7-cloro 5mn y 1,2,3, triazol. El precursor 7-cloro se preparó similarmente al precursor 5d excepto que la 2-(R)metil piperazin benzamida (precursor 17b) se utilizó. Ejemplo 355, 4-azaindol-7-(2'-triazol): ^{1}H RMN (500 MHz, CD_3OD) δ 8.79-8.76 (m, 1H), 8.78 (S, 0.5H), 8.70 (s, 0.5H), 8.44 (d, J= 5.9 Hz, 0.5H), 8.43 (d, J= 5.9 Hz, 0.5H), 8.38 (s, 1H), 8. 38 (s, 1H), 7.51-7.42 (m, 5H), 4.50-3.21 (m, 7H), 1.37 (d, J = 6.7 Hz, 1.5H) 1.32 (d, J = 6.7 Hz, 1.5H). EM -m/z: $(M+H)^+$ calculado para $C_{23}H_{22}N_7O_3$: 444.17; encontrado 444.26. Tiempo de retención CLAR: 0.90 minutos (columna G).

Ejemplo 356



Ejemplo 356

El Ejemplo 356 se preparó por medio del procedimiento

usado por el Ejemplo 205 a partir del correspondiente precursor 7-cloro 5mn y 3-metil pirazol. El precursor 7-cloro se preparó similarmente al precursor 5d excepto que la 2-(R)metil piperazin benzamida (precursor 17b) se utilizó. Ejemplo 356, 4-azaindol-7-(3'-metil-2'-pirazol): ^{1}H RMN (500 MHz, CD_3OD) δ 8.73-8.71 (m, 1H), 8.70 (s, 0.5H), 8.63 (s, 0.5H), 8.64-8.60 (m, 1H), 8.06 (s, 0.5H), 8.04 (s, 0.5H), 7.52-7.42 (m, 5H), 6.68 (s, 0.5H), 6.67 (s, 0.5H), 4.61-3.21 (m, 7H), 2.51 (s, 3H), 1.35 (d, J= 6.5 Hz, 1.5H) 1.32 (d, J = 6.5 Hz, 1.5H). EM m/z: $(M+H)^+$ calculado para $C_{25}H_{25}N_6O_3$: 457.19; encontrado 457.33. Tiempo de retención CLAR: 1.04 minutos (columna G).

Biología

- "μM" significa micromolar;
- "mL" significa mililiro;
- "μl" significa microlitro;
- "mg" significa miligramo;

Los materiales y procedimientos experimentales usados para obtener los resultados reportador en las Tablas 1-5 se describen abajo.

Células:

Producción de Virus-línea celular de riñón embriónico humano, 293, propagado en Medio Eagle Modificado por Dulbecco (Life Technologies, Gaithersburg, MD) que contiene 10% de suero de bovino fetal (FBS, Sigma, St. Louis , MO).

Infección del Virus - línea celular epitelial humana, HeLa, que expresa los receptores del VIH-1 CD4 y CCR5 se propagó en Medio Eagle Modificado de Dulbecco (Life Technologies, Gaithersburg, MD) que contiene 10% de suero de bovino fetal (FBS, Sigma, St. Louis , MO) y complementado con 0.2 mg/mL de Geneticina (Life Technologies, Gaithersburg, MD) y 0.4 mg/mL de Zeocina (Invitrogen, Carlsbad, CA).

Virus - Se produjo un virus indicador infecciosos de ronda sencilla al co-transfectar células 293 de riñón embriónico humano con un vector de expresión de ADN de envolvente de VIH-1, y un ADNc proviral que contiene una mutación de la eliminación de la envolvente y un gen reportero de luciferasa insertado en lugar de las secuencias nef de VIH-1 (Chen et al, Ref. 41). Las transfecciones se efectuaron usando reactivo de lipofectAMINA PLUS como se describe por el fabricante (Life Technologies, Gaithersburg, MD).

Experimento

1. El compuesto se agregó a las células HeLa CD4 CCR5 formadas en placas de 96 pozos a una densidad celular de 5 X 10^4 células por pozo en 100 µl de Medio Eagle Modificado de Dulbecco que contiene 10% de suero de bovino fetal a una concentración de <20 µM.

2. 100 µl de virus reportero infeccioso de ronda sencilla en Medio Eagle Modificado de Dulbecco, luego se agregó a las células formadas en placas y compuesto a una multiplicidad de infección aproximada (MOI) de 0.01, resultando en un volumen final de 200 µl por pozo y una concentración final de compuesto de <10 µM.

3. Se cosecharon las muestras 72 h después de la infección.

4. La infección viral se observó al medir la expresión de la luciferasa del ADN viral en las células infectadas usando un kit de ensayo de un gen reportero de luciferasa (Roche Molecular Biochemicals, Indianapolis. IN). Los sobrenadantes de células infectadas se separaron y se agregaron por pozo, 50 µl de Medio Eagle Modificado de Dulbecco (sin rojo de fenol) y 50 µl de reactivo de ensayo de luciferasa reconstituido como se describe por el fabricante (Roche Molecular Biochemicals, Indianapolis. IN). La actividad de la luciferasa se cuantificó luego al medir la luminiscencia usando un contador de escintilación microbeta Wallac.

5. El porcentaje de inhibición para cada compuesto se calculó al cunatificar el nivel de expresión de luciferasa en las

células infectadas en presencia de cada compuesto como un porcentaje de aquel observado para las células infectadas en ausencia del compuesto y restando tal valor determinado de 100.

6. Una EC_{50} proporciona un método para comparar la potencia antiviral de los compuestos de esta invención. La concentración efectiva para una inhibición al cincuenta por ciento (EC_{50}) se calculó con el software de ajuste de curvas de Microsoft Excel Xlfit. Para cada compuesto, se generaron curvas del porcentaje de inhibición calculado a 10 concentraciones diferentes al usar un modelo logístico de cuatro parámetros (modelo 205). Los datos EC_{50} dpara los compuestos se muestra en las Tablas 2-4.La Tabla 1 es la clave para los datos en las Tablas 2-4.

Los ensayos de citotoxicidad se efectuaron con los mismos HeLa usando la metodología bien conocida en el arte. Este método se ha descrito en la literatura (S Weilow, R Kiser, DL Fine, J Bader, RH Shoemaker and MR Boyd: New soluble-formazan assay for HIV-1 citopathic effects: application to high-flux screening of synthetic and natural products for AIDS-antiviral activity. Journal of the Nacional Cancer Institute. 81(8):577-586, 1989.

Se incubaron las células en presencia de fármaco por 6 días, después de lo cual se midió la viabilidad celular usando un ensayo de reducción con colorante (MTT) y se determinó como un CC50. Este ensayo mide la actividad intracelular reductora presente en células que respiran activamente.

920

Resultados

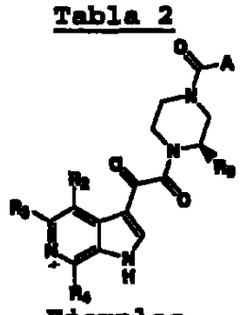
Tabla 1. Datos biológicos clave para EC_{50}

Compuestos* Con EC_{50} > 5μM	Compuestos con EC_{50} > 1 μM pero < 5 μM	Compuestos con EC50 > 50 nM pero no se prueba aun a altas concentraciones	Compuestos con EC50 < 1 μM
Grupo C	Grupo B	Grupo A'	Grupo A

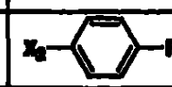
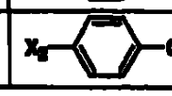
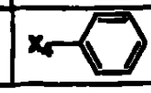
*Algunos de estos compuestos pueden probarse a una concentración menor que su EC_{50}, pero muestran alguna capacidad para causar inhibición y de esta manera se evaluaran a una concentración más alta para determinar el EC_{50} exacto.

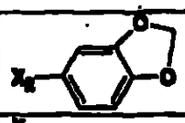
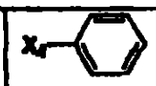
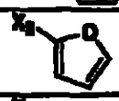
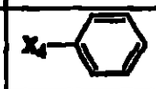
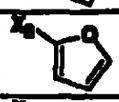
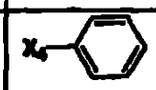
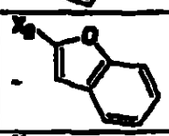
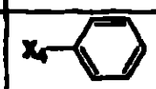
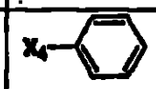
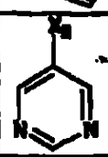
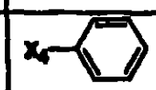
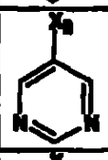
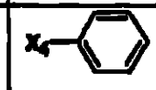
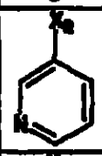
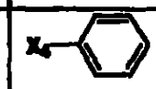
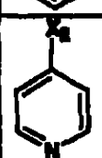
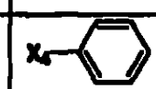
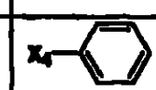
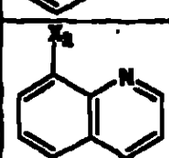
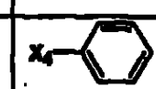
En las tablas 2-5, X_2, X_4, etc. indica el punto de enlace.

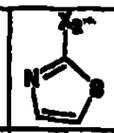
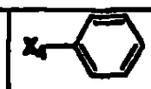
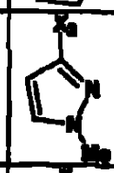
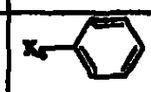
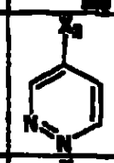
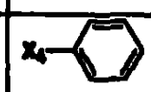
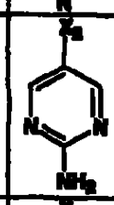
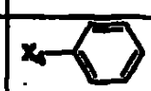
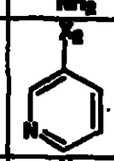
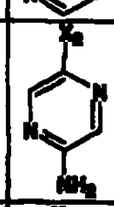
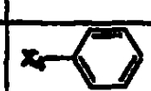
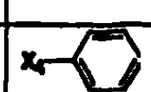
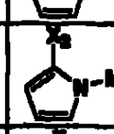
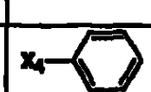
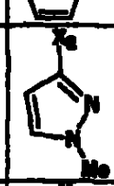
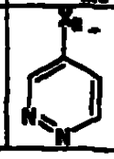
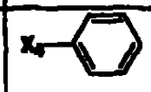
Tabla 2



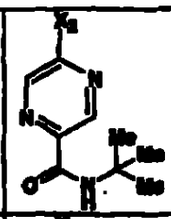
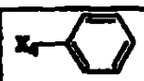
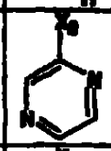
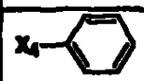
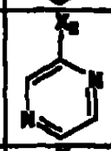
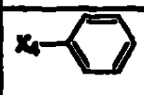
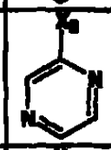
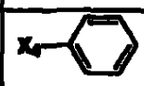
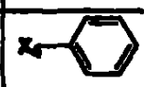
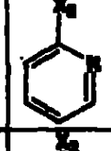
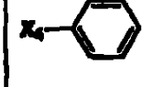
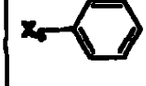
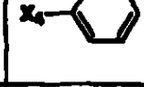
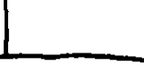
Ejemplos

Entrada a la tabla (número de ejemplo)	R2	R3	R4	R9	A	Grupo EC_{50} de Tabla 1
1 (Ejemplo 1)	H	H		CH_3		A
2 (Ejemplo 2)	H	H		CH_3		A
4 (Ejemplo 4)	H	H		H		A

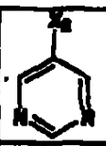
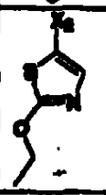
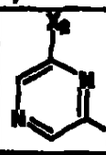
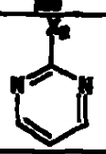
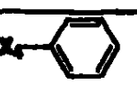
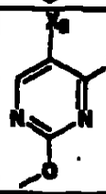
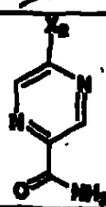
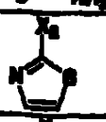
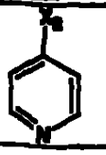
5 (Ejemplo 5)	H	H		CH_3		A
6 (Ejemplo 6)	H	H		CH_3		A
7 (Ejemplo 7)	H	H		H		A
8 (Ejemplo 8)	H	H		H		A
9 (Ejemplo 9)	H	H		CH_3		A
10 (Ejemplo 16)	H	H		CH_3		A
11 (Ejemplo 17)	H	H		H		A
12 (Ejemplo 18)	H	H		CH_3		A
13 (Ejemplo 10)	H	H		H		A
14 (Ejemplo 19)	H	H		H		A
15 (Ejemplo 11)	H	H		H		A'
16 (Ejemplo 20)	H	H		CH_3		A

17 (Ejemplo 21)	H	H		H		A
18 (Ejemplo 22)	OMe	H		H		A
19 (Ejemplo 23)	OMe	H		H		A
20 (Ejemplo 24)	OMe	H		H		A
21 (Ejemplo 25)	OMe	H		H		A
22 (Ejemplo 26)	OMe	H		H		A
23 (Ejemplo 27)	OMe	H		H		A
24 (Ejemplo 28)	OMe	H		H		A
25 (Ejemplo 29)	F	H		H		A
26 (Ejemplo 30)	F	H		H		A

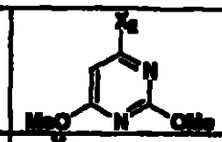
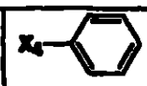
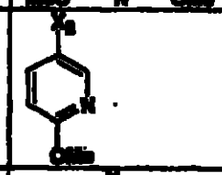
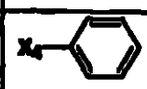
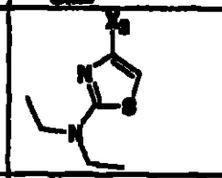
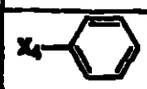
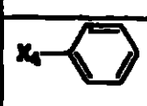
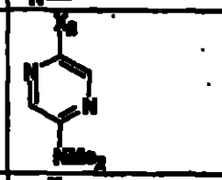
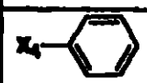
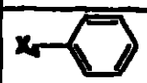
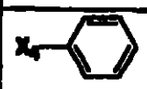
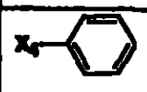
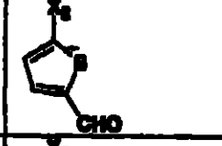
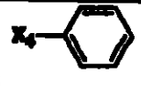
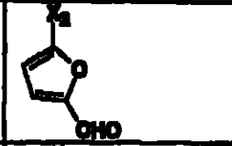
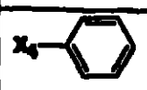
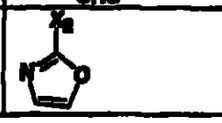
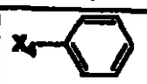
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27 (Ejemplo 15)	OMe	H		H		A
28 (Ejemplo 32)	OMe	H		H		A
29 (Ejemplo 33)	H	H		Me		A
30 (Ejemplo 34)	H	H		H		A
31 (Ejemplo 35)	OMe	H		H		A
32 (Ejemplo 36)	OMe	H		H		A
33 (Ejemplo 37)	F	H		Me		A
34 (Ejemplo 38)	F	H		H		A
35 (Ejemplo 39)	OMe	H		H		A
36 (Ejemplo 40)	OMe	H		H		A
37 (Ejemplo 41)	F	H		Me		A

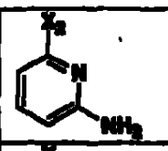
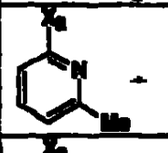
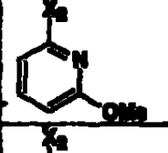
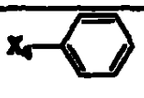
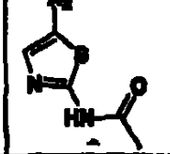
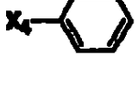
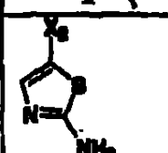
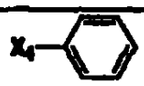
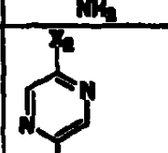
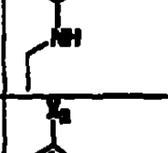
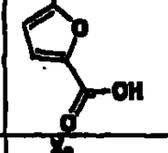
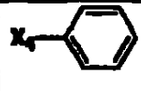
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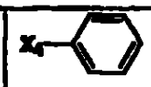
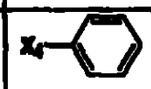
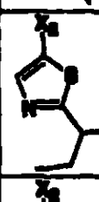
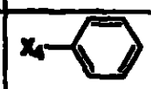
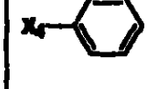
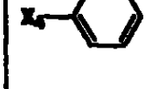
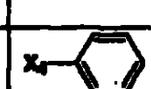
38 (Ejemplo 42)	F	H		H		A
41 (Ejemplo 45)	OMe	H		H		A
42 (Ejemplo 46)	OMe	H		H		A
43 (Ejemplo 47)	OMe	H		H		A
45 (Ejemplo 49)	OMe	H		H		A
46 (Ejemplo 13)	OMe	H		H		A
47 (Ejemplo 55)	OMe	H		H		A
48 (Ejemplo 50)	OMe	H		H		A
49 (Ejemplo 14)	OMe	H		H		A

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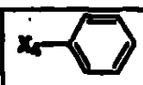
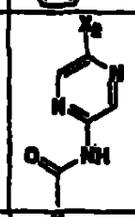
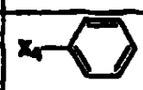
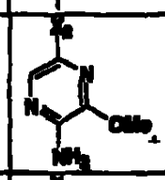
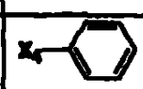
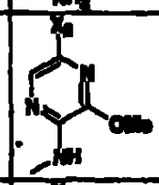
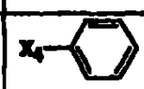
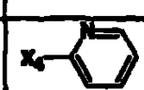
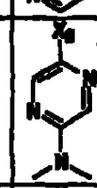
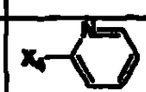
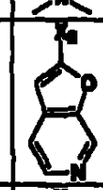
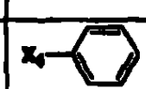
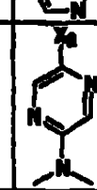
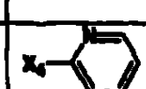
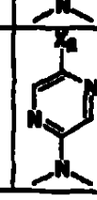
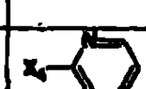
50 (Ejemplo 68)	OMe	H		H		A
51 (Ejemplo 69)	OMe	H		H		A
52 (Ejemplo 70)	OMe	H		H		A
53 (Ejemplo 71)	OMe	H		H		A
54 (Ejemplo 72)	OMe	H		H		A
55 (Ejemplo 82)	OMe	H		H		A
56 (Ejemplo 73)	OMe	H		H		A
57 (Ejemplo 83)	OMe	H		H		A
58 (Ejemplo 84)	OMe	H		H		A
59 (Ejemplo 85)	OMe	H		H		A
60 (Ejemplo 74)	OMe	H		H		A

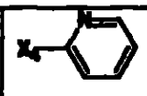
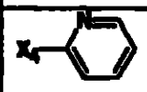
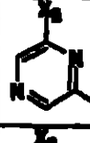
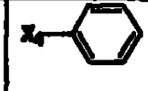
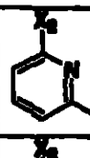
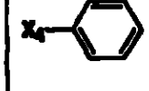
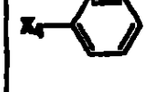
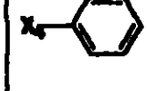
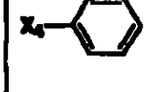
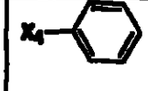
926

61 (Ejemplo 75)	OMe	H		H		A
62 (Ejemplo 76)	OMe	H		H		A
63 (Ejemplo 77)	OMe	H		H		A
64 (Ejemplo 78)	OMe	H		H		A
65 (Ejemplo 80)	OMe	H		H		A
66 (Ejemplo 79)	OMe	H		H		A
67 (Ejemplo 87)	OMe	H		H		A
68 (Ejemplo 81)	OMe	H		H		A
69 (Ejemplo 88)	OMe	H		H		A

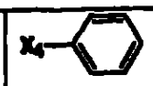
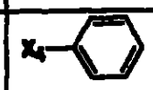
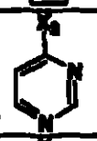
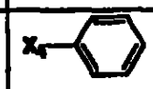
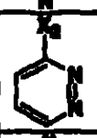
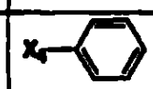
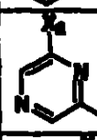
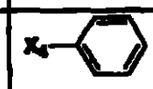
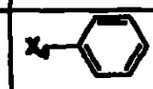
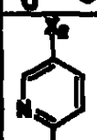
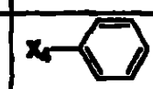
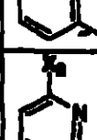
70 (Ejemplo 89)	H	H		H		A
71 (Ejemplo 90)	OMe	H		H		A
72 (Ejemplo 91)	OMe	H		H		A
72 (Ejemplo 92)	OMe	H		H		A
73 (Ejemplo 93)	OMe	H		H		A
74 (Ejemplo 94)	OMe	H		H		A
75 (Ejemplo 95)	F	H		H		A
76 (Ejemplo 96)	Cl	H		H		A
77 (Ejemplo 97)	OMe	H		H		A

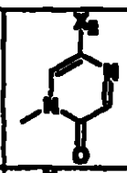
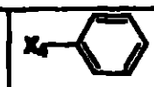
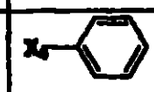
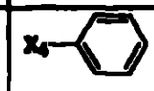
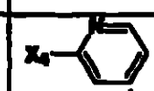
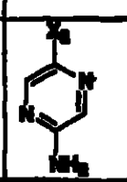
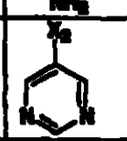
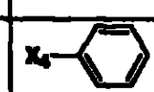
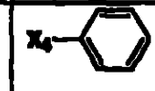
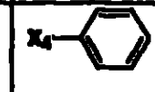
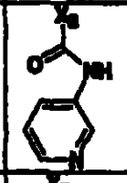
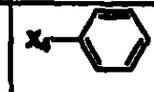
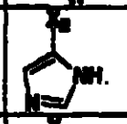
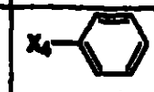
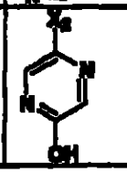
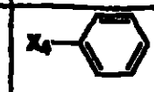
928

78 (Ejemplo 98)	OMe	H		H		A
79 (Ejemplo 99)	OMe	H		H		A
80 (Ejemplo 100)	OMe	H		H		A
81 (Ejemplo 101)	OMe	H		H		A
82 (Ejemplo 102)	OMe	H		H		A
83 (Ejemplo 103)	OMe	H		H		A
84 (Ejemplo 104)	OMe	H		H		A
85 (Ejemplo 105)	H	H		(R)-Me		A
86 (Ejemplo 106)	H	H		(S)-Me		A

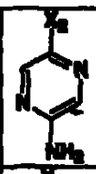
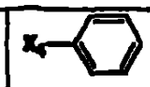
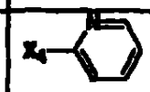
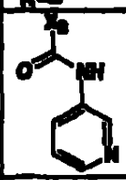
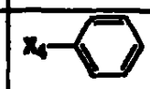
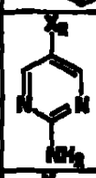
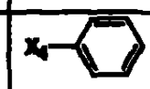
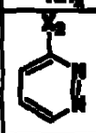
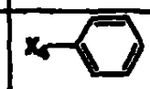
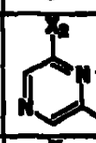
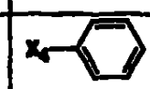
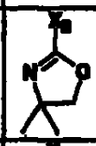
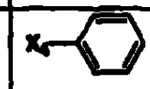
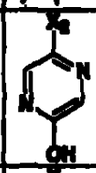
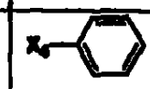
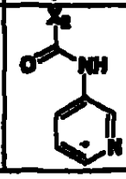
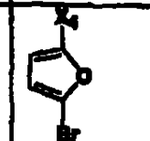
87 (Ejemplo 107)	H	H		(R)-Me		A
88 (Ejemplo 108)	H	H		(S)-Me		A
89 (Ejemplo 109)	H	H		(R)-Me		A
90 (Ejemplo 110)	H	H		(S)-Me		A
91 (Ejemplo 111)	H	H		(R)-Me		A
92 (Ejemplo 112)	H	H		(R)-Me		A
93 (Ejemplo 113)	H	H		(R)-Me		A
94 (Ejemplo 114)	H	H		(R)-Me		A
95 (Ejemplo 115)	OMe	H		H		A
96 (Ejemplo 116)	OMe	H		H		A

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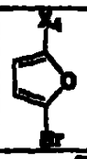
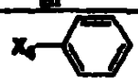
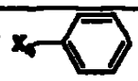
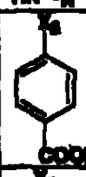
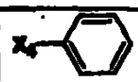
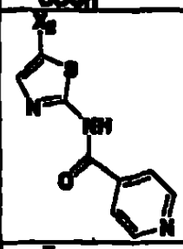
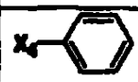
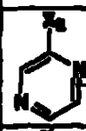
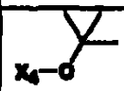
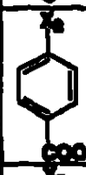
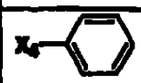
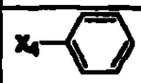
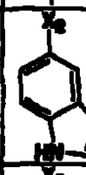
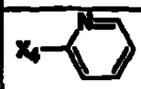
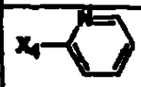
97 (Ejemplo 117)	OMe	H		H		A
98 (Ejemplo 118)	OMe	H		H		A
99 (Ejemplo 119)	OMe	H		H		A
100 (Ejemplo 120)	OMe	H		H		A
101 (Ejemplo 121)	H	H		(R)-Me		A
102 (Ejemplo 121-2)	H	H		(R)-Me		A
103 (Ejemplo 122)	H	H		(R)-Me		A
104 (Ejemplo 123)	H	H		(R)-Me		A
105 (Ejemplo 124)	H	H		(R)-Me		A
106 (Ejemplo 125)	F	H		H		A

107 (Ejemplo 138)	OMe	H		H		A
108 (Ejemplo 139)	Br	H		(R)-Me		A
109 (Ejemplo 140)	F	H		H		A
110 (Ejemplo 141)	F	H		(R)-Me		A
111						
112 (Ejemplo 143)	Cl	H		H		A
113 (Ejemplo 144)	Cl	H		H		A
114 (Ejemplo 145)	F	H		H		A
115 (Ejemplo 146)	F	H		H		A
116 (Ejemplo 147)	F	H		H		A
117 (Ejemplo 148)	F	H		H		A
118 (Ejemplo 149)	Cl	H		H		A

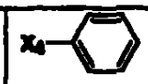
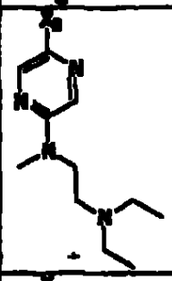
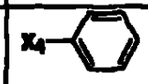
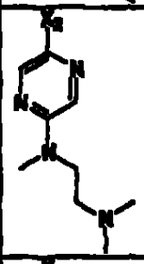
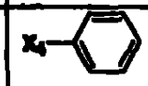
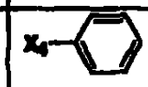
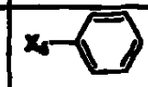
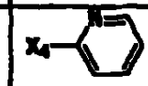
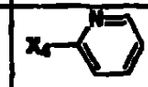
932

119 (Ejemplo 150)	H	H		(R)-Me		A
120 (Ejemplo 151)	OMe	H		H		A
121 (Ejemplo 152)	Cl	H		H		A
122 (Ejemplo 153)	H	H		(R)-Me		A
123 (Ejemplo 154)	F	H		H		A
124 (Ejemplo 155)	OMe	H		H		A
125 (Ejemplo 156)	OMe	H		H		A
126 (Ejemplo 157)	H	H		(R)-Me		A
127 (Ejemplo 165)	Cl	H		H		A
128 (Ejemplo 166)	F	H		H		

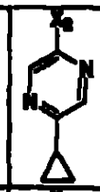
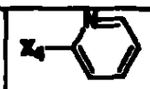
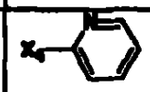
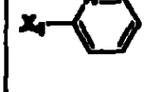
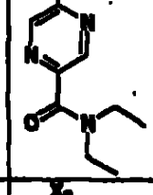
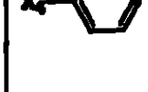
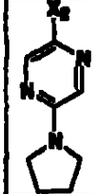
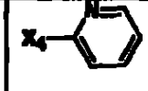
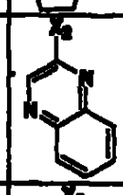
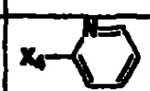
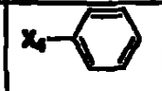
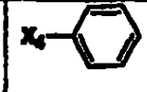
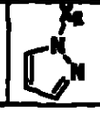
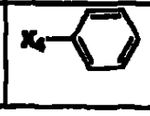
133

129 (Ejemplo 167)	F	H		H		
130 (Ejemplo 162)	H	H		(R)-Me		A
131 (Ejemplo 163)	Cl	H		H		A
132 (Ejemplo 164)	H	H		(R)Me		A
133 (Ejemplo 169)	OMe	H		H		
134 (Precursor 50)	OMe	H		H		A
135 (Ejemplo 170)	H	H		(R)-Me		A
136 (Ejemplo 171)	OMe	H		H		A
137 (Ejemplo 172)	OMe	H		H		A
138 (Ejemplo 173)	OMe	H		H		A

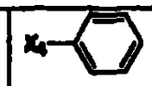
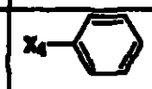
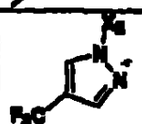
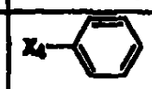
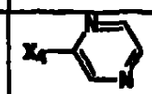
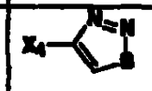
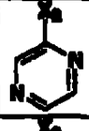
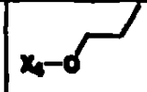
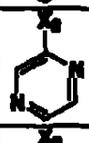
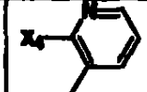
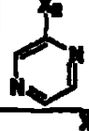
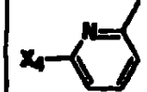
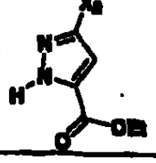
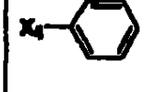
934

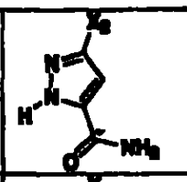
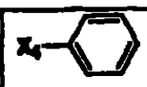
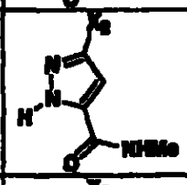
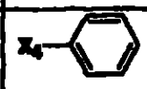
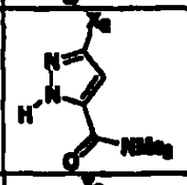
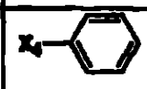
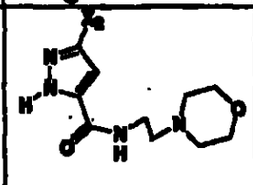
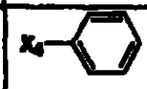
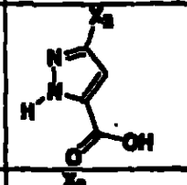
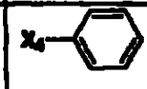
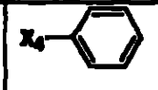
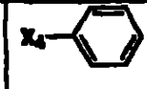
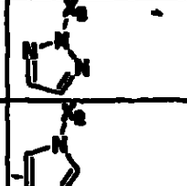
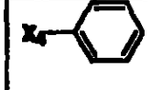
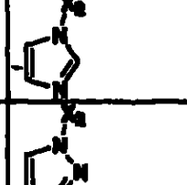
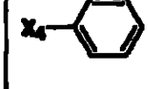
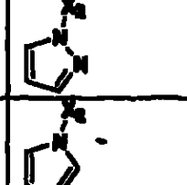
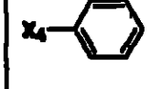
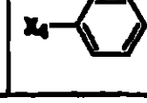
139 (Ejemplo 174)	OMe	H		H		A
140 (Ejemplo 175)	OMe	H		H		A
141 (Ejemplo 176)	OMe	H		H		A
142 (Ejemplo 177)	OMe	H		H		A
143 (Ejemplo 178)	OMe	H		H		A
144 (Ejemplo 179)	OMe	H		H		A
145 (Ejemplo 180)	OMe	H		H		A

935

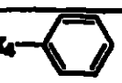
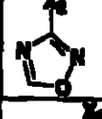
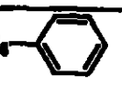
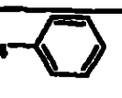
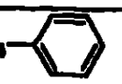
146 (Ejemplo 181)	OMe	H		H		A
147 (Ejemplo 182)	OMe	H		H		A
148 (Ejemplo 183)	OMe	H		H		A
149 (Ejemplo 184)	OMe	H		H		A
150 (Ejemplo 185)	OMe	H		H		A
151 (Ejemplo 186)	OMe	H		H		A
152 (Ejemplo 187)	OMe	H		H		A
153 (Ejemplo 188)	OMe	H		H		A
154 (Ejemplo 189)	OMe	H		H		A

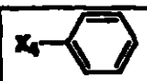
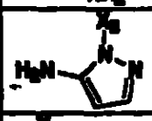
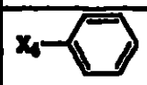
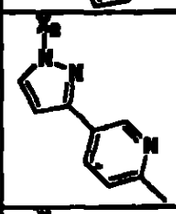
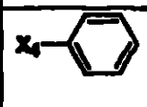
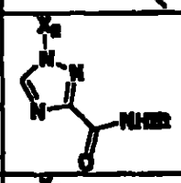
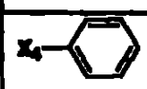
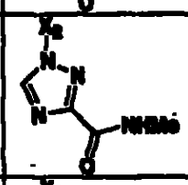
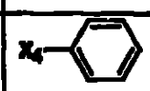
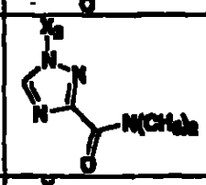
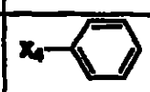
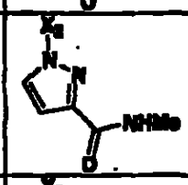
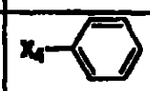
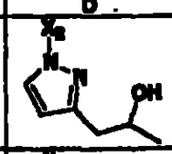
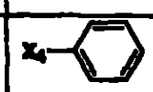
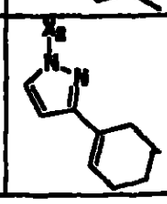
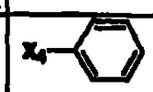
936

155 (Ejemplo 190)	OMe	H		H		A
156 (Ejemplo 191)	OMe	H		H		A
157 (Ejemplo 192)	OMe	H		H		A
158 (Ejemplo 193)	OMe	H		H		A
159 (Ejemplo 195)	OMe	H		H		A
160 (Ejemplo 196)	OMe	H		H		A
161 (Ejemplo 197)	OMe	H		H		A
162 (Ejemplo 198)	OMe	H		H		A
163 (Ejemplo 199)	OMe	H		H		A
164 (Ejemplo 200)	OMe	H		H		A
165 (Ejemplo 201)	OMe	H		H		A
166 (Ejemplo 209)	F	H		H		A

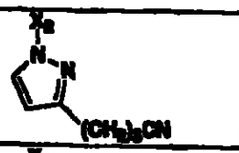
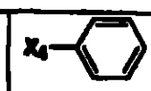
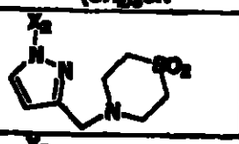
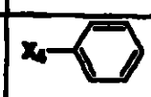
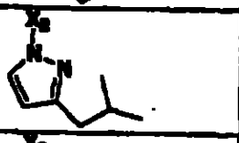
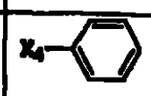
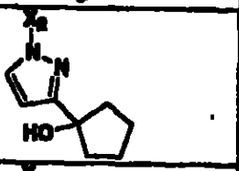
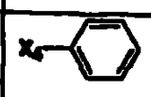
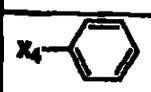
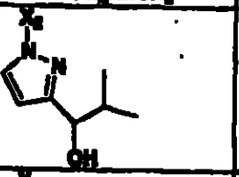
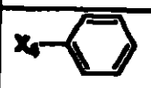
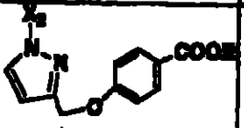
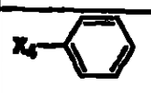
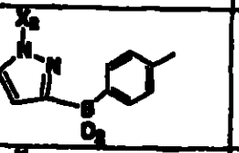
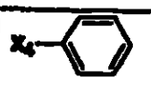
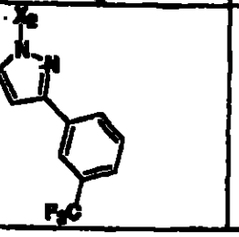
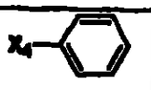
167 (Ejemplo 210)	F	H		H		A
168 (Ejemplo 211)	F	H		H		A
169 (Ejemplo 212)	F	H		H		A
170 (Ejemplo 213)	F	H		H		A
171 (Ejemplo 214)	F	H		H		A
172 (Ejemplo 215)	F	H		H		A
173 (Ejemplo 216)	F	H		H		A
174 (Ejemplo 217)	F	H		H		A
175 (Ejemplo 218)	F	H		H		A
176 (Ejemplo 219)	F	H		H		A
177 (Ejemplo 220)	F	H		H		A

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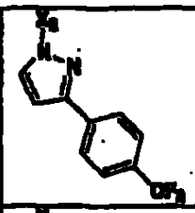
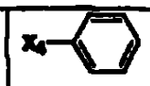
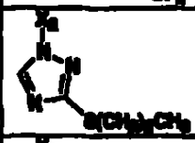
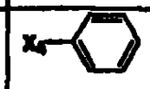
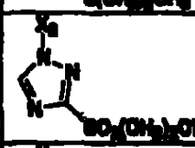
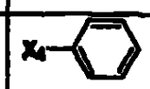
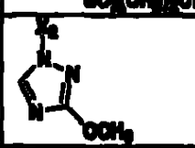
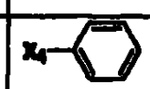
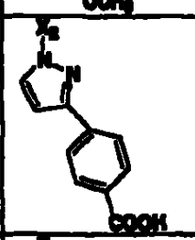
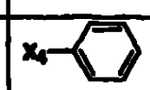
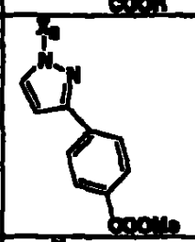
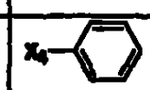
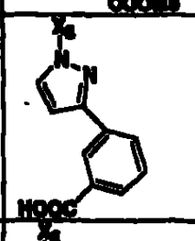
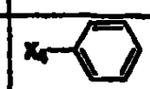
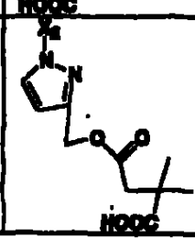
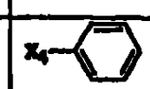
178 (Ejemplo 221)	F	H		H		A
179 (Ejemplo 222)	F	H		H		A
180 (Ejemplo 223)	OMe	H		H		A
181 (Ejemplo 224)	OMe	H		H		A
182 (Ejemplo 225)	OMe	H		H		A
183 (Ejemplo 226)	OMe	H		H		A
185 (Ejemplo 240)	OMe	H		H		A
186 (Ejemplo 247)	OMe	H		H		A
187 (Ejemplo 248)	OMe	H		H		A
188 (Ejemplo 249)	OMe	H		H		A
189 (Ejemplo 250)	OMe	H		H		A

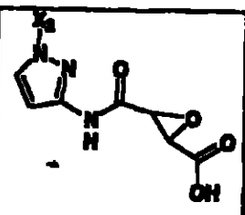
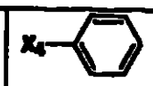
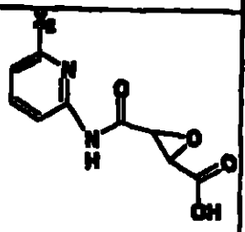
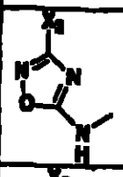
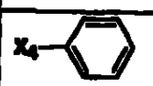
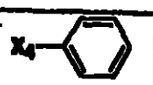
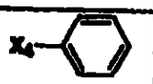
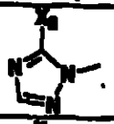
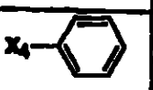
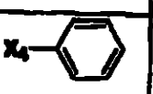
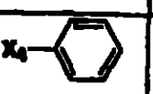
190 (Ejemplo 251)	OMe	H		H		A
191 (Ejemplo 252)	OMe	H		H		A
192 (Ejemplo 264)	OMe	H		H		A
193 (Ejemplo 273)	OMe	H		H		A
194 (Ejemplo 274)	OMe	H		H		A
195 (Ejemplo 275)	OMe	H		H		A
196 (Ejemplo 276)	OMe	H		H		A
197 (Ejemplo 277)	OMe	H		H		A
198 (Ejemplo 278)	OMe	H		H		A

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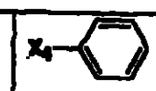
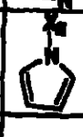
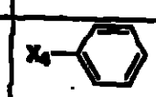
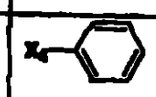
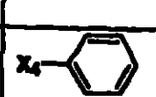
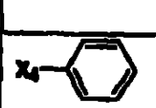
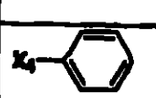
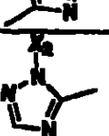
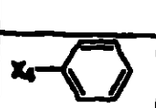
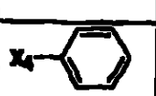
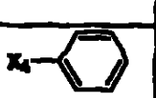
199 (Ejemplo 279)	OMe	H		H		A
200 (Ejemplo 280)	OMe	H		H		A
201 (Ejemplo 281)	OMe	H		H		A
202 (Ejemplo 282)	OMe	H		H		A
203 (Ejemplo 283)	OMe	H		H		A
204 (Ejemplo 284)	OMe	H		H		A
205 (Ejemplo 285)	OMe	H		H		A
206 (Ejemplo 286)	OMe	H		H		A
207 (Ejemplo 287)	OMe	H		H		A

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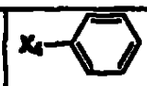
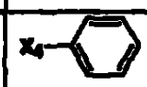
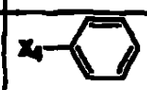
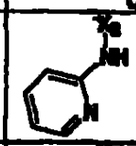
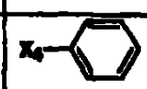
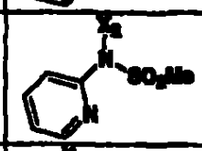
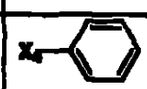
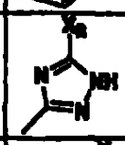
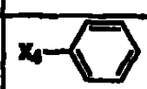
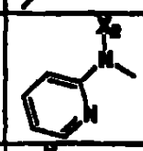
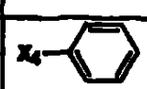
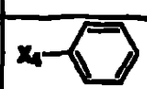
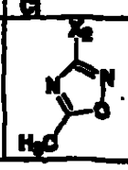
208 (Ejemplo 288)	OMe	H		H		A
209 (Ejemplo 289)	OMe	H		H		A
210 (Ejemplo 290)	OMe	H		H		A
211 (Ejemplo 291)	OMe	H		H		A
212 (Ejemplo 292)	OMe	H		H		A
213 (Ejemplo 293)	OMe	H		H		A
214 (Ejemplo 294)	OMe	H		H		A
215 (Ejemplo 295)	OMe	H		H		A

216 (Ejemplo 296)	OMe	H		H		A
217 (Ejemplo 297)	OMe	H		(R)-Me		A
218 (Ejemplo 298)	F	H		H		A
219 (Ejemplo 299)	F	H		H		A
220 (Ejemplo 300)	F	H		H		A
221 (Ejemplo 301)	F	H		H		A
222 (Ejemplo 303)	F	H		H		A
223 (Ejemplo 304)	F	H		H		A
223 (Ejemplo 305)	F	H		H		A
224 (Ejemplo 306)	F	H		H		A

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225 (Ejemplo 307)	F	H		H		A
226 (Ejemplo 308)	F	H		H		A
227 (Ejemplo 309)	F	H		H		A
228 (Ejemplo 310)	F	H		H		A
229 (Ejemplo 311)	F	H		H		A
230 (Ejemplo 312)	F	H		H		A
231 (Ejemplo 313)	F	H		H		A
232 (Ejemplo 316)	MeO	H		H		A
233 (Ejemplo 318)	MeO	H		H		A
234 (Ejemplo 319)	MeO	H		H		A
234 (Ejemplo 321)	MeO	H		H		A
235 (Ejemplo 323)	MeO	H		H		A

944

236 (Ejemplo 325)	MeO	H		H		A
237 (Ejemplo 327)	MeO	H		H		A
238 (Ejemplo 329)	MeO	H		H		A
239 (Ejemplo 330)	MeO	H		H		A
240 (Ejemplo 331)	MeO	H		H		B
241 (Ejemplo 342)	MeO	H		H		A
242(Ejemplo 341)	MeO	H		H		C
243 (Ejemplo 343)	OMe	H		H		A
244 (Ejemplo 344)	OMe	H		H		A
245 (Ejemplo 346)	OMe	H		H		A

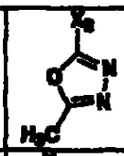
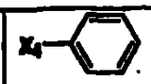
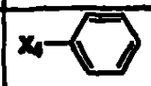
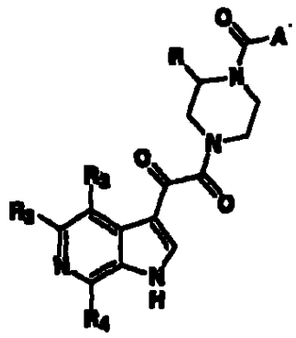
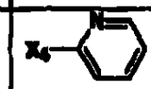
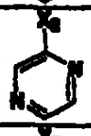
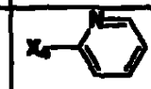
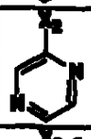
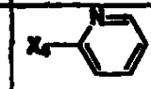
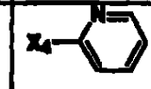
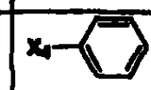
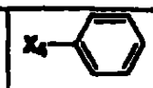
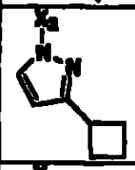
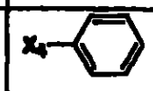
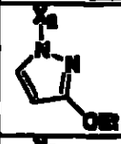
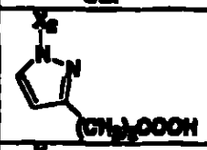
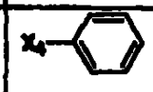
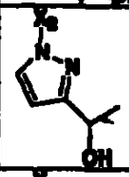
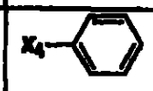
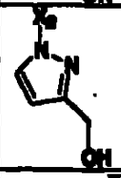
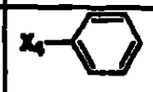
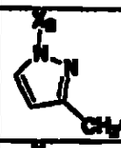
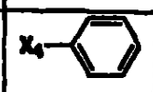
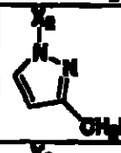
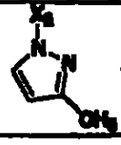
246 (Ejemplo 349)	OMe	H		H		A
247 (Ejemplo 351)	OMe	H		H		A

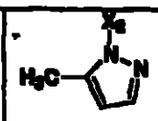
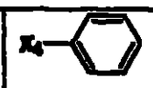
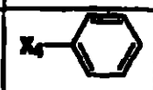
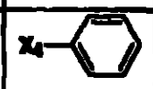
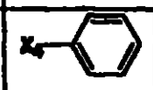
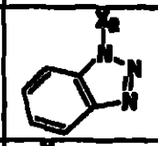
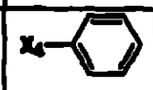
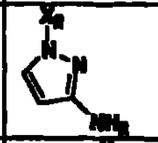
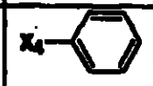
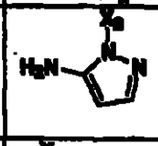
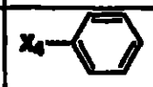
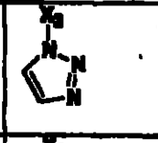
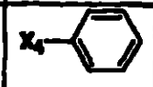
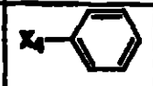
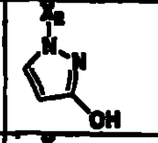
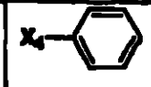
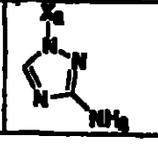
Tabla 2-1

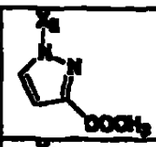
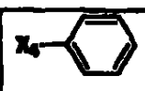
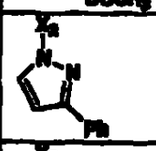
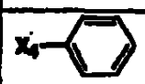
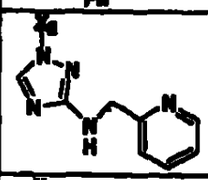
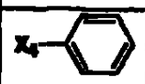
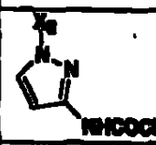
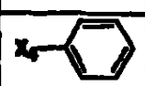
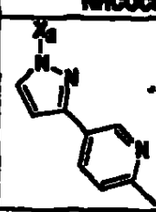
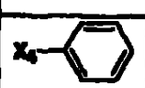
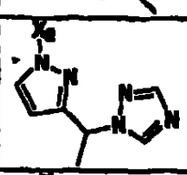
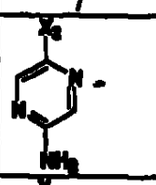
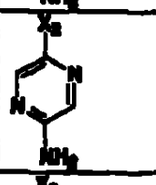
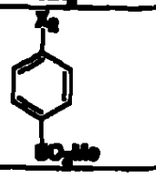
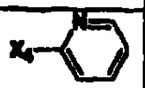


Entrada a la Tabla (número de Ejemplo)	R2	R3	R4	R	A	Grupo EC_{50} de Tabla 1
1 (Ejemplo 194)	OMe	H		Me		A
2 (Ejemplo 227)	OMe	H		(R)-Me		A
3(Ejemplo 228)	OMe	H		(S)-Me		A
4 (Ejemplo 229)	OMe	H		Et		A
5 (Ejemplo 230)	OMe	H		(R)-Me		A

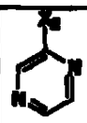
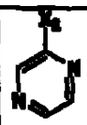
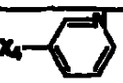
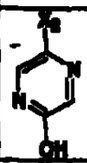
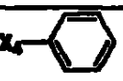
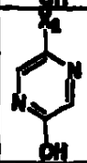
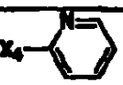
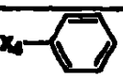
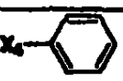
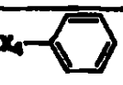
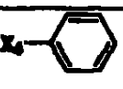
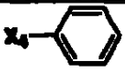
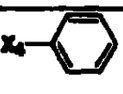
946

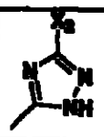
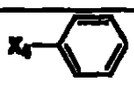
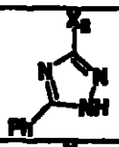
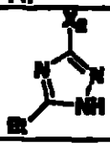
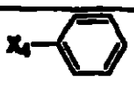
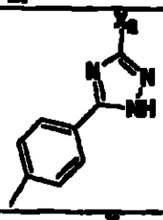
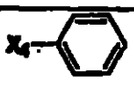
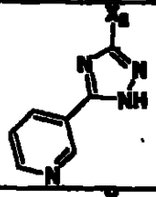
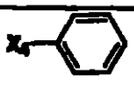
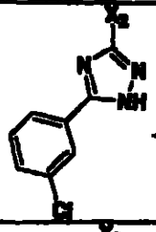
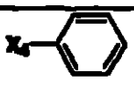
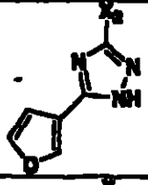
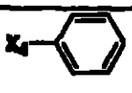
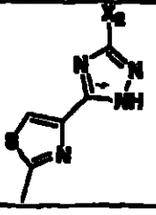
6 (Ejemplo 231)	OMe	H		(R)-Me		A
7 (Ejemplo 232)	OMe	H		(R)-Me		A
7 (Ejemplo 233)	OMe	H		(R)-Me		A
8 (Ejemplo 234)	OMe	H		(R)-Me		A
8 (Ejemplo 235)	OMe	H		(R)-Me		A
9 (Ejemplo 236)	OMe	H		(R)-Me		A
10 (Ejemplo 237)	OMe	H		(R)-Me		A
11 (Ejemplo 238)	OMe	H		(R)-Me		A
12 (Ejemplo 239)	OMe	H		(R)-Me		A
13 (Ejemplo 241)	OMe	H		(R)-Me		A

14 (Ejemplo 242)	OMe	H		(R)-Me		A
15 (Ejemplo 243)	OMe	H		(R)-Me		A
16 (Ejemplo 244)	OMe	H		(R)-Me		A
17 (Ejemplo 245)	OMe	H		(R)-Me		A
18 (Ejemplo 246)	OMe	H		(R)-Me		A
19 (Ejemplo 253)	OMe	H		(R)-Me		A
20 (Ejemplo 254)	OMe	H		(R)-Me		A
21 (Ejemplo 255)	OMe	H		(R)-Me		A
22 (Ejemplo 256)	OMe	H		(R)-Me		A
23 (Ejemplo 257)	OMe	H		(R)-Me		A
24 (Ejemplo 258)	OMe	H		(R)-Me		A

25 (Ejemplo 259)	OMe	H		(R)-Me		A
26 (Ejemplo 260)	OMe	H		(R)-Me		A
27 (Ejemplo 261)	OMe	H		(R)-Me		A
28 (Ejemplo 262)	OMe	H		(R)-Me		A
29 (Ejemplo 263)	OMe	H		(R)-Me		A
30 (Ejemplo 265)	OMe	H		(R)-Me		A
31 (Ejemplo 266)	OMe	H		(R)-Me		A
32 (Ejemplo 267)	OMe	H		(R)-Me		A
33 (Ejemplo 268)	OMe	H		(R)-Me		A

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34 (Ejemplo 269)	OMe	H		(R)-Me		A
35 (Ejemplo 270)	OMe	H		(R)-Me		A
36 (Ejemplo 271)	OMe	H		(R)-Me		A
37 (Ejemplo 272)	OMe	H		(R)-Me		A
38 (Ejemplo 314)	F	H		(R)-Me		A
39 (Ejemplo 315)	F	H		(R)-Me		A
40 (Ejemplo 317)	OMe	H		(R)-Me		A
41 (Ejemplo 322)	MeO	H		(R)-Me		A
42 (Ejemplo 324)	MeO	H		(R)-Me		A
43 (Ejemplo 326)	MeO	H		(R)-Me		A
44 (Ejemplo 328)	MeO	H		(R)-Me		A

45 (Ejemplo 334)	MeO	H		(R)-Me		A
46 (Ejemplo 335)	MeO	H		(R)-Me		A
47 (Ejemplo 336)	MeO	H		(R)-Me		A
48 (Ejemplo 337)	MeO	H		(R)-Me		A
49 (Ejemplo 338)	MeO	H		(R)-Me		A
50 (Ejemplo 339)	MeO	H		(R)-Me		A
51 (Ejemplo 340)	MeO	H		(R)-Me		A
52 (Ejemplo 341)	MeO	H		(R)-Me		A

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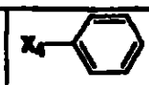
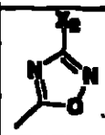
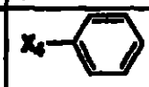
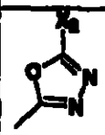
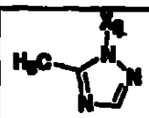
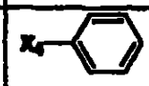
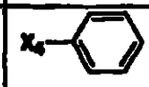
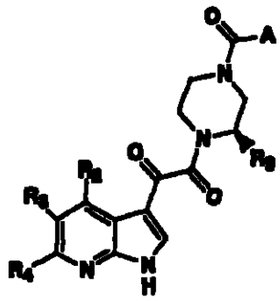
53 (Ejemplo 345)	MeO	H		(R)-Me		A
54 (Ejemplo 347)	MeO	H		(R)-Me		A
55 (Ejemplo 348)	MeO	H		(R)-Me		A
56 (Ejemplo 350)	MeO	H		(R)-Me		A
57 (Ejemplo 352)	MeO	H		(S)-Me		A

Tabla 3

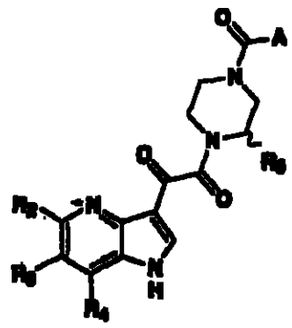


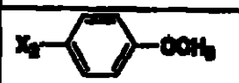
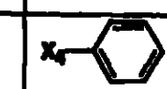
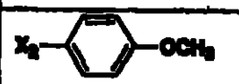
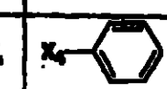
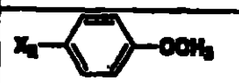
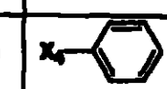
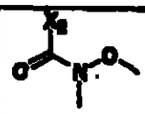
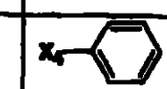
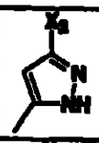
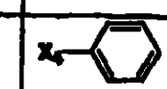
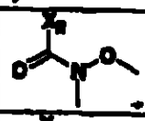
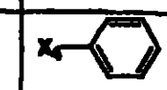
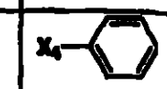
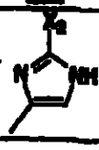
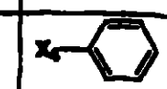
Ejemplo 56

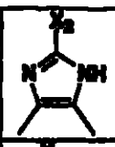
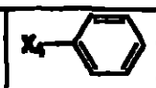
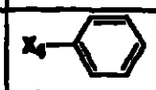
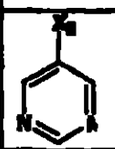
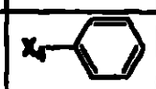
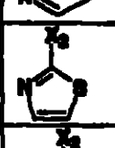
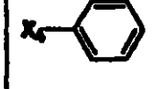
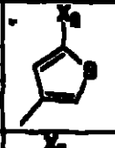
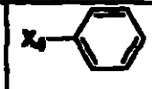
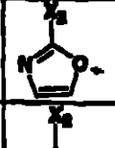
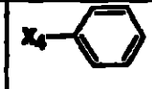
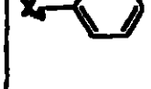
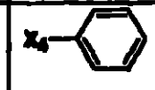
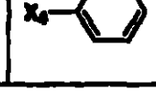
Entrada a la Tabla (número de Ejemplo	R2	R3	R4	R9	A	Grupo EC_{50} de Tabla 1
1 (Ejemplo 56)	H	H		CH_3		B

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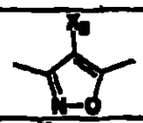
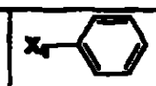
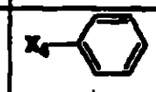
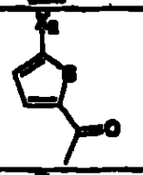
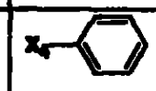
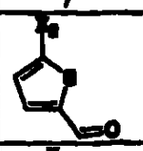
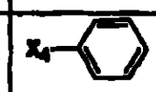
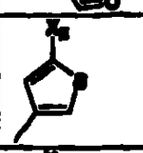
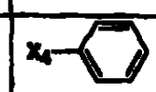
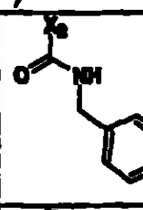
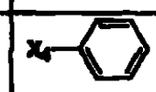
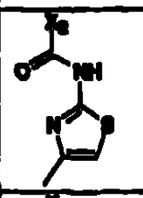
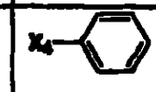
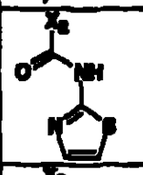
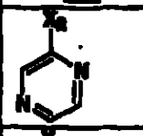
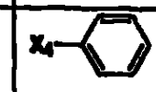
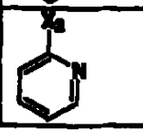
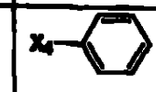
Tabla 4



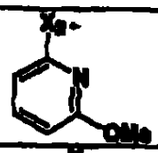
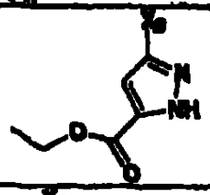
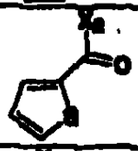
Entrada a la Tabla (no. de Ejemplo)	R2	R3	R4	R9	A	Grupo EC_{50} de Tabla 1
1 (Ejemplo 65)	H	H		H		A
2 (Ejemplo 66)	H	H		(S)-CH_3		A
3 (Ejemplo 67)	H	H		(R)-Me		A
4 (Ejemplo 87)	H	H		(R)-Me		A
6 (Ejemplo 64)	Cl	H		(R)-Me		A
7 (Ejemplo 86)	Cl	H		(R)-Me		A
8 (Ejemplo 60)	Cl	H		(R)-Me		A
9 (Ejemplo 61)	Cl	H		(R)-Me		A

10 (Ejemplo 82)	Cl	H		(R)-Me		A
11 (Ejemplo 83)	Cl	H		(R)-Me		A
12						
13 (Ejemplo 81)	H	H		(R)-Me		A
14 (Ejemplo 82)	H	H		(R)-Me		A
15 (Ejemplo 83)	H	H		(R)-Me		A
16 (Ejemplo 84)	H	H		(R)-Me		A
17 (Ejemplo 86)	H	H		(R)-Me		A
18 (Ejemplo 126)	H	H		(R)-Me		A
19 (Ejemplo 127)	H	H		(R)-Me		A
20 (Ejemplo 128)	H	H		(R)-Me		A
21 (Ejemplo 129)	H	H		(R)-Me		A

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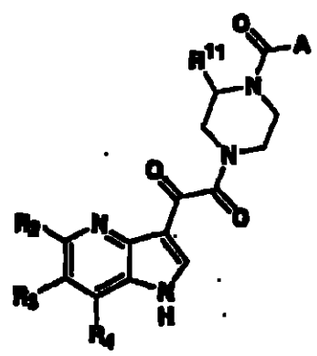
22 (Ejemplo 130)	H	H		(R)-Me		A
23 (Ejemplo 131)	H	H		H		A
24 (Ejemplo 132)	H	H		H		A
25 (Ejemplo 133)	H	H		H		A
26 (Ejemplo 134)	H	H		H		A
27 (Ejemplo 135)	H	H		(R)-Me		A
28 (Ejemplo 136)	H	H		(R)-Me		A
29 (Ejemplo 137)	H	H		(R)-Me		A
30 (Ejemplo 138)	H	H		H		A
31 (Ejemplo 139)	H	H		H		A

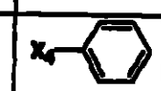
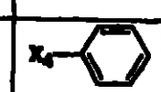
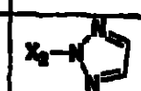
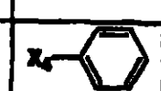
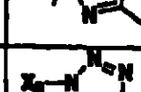
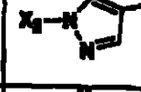
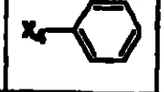
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32 (Ejemplo 160)	H	H		H		A
33 (Ejemplo 161)	H	H		H		A
34 (Ejemplo 202)	H	H		H		A
35 (Ejemplo 203)	H	H		H		A
36 (Ejemplo 204)	H	H		H		A
37 (Ejemplo 168)	H	H		H		A
38 (Ejemplo 205)	H	H		H		A
39 (Ejemplo 206)	H	H		H		A
40 (Ejemplo 207)	H	H		H		A
41 (Ejemplo 208)	H	H		H		A

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Tabla 4-1



Entrada a la Tabla (número de Ejemplo)	R2	R3	R4	R9	A	Grupo BC_m de Tabla 1
1 (Ejemplo 353)	H	H		H		A
2 (Ejemplo 354)	H	H		(S)-CH_3		A
3 (Ejemplo 355)	H	H		(R)-Me		A
4 (Ejemplo 356)	H	H		(R)-Me		A
6 (Ejemplo 357)	Cl	H		(R)-Me		A
7 (Ejemplo 358)	Cl	H		(R)-Me		A
8 (Ejemplo 359)	Cl	H		(R)-Me		A
9 (Ejemplo 360)	Cl	H		(R)-Me		A
10 (Ejemplo 361)	Cl	H		(R)-Me		A

Método para extrapolar el % de inhibición a 10 μM

Los compuestos de la tabla 5 a continuación, todos se encontraron que son muy potentes en el ensayo antes descrito usando como criterio el porcentaje de inhibición. En la tabla 5, X_2, X_4, etc., se indica el punto de colocación. La amplia mayoría de los compuestos mostraron más de un 98% de inhibición a una concentración de 10 uM. Los datos a 10 μM se calcularon de la siguiente forma.

Método para la extrapolación del % de inhibición a 10 μM

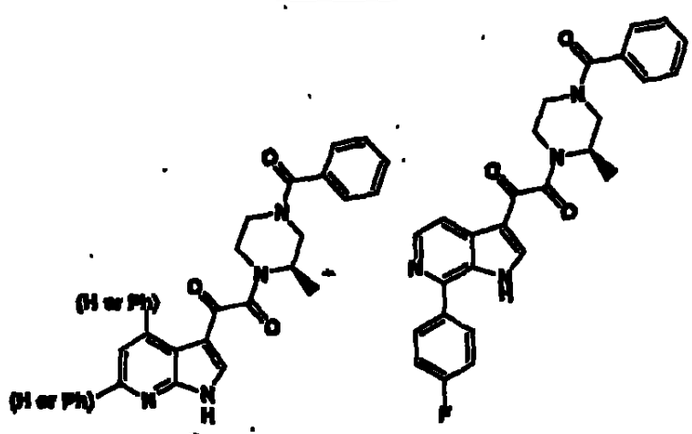
Se obtuvieron los datos en la tabla 5 usando los procedimiento generales anteriores y por los siguientes métodos. No se reportan datos para todos los compuestos ya que los datos para todos los compuestos se reportan por el método alternativo en las tablas previas 1-4. El porcentaje de inhibición para cada compuesto se calcula al cuantificar el nivel de expresión de luciferasa en las células infectadas en presencia de un compuesto como porcentaje de aquel observado para las células infectadas en ausencia de un compuesto y restando tal valor determinado de 100. Para los compuestos probados a concentraciones menores a 10 μM, el porcentaje de inhibición a 10 μM se determina por extrapolación usando la característica de ajuste de curvas XLfit del software de hoja de calculo Microsoft Excel. Se obtuvieron curvas de 10 puntos de datos (% de inhibición determinado a 10 concentraciones de compuestos) al usar un modelo logístico de 4 parámetros (XLfit

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modelo 205; y = A + ((B-A)/(1+((C/x)^D))), en donde, A = mínimo y B = máximo, C = logEC_{50}, D = factor dependiente y x e y son valores de datos conocidos. Se efectuaron las extrapolaciones con los parámetros A y B sin cerrar.

Así, todos los compuestos de esta invención son inhibidores antivirales potentes con base en este ensayo.

Tabla 5



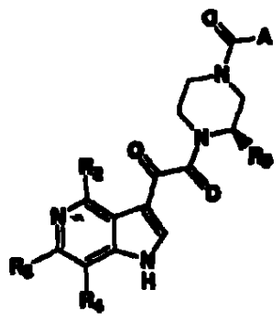
Compuesto #	% de inhibición promedio a 10 μM
Precursor 8	85%
Ejemplo 1	56%

Otros compuestos de la invención:

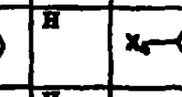
Los inhibidores 5-aza que se muestra en la tabla 6 también deben ser agentes antivirales activos. También son

parte de la invención y se pueden preparar a partir de los precursores 1a ó 2s o los precursores correspondientes de 7-desbromo-7-cloro que se preparan análogamente y los métodos en la presente o por el uso de otros métodos aquí descritos.

Tabla 6



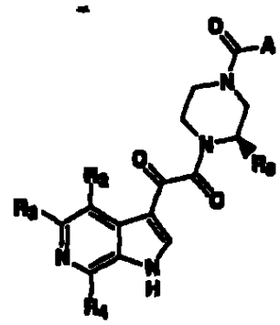
Inhibidores 5-aza

Entrada a la Tabla (número de Ejemplo)	R2	R3	R4	R9	A
1	MeO	H		H	
2	MeO	H		H	
3	MeO	H		H	
4	MeO	H		H	

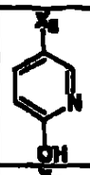
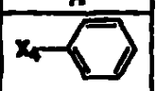
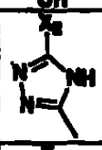
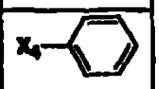
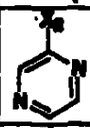
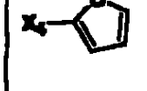
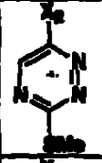
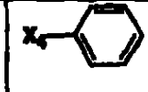
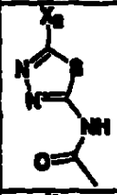
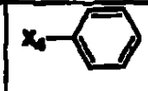
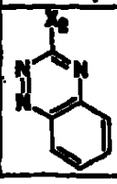
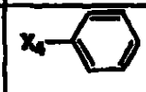
Los compuestos en las siguientes tablas se ejemplifican sin restricción alguna de los inhibidores adicionales que se pueden preparar por el uso de la metodología aquí contenido o ejemplificada en la preparación de los compuestos de la invención.

960

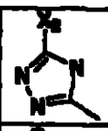
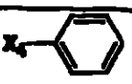
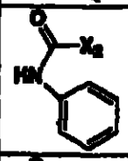
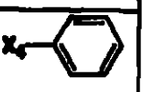
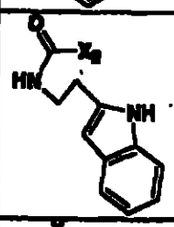
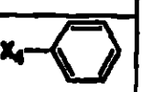
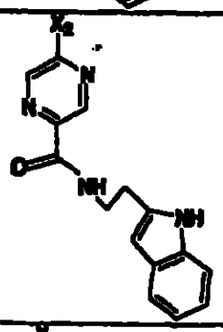
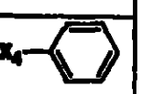
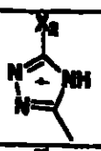
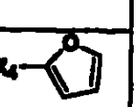
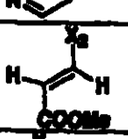
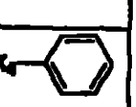
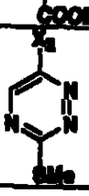
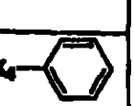
Tabla 2a



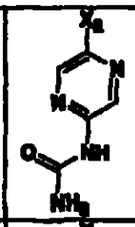
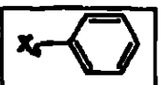
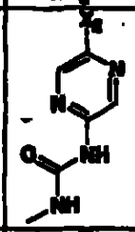
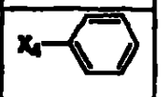
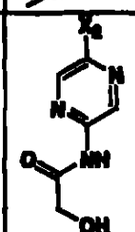
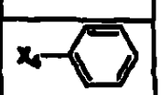
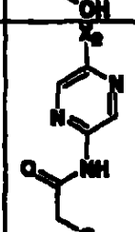
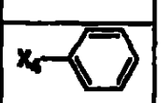
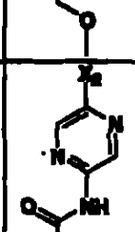
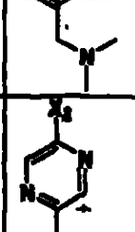
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	Cl	H		H	
	F	H		H	
	OMe	H		H	
	OMe	H		H	

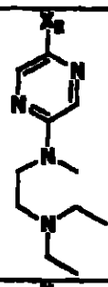
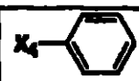
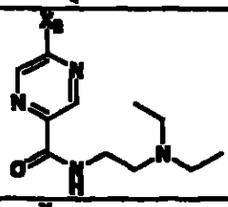
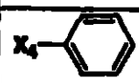
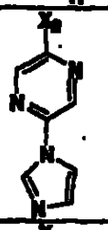
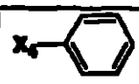
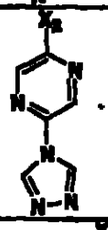
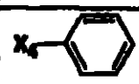
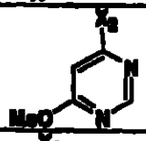
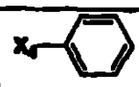
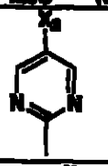
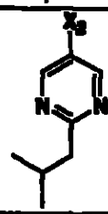
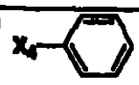
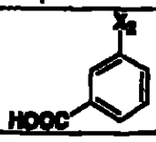
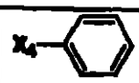
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	F	H		H	
	F	H		H	
	F	H		H	
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	F	H		H	
	Cl	H		H	
	Cl	H		(R)-Me	
	F	H		H	

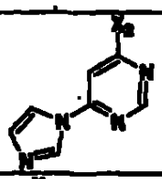
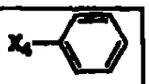
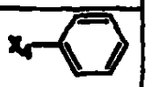
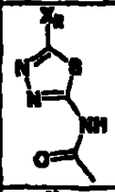
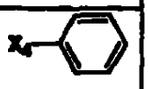
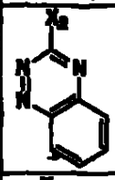
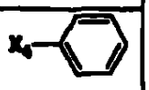
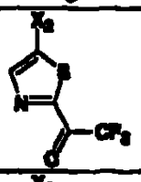
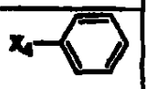
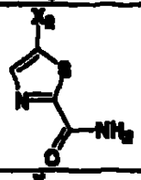
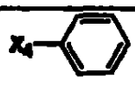
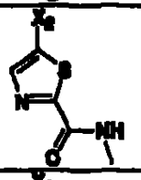
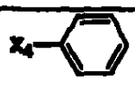
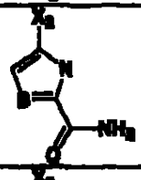
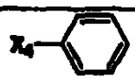
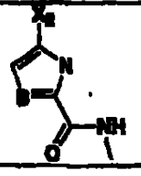
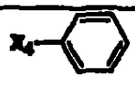
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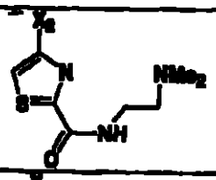
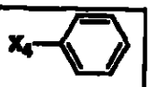
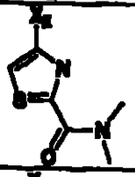
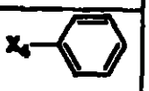
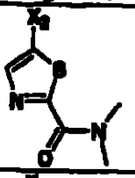
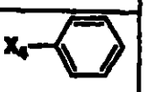
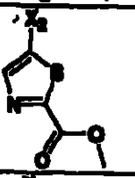
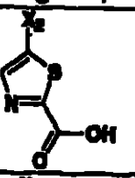
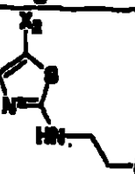
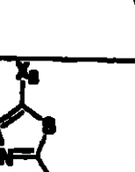
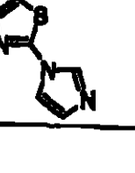
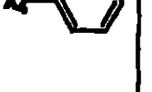
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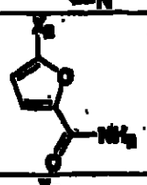
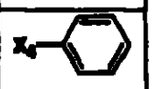
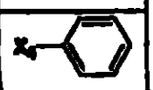
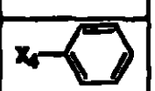
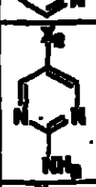
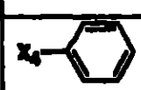
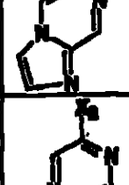
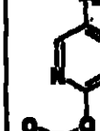
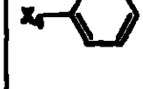
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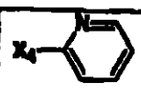
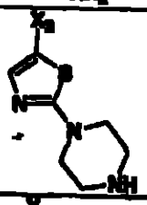
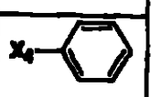
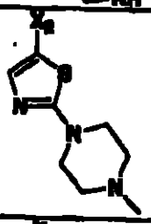
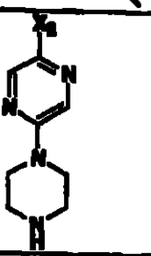
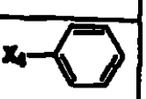
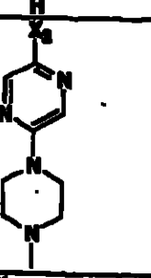
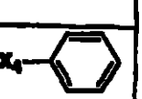
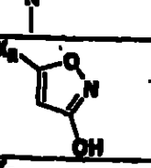
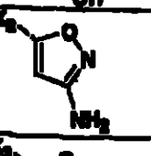
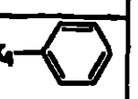
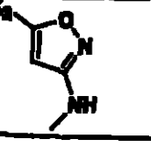
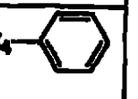
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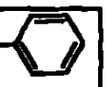
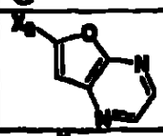
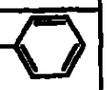
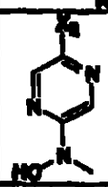
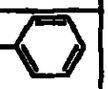
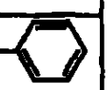
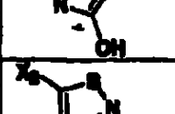
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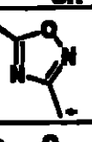
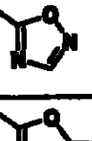
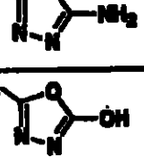
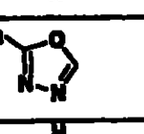
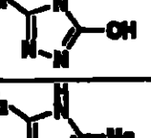
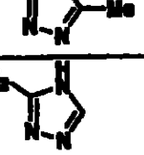
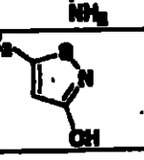
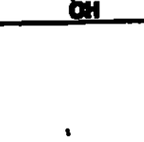
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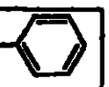
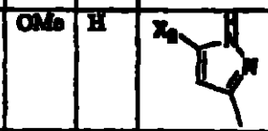
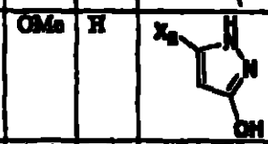
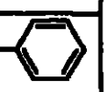
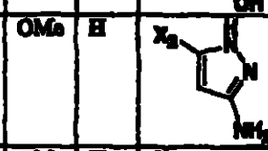
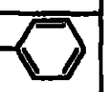
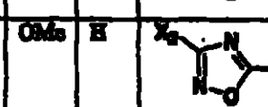
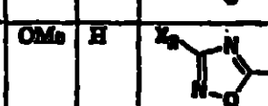
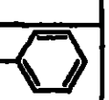
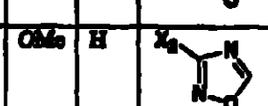
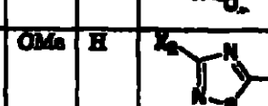
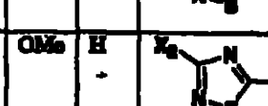
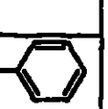
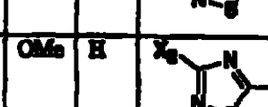
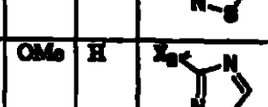
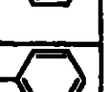
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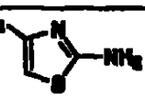
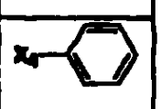
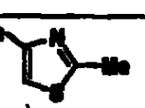
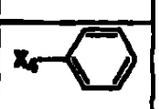
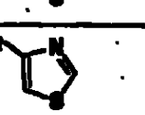
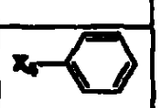
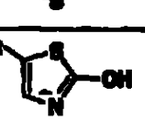
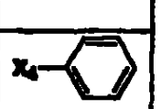
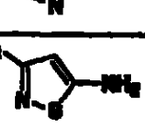
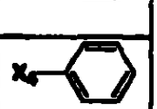
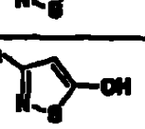
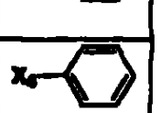
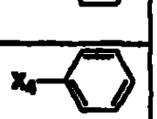
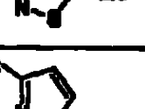
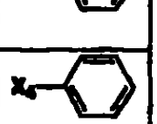
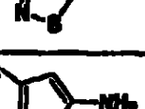
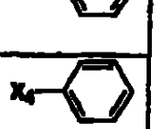
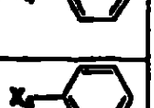
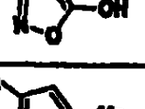
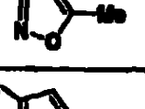
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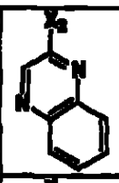
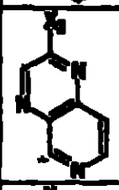
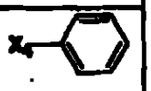
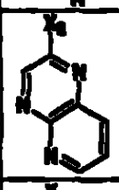
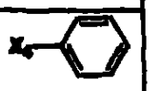
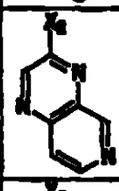
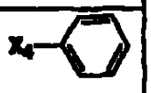
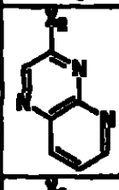
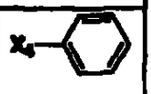
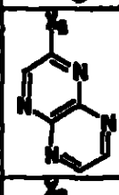
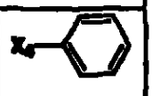
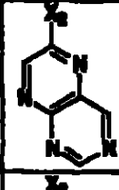
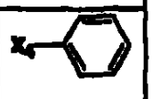
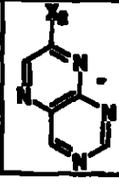
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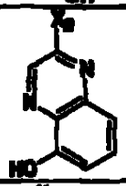
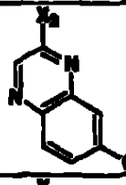
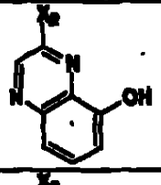
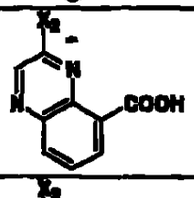
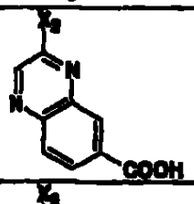
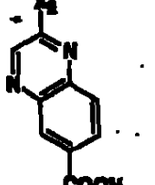
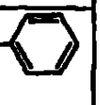
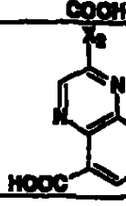
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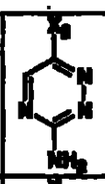
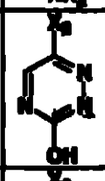
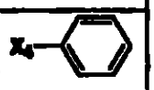
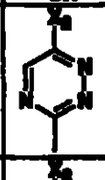
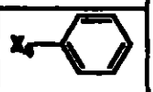
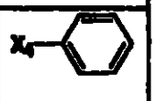
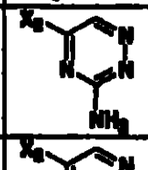
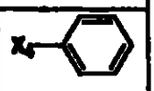
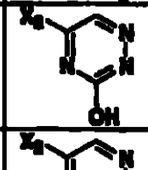
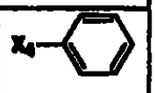
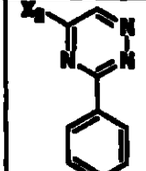
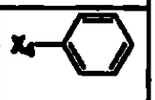
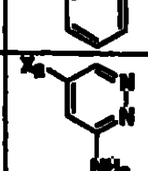
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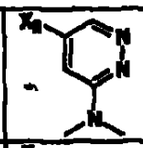
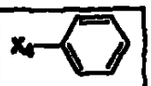
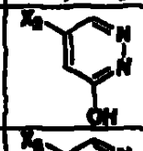
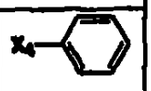
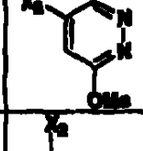
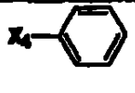
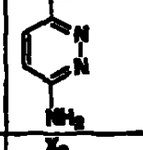
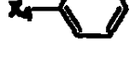
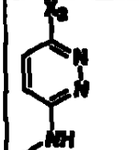
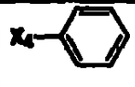
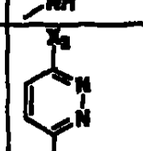
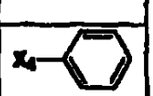
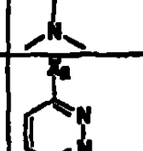
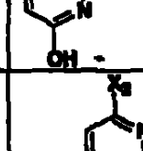
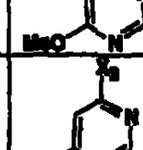
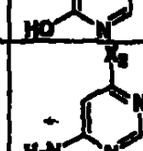
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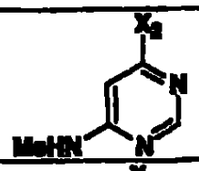
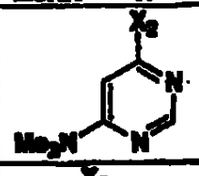
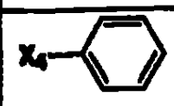
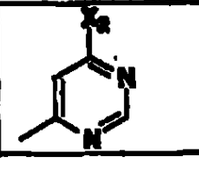
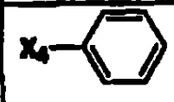
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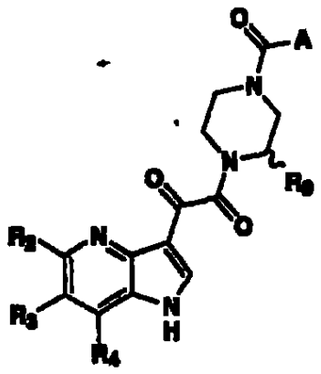
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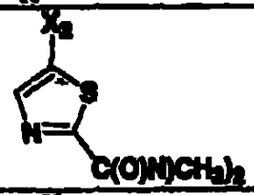
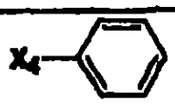
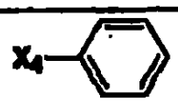
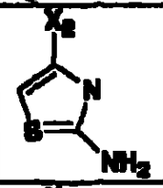
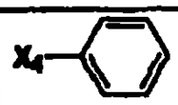
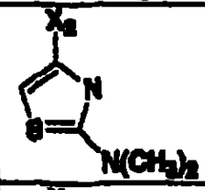
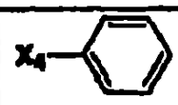
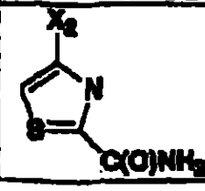
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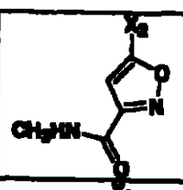
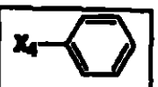
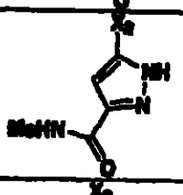
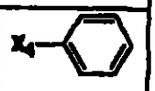
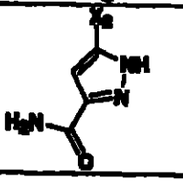
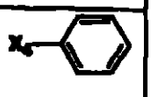
Los inhibidores en la tabla 4a pueden prepararse usando procedimientos análogos los cuales se demostraron para preparar los ejemplos en la tabla 4.

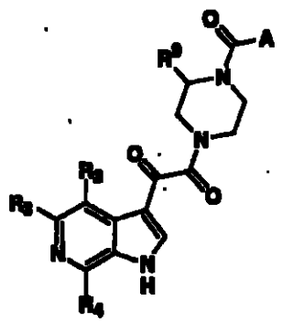
Tabla 4a

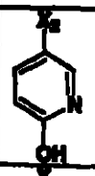
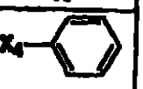
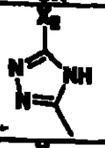
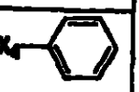
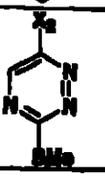


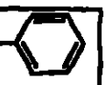
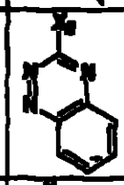
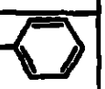
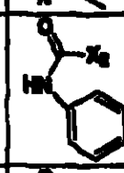
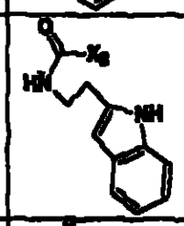
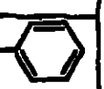
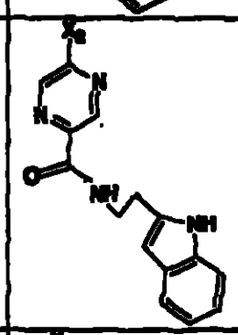
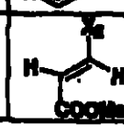
Otros inhibidores

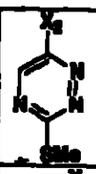
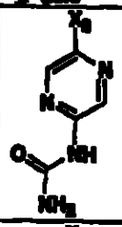
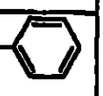
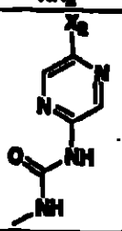
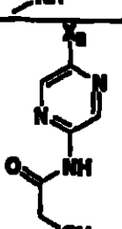
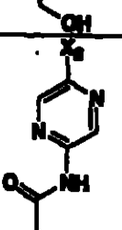
Entrada a la Tabla	R2	R3	R4	R9	A
1	H	H		H	
2	H	H		H	
3	H	H		H	
4	H	H		H	
5	H	H		H	
6	H	H		H	

7	H	H		H	
8	H	H		H	
9	H	H		H	

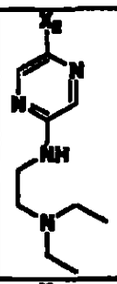
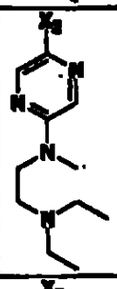
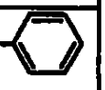
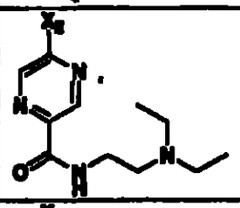
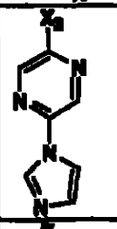
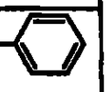
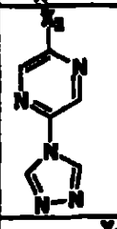
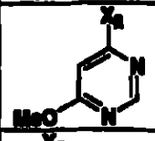


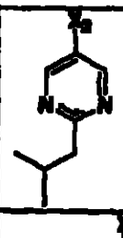
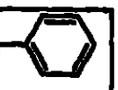
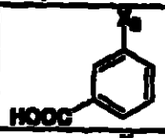
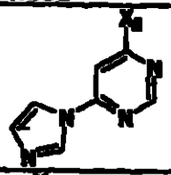
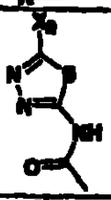
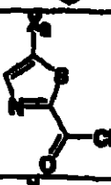
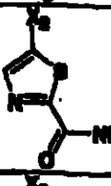
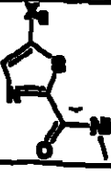
	R2	R3	R4	R9	A
	OMe	H		(R) o (S) Me	
	F	H		(R) o (S) Me	
	Cl	H		(R) o (S) Me	
	F	H		(R) o (S) Me	

	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	F	H		(R) o (S) Me	
	F	H		(R) o (S) Me	
	F	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	F	H		(R) o (S) Me	
	Cl	H		(R) o (S) Me	
	Cl	H		(R) o (S) Me	

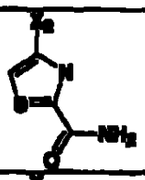
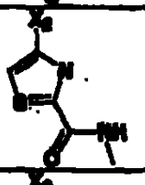
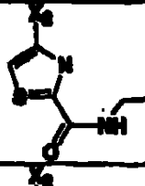
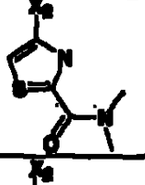
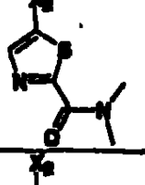
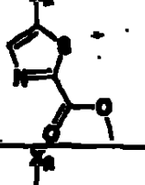
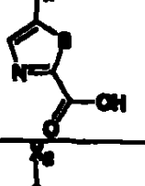
	F	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
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	OMe	H		(R) o (S) Me	

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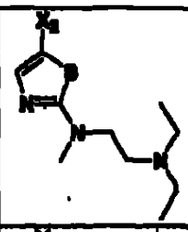
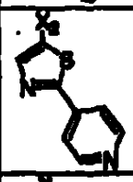
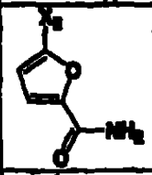
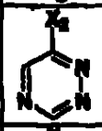
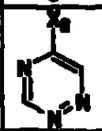
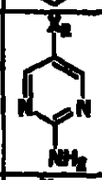
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	

	OMe	H		(R) o (S) Me	
	H	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
	OMe	H		(R) o (S) Me	
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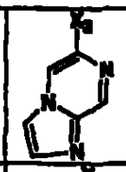
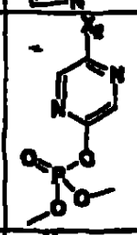
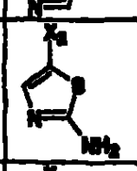
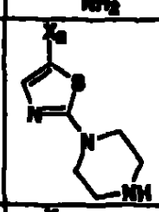
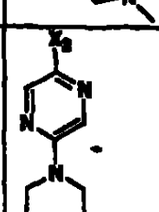
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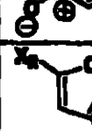
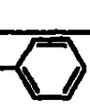
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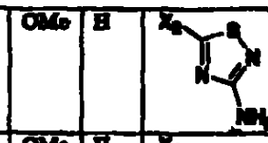
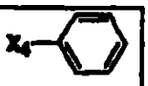
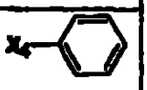
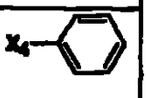
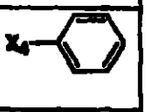
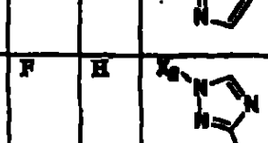
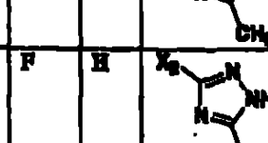
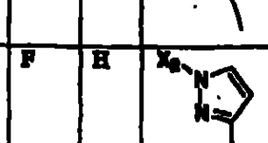
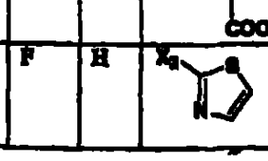
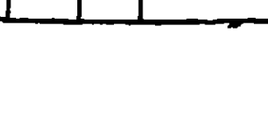
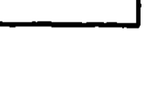
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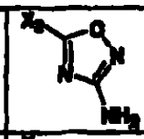
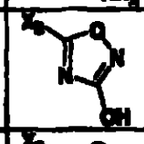
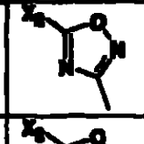
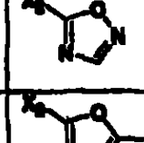
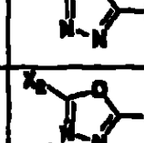
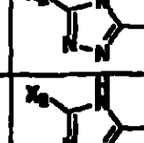
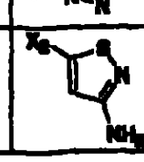
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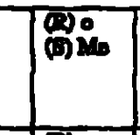
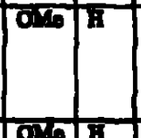
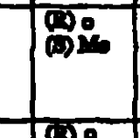
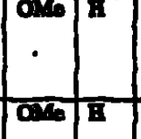
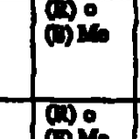
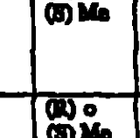
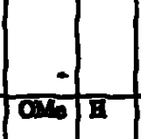
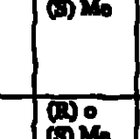
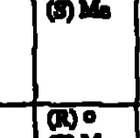
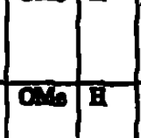
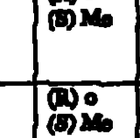
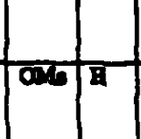
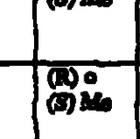
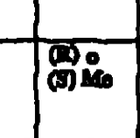
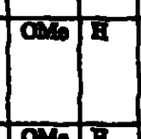
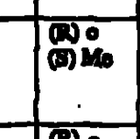
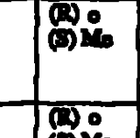
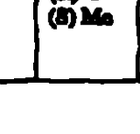
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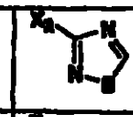
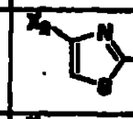
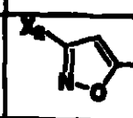
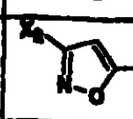
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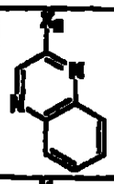
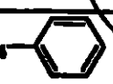
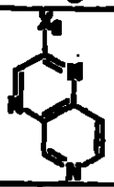
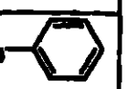
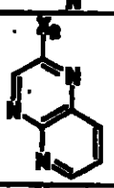
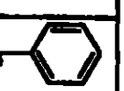
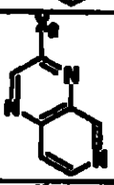
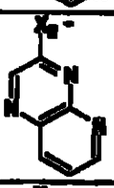
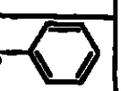
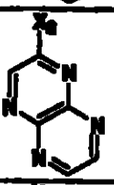
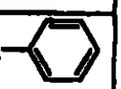
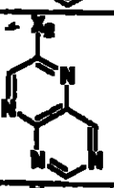
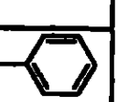
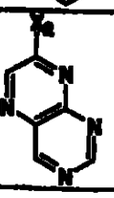
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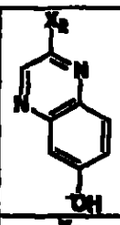
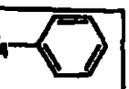
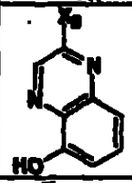
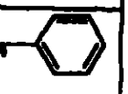
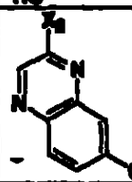
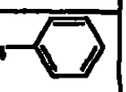
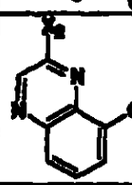
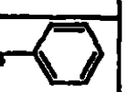
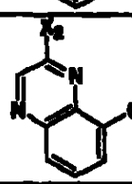
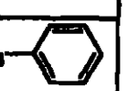
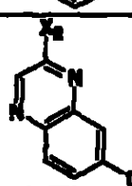
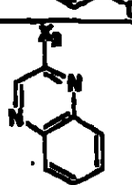
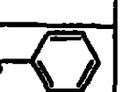
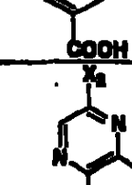
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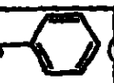
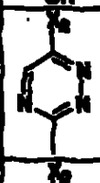
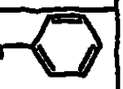
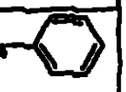
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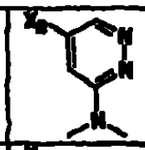
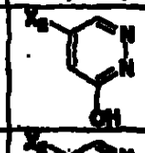
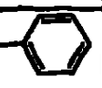
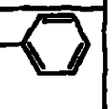
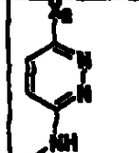
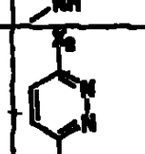
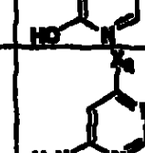
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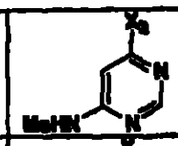
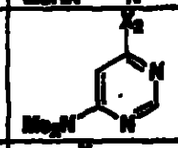
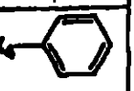
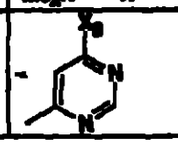
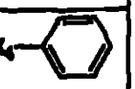
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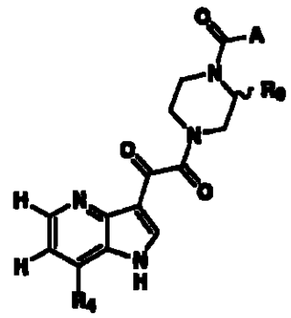
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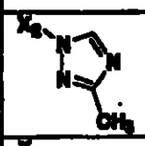
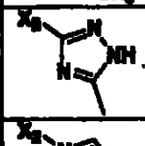
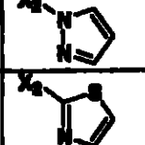
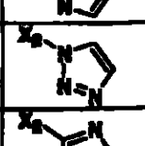
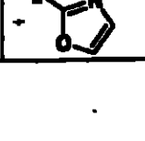
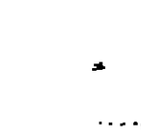
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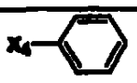
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OTROS INHIBIDORES

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		(R) o (S) Me	
		(R) o (S) Me	

Estudios de estabilidad metabólica de compuestos en microsomas de hígado. La estabilidad metabólica de los compuestos se investigó en microsomas de hígado acumulados de humano. Los microsomas de hígado de humano se obtuvieron de BD Gentest (Lot # 16, Woburn, MA) con una concentración de proteína de 20 mg/ml y un citocromo total P450 (CYP) con una concentración de 0.55 nmol/mg de proteína.

Se preparó una solución de reserva del fármaco en acetonitrilo a 1 mM. Se agregó una alícuota de la solución de reserva a los medios de incubación para dar una concentración final de 3μM de fármaco, y una concentración de acetonitrilo que no supera el 1% en la incubación. Los medios de incubación consistieron de solución amortiguadora de fosfato de potasio (0.1 M, pH 7.4) microsomas de hígado (concentración final 0.9 mg/ml), cloruro de magnesio (0.033 mM) y un sistema regenerador NADPH. Los cofactores del sistema regenerador NADPH consistieron de NADPH (concentración final 0.425 mg/ml), glucosa-6-fosfato (concentración final 0.512 mg/ml) y glucosa6-fosfato deshidrogenasa (concentración final 0.6 unit/ml). Se pre-incubó el compuesto de prueba en los medios por 2 minutos. Se inicio la reacción por la adición de los cofactores. Se efectúo la incubación a 37°C durante 10 minutos. Se finalizó la reacción al extraer una alícuota de

100μL de la incubación y agregarla en 200μL de acetonitrilo que contiene un compuesto de referencia como un estándar analítico externo. Después del mezclado con vórtice y centrifugación, se analizó una alícuota de 10μL del sobrenadante por LC/EM.

Se pueden usar los lineamientos para categorizar las substancias de prueba como compuestos de baja, intermedia y alta depuración.

Proporción (nmol/min/mg)	estimado de la depuración
0 - 0.100	bajo
0.101 - 0.200	intermedio
0.201 0.300	altos

Estudios farmacocinéticos en ratas.

Para los estudios farmacocinéticos IV y PO de los compuestos en ratas, se disolvió el compuesto en PEG-400/etanol (90/10) como una solución.

Rata. Las ratas macho Sprague-Dawley 8300-350 g, Hilltop Lab Animals, Inc., Scottdale, PA) con cánulas implantadas en la vena yugular se usaron. Se dejaron ayunar las ratas durante la noche en los estudios farmacocinéticos PO. Se recolectaron muestras de sangre de 0.3 ml de la vena yugular en tubos microtainer que contienen EDTA (Becton Dickinson, Franklin Lakes, NJ) y se centrifugaron para separar el plasma.

En el estudio IV en el compuesto de prueba se suministro a 1 mg/kg como un bolo durante 0.5 min (n=3). Las muestras en

serie de sangre se recolectaron antes de dosificar y 2, 10, 15, 30, 45, 60, 120, 240, 360, 480 y 1440 min después de dosificar.

En el estudio PO del compuesto de prueba, las ratas (n=3) recibieron una dosis oral de 5mg/kg de BMS-585248. Las muestras en serie de sangre se recolectaron antes de dosificación y 15, 30, 45, 60, 120, 240, 360, 480 y 1440 después de la dosificación.

Cuantificación de los compuestos en plasma. Se prepararon alícuotas de muestra de plasma de rata, en estudios para análisis por precipitación de proteínas de plasma con 2 volúmenes de acetonitrilo que contienen un estándar interno de un compuesto similar. Los sobrenadantes resultantes se separaron de las proteínas precipitadas por centrifugación por 10 minutos y se transfirieron a viales de automuestreo. Las muestras se prepararon manualmente o con el uso de una manejador de líquido automatizado Tomtec. Se inyectó una alícuota de 5μL para análisis.

El sistema CLAR consistió de 2 bombas Shimadzu LC10AD (Columbia, MD), un automuestreador Shimadzu SIL-HTC (columbia, MD) y un compartimiento de columna Hewlett Packard Series 1100 (Palo Alyo, CA). La columna fue una YMC Pro C18 (2.0 x 50 mm, partículas de 3 μm Waters Co., Milford, MA), que se conservó a 60°C y una relación de flujo de 0.3 ml/min.

la fase móvil consistió de formiato de amonio 10 mM y ácido fórmico en agua 0.1% (A) y 100% de formiato de amonio 10 mM y 0.1% de ácido fórmico en metanol (B). la composición inicial de la fase móvil fue de 95% A. Después de la inyección de la muestra, se cambió la fase móvil 15% A/85% B durante 2 minutos y se mantuvo esa composición por 1 minuto adicional. Luego se regresó la fase móvil a las condiciones iniciales y se volvió a equilibrar la columna por 1 minuto. El tiempo total de análisis fue de 4 minutos.

El CLAR formó un interfaz con Micromass Quattro LC. Se usó nitrógeno de ultra alta pureza como el gas para nebulización y desolvatación a relaciones de flujo de 100L/hr para nebulización y 1100 L/hr para desolvatación. La temperatura de desolvatación fue de 300°C y la temperatura de la fuente fue de 150°C. La adquisición de datos utilizó un monitoreo de reacción seleccionado (SRM). Los iones que representan la especie $(M+H)^+$ para el compuesto y el estándar interno se seleccionaron en MS1 Y se disociaron por colisión con argón a una presión de 2×10^{-3} para formar iones de producto específico que se observaron posteriormente por MS2.

Los compuestos de la presente invención pueden administrarse oralmente, parenteralmente (incluyendo inyecciones subcutáneas, intravenosas, intramusculares, inyección intrasternal o técnicas de infusión), por rocío de inhalación, o rectalmente, en formulaciones de dosis unitaria

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que contienen portadores, adyuvantes y vehículos farmacéuticamente aceptable no tóxicos.

De esta manera, de conformidad con la presente invención se proporciona además un método para el tratamiento y una composición farmacéutica para el tratamiento de infecciones virales tales como infección por VIH y SIDA. El tratamiento involucra administrar a un paciente que necesite de tal tratamiento, una composición farmacéutica que comprende un portador farmacéutico y una cantidad terapéuticamente efectiva de un compuesto de la presente invención.

La composición farmacéutica puede estar en forma de suspensiones o tabletas que se administran oralmente; rocíos nasales, preparaciones inyectables estériles, por ejemplo, como suspensiones acuosas u oleaginosas o supositorios.

Cuando se administran oralmente como una suspensión, estas composiciones se preparan de conformidad con las técnicas bien conocidas en el arte de la formulación farmacéutica, y pueden contener celulosa microcristalina para impartir volumen, ácido algínico o alginato de sodio como agente de suspensión, metilcelulosa como aumentador de la viscosidad, y agentes endulzantes/saborizantes conocidos en el arte. Como tabletas de liberación inmediata, estas composiciones pueden contener celulosa microcristalina, fosfato dicálcico, almidón, estearato de magnesio y lactosa

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y/u otros excipientes, aglutinantes, extendedores, desintegrantes, diluyentes y lubricantes conocidos en el arte.

Las soluciones o suspensiones inyectables pueden formularse de conformidad con el arte conocido, usando diluyentes o solventes parenteralmente aceptables, no tóxicos, apropiados, tales como manitol, 1,3-butanodiol, agua, solución de Ringer o solución de cloruro de sodio isotónica, o agentes de dispersión o humectantes y de suspensión apropiados, tales como aceites estériles, blandos, fijos, que incluyen mono- o diglicéridos sintéticos, y ácidos grasos, que incluyen ácido oléico.

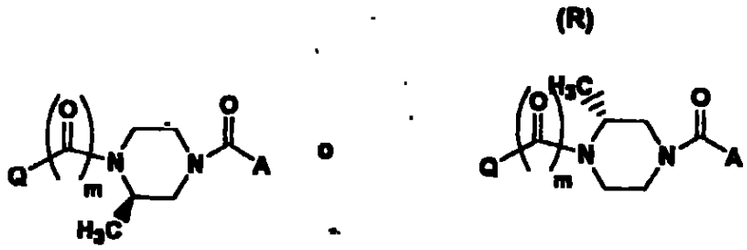
Los compuestos de esta invención pueden administrarse oralmente a los humanos en un rango de dosis de 1 hasta 100 mg/kg de peso corporal en dosis divididas. Un rango de dosis preferido es de 1 hasta 10 mg/kg de peso corporal oralmente en dosis divididas. Otro rango de dosis preferida es de 1 hasta 20 mg/kg de peso corporal oralmente en dosis divididas. Se entenderá, sin embargo, que el nivel de dosis específico y la frecuencia de dosis de cualquier paciente en particular puede variar y dependerá de una variedad de factores que incluyen la actividad del compuesto específico empleado, la estabilidad metabólica y la longitud de acción de tal compuesto, la edad, peso corporal, salud general, sexo, dieta, modo y tiempo de administración, velocidad de

excreción, combinación de fármaco, la severidad de la condición particular, y la terapia que experimenta el hospedador.

El esquema 41a describe la metodología para convertir el ácido carboxílico a una alquinil cetona. Los precursores de alquinil cetona pueden luego convertirse a pirazoles o isoxazoles durante la reacción con hidrazinas o hidroxil aminas, respectivamente.

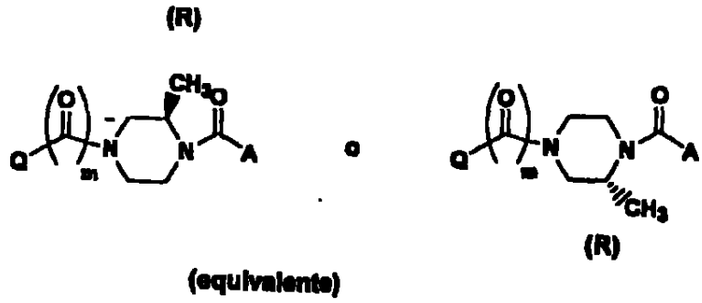
La invención se pretende que cubra isómeros, diaestereoisómeros, estereoisómeros, y enantiómeros de las fórmulas descritas, donde se presentan uno o más carbonos asimétricos en las moléculas. Un carbono asimétrico es uno en el cual el carbono se enlaza a cuatro substituciones diferentes. En particular, la invención se pretende que cubra isómeros o un enantiómero sencillo especialmente cuando un enantiómero exhibe propiedades superiores. Los enantiómeros difieren uno del otro en que la colocación espacial de los substituyentes alrededor de los centros quirales de los carbonos asimétricos resulta en cada molécula siendo una imagen de espejo que no se puede superponer de la otra. En esta solicitud, la configuración de los substituyentes alrededor de un carbono asimétrico se definen no ambiguamente ya sea como (R) que es la representación estándar que se establece para recto en Latín, derecho o (S) que es la representación estándar para siniestro en Latín, izquierdo en

el sistema de nomemclatura Cahn-Ingold-Prelog que se usa desde la década de 1960. Las reglas estándar para definir la configuración de estos centros se encuentra en cualquier libro de texto de química orgánica básico. En particular, para esta solicitud y con base en los ejemplos iniciales, cuando W contiene un grupo metilo sencillo como se describe a continuación, cuando el carbono porta el grupo metilo en la configuración (R), puede mostrar una ventaja potencial sobre el enantiómero (S). Ocasionalmente, la (R)-metil piperazina puede mostrar una ventaja de potencia sobre la piperazina no substituida. Estas observaciones son efectos específicos del compuesto y no siempre están presentes. La piperazina no substituida y los enantiómeros (S) todavía son compuestos antivirales potentes descritos ocasionalmente siendo menos potentes que el enantiómero (R).



Cuando la configuración de una metil piperazina mostrada como a continuación es (R), el grupo metilo puede mejorar la estabilidad metabólica de la amida adyacente cuando se compara con la (S) metil piperazina o la piperazina no substituida.

Sin embargo, la estabilidad metabólica del enlace amida es un compuesto específico y no se requiere necesariamente un substituyente metilo para propiedades óptimas.



Se ha encontrado ahora sorprendentemente que los compuestos de fórmula Ia en los cuales específicamente R_4 es un grupo triazolilo ligado en N colocado a la posición de nitrógeno 1, son particularmente efectivos para inhibir el VIH. Esto se discute más completamente a continuación.

El tratamiento efectivo del VIH y otros virus requiere de compuestos que sean inhibidores potentes del virus, sean selectivos para el virus y tengan las propiedades que les permitan alcanzar con seguridad y mantener las concentraciones en el nivel del plasma que sean múltiplos de un número máximo arriba de la concentración requerida para inhibir de forma mínima el virus. Las exposiciones mayores suprimen la replicación viral y las tasas reducidas de replicación significan que las cepas del virus con resistencia al tratamiento de fármacos se desarrollarán a una velocidad inferior. Los fármacos potentes muestran una

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actividad equivalente a partir de una concentración inferior o dosis inferior que la necesaria para lograr el mismo efecto a partir de un fármaco menos potente. Los fármacos que producen intrínsecamente exposiciones mayores a partir de una dosis equivalente en modelos animales o pacientes (como se determina por las mediciones farmacocinéticas tales como AUC (las suma de la concentración de fármaco en un tiempo en particular), Cmax, o Cmin proporcionarán también un mayor beneficio al paciente. Los fármacos que tienen una mayor estabilidad en presencia de trayectorias metabolizantes y encimas mantendrán sus concentraciones por mayor tiempo y requieren así una dosificación menos frecuente o dosificación de cantidades frecuentes. En los animales o en las personas la relación de depuración es un parámetro frecuentemente medido para evaluar esta propiedad pero también se usa el tiempo de retención medio. Por precisión, la medida determinada de inhibición viral es un EC50, pero las concentraciones mínimas de plasma que se deben contener en un paciente se cree generalmente que están al menos de 4 a 5 veces arriba. Así, los candidatos de fármaco antiVIH o antivirales que será más probablemente que suministren los beneficios máximos en pacientes y aquellos que luchan los programas de investigación preclínica para identificar mostrarán 1) máxima potencia 2) ninguna citotoxicidad general contra la línea celular usada para el ensayo 3) proporciones

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bajas predichas de metabolismo en humanos con base en los modelos in vitro 4) alta exposición después de la dosificación oral. Muchas otras propiedades de los candidatos a fármacos potenciales se evalúan con objeto de determinar cuales compuestos tendrán la mejor posibilidad de mostrar una utilidad optima en paciente humanos, pero los compuestos de esta invención se evaluaron inicialmente en parte al determinar:

1) potencia contra VIH como se determina por un EC50 en un ensayo de pseudo tipo inicial como se describe en la sección de biología.

2) carencia de una citotoxicidad general contra una línea celular Hela. >100uM se usó como un corte arbitrario por seguridad.

3) medición de la relación de metabolismo contra preparaciones microsomales de hígado humano de a partir de estos datos proyectar la relación humana de depuración. Entre más bajo mejor.

4) estimar la exposición potencial del hombre al medir parámetros tales como AUC y la velocidad de depuración de dosificación oral de iv en ratas. Se desea una alta exposición y una baja depuración.

Las amidas de piperazina de azaindol oxoacético se han descrito en 2 series de solicitudes de patentes. La primera serie describe derivados de azaindol que tienen un potencial

prometedor como agentes antivirales (de aquí en adelante denominada referencia 94) Wang, Tao et al, patente de EUA 6476034 y WO 0162255 A1, presentada el 19 de Enero de 2001, publicada en agosto 30 de 2001. la segunda serie (denominada de aquí en adelante referencia 106) Wang, Tao et al, describe la actividad antiviral del VIH de derivados de piperazina azaindoloxoacetico substituidos en la solicitud de patente de EUA No. de serie 10/214,982 presentada el 7 de agosto de 2002, que es una solicitud de continuación parcial del No. de serie de EUA 10/038, 306presentada el 2 de enero de 2002 (que corresponde a la solicitud internacional PCT (PCT/US02/00455), WO02/062423 A1 presentada el 2 de enero de 2002, publicada en agosto 15 de 2002. todas las referencias para estas 2 series se incorporan aquí como referencia. La referencia 106 describe en parte C-7 heteroarilo, arilo o -4,5,6 o 7 azaindoles substituidos como agentes antivirales y es el arte previo más relevante.

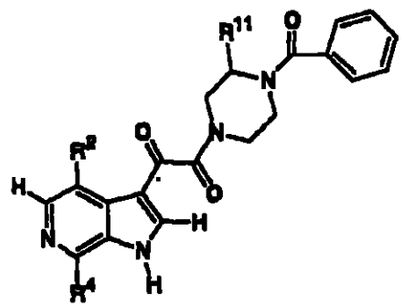
Se han evaluado las propiedades de muchos compuestos cubiertos dentro de las referencias 94 y 106 y se ha encontrado que los compuestos que tienen grupos C-7 triazol ligados en N son sorprendentemente e· inesperadamente superiores.

Se evaluaron inicialmente compuestos para determinar cuales tienen una potencia máxima o el EC50 más bajo usando el ensayo de pseudo tipo descrito en la sección de biología

de esta sección. En este caso los compuestos con EC50 menor que 0.20 nM se consideraron de mayor interés ya que cubren la mayoría de los compuestos potentes y cuentan por la variabilidad de ensayo de la separación por exclusión inicial. También se evaluó la estabilidad de los compuestos para determinar la estabilidad metabólica cuando se incubaron en preparaciones in vitro de microsomas del hígado humano. (HLM). Este es un sistema predictivo comúnmente usado para evaluar el potencial del metabolismo humano y proyectar tasas de depuración en el hombre. Los compuestos con tasas bajas fueron los más deseables. Los compuestos con una depuración intermedia y alta sería más probable que tuvieran dificultad en lograr un régimen de dosificación factible en el hombre contra compuestos de baja depuración. Los compuestos para los cuales no se pueden hacer determinaciones precisas tampoco avanzaron.

Sorprendentemente cuando la mayoría de los compuestos prometedores de los criterios metabólicos y de potencia con estabilidad se evaluaron en ratas para medir sus propiedades farmacocinéticas, un tipo de los substituyentes C7, triazoles ligados en N de fórmula Ia mostraron una muy baja depuración y una muy alta AUCs (exposición) cuando se compara con los compuestos de las referencias 94 y 106.

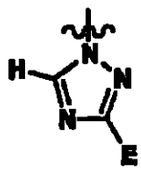
Los compuestos I que tienen la fórmula Ia se describen a continuación:



Ia

en donde:

R^2 es metoxi, flúor o cloro;

R^4 es  o  ;

D es hidrogeno o C_1-C_3 alquilo;

E es seleccionado del grupo que consiste de hidrógeno C_1-C_3 alquilo, $O(C_1$-$C_3)$alquilo o CH_2OCH_3.

R^{11} es ya sea hidrógeno o metilo en el cual la configuración para el cual el metilo está unido es (R) con la condición de que cuando R^4 es 1,2,3-triazol, entonces R^{11} es hidrógeno.

Los triazoles ligados en N C-7 muestran así propiedades sorprendentes ya que fueron esencialmente equivalentes en potencia a los compuestos más potentes cubiertos por las referencias 94 y 106 que se han evaluado hasta la fecha. Mostraron una estabilidad metabólica en los microsomas de hígado humano que fue equivalente a los mejores compuestos de la solicitud. Inesperadamente, mostraron relaciones de

depuración en ratas que fueron mucho menores, usualmente 10 veces menores que los mejores compuestos a partir de aquellos descritos en las solicitudes de la referencia 94 y fueron los mejores de cualquier compuesto evaluado en la referencia 106. Aún más sorprendentemente, fueron el único tipo de compuestos que mostraron una exposición crecientemente importante en ratas como se muestra por sus AUCs.

En resumen estos triazoles ligados en N muestran una combinación sorprendente en propiedades que no serían obvias para alguien experto en la técnica basado en la descripción de las referencias 94 y 106. Solamente en un triazol sencillo se describe en WO 02/06423. Este compuesto tiene un substituyente de R^4 que es un triazol ligado en C y no un triazol ligado en N y muestra una potencia que no fue comparable a los triazoles ligados en N. No se describieron triazoles ligados en N en los ejemplos de la solicitud PCT publicada de la referencia 106.

Las siguientes tablas de datos resumen la potencia, depuración humana predicha basada en los microsomas de hígado humano, y el AUC y depuración por los estudios determinados por farmacocinéticos en ratas para estos triazoles ligados en N de la invención en la presente comparados con los compuestos representativos y análogos cercanos contenidos en la solicitud PCT WO 02/062424 A1, presentada el 2 de enero de 2002, publicada en agosto 15

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de 2002 y la solicitud publicada y patentes contenidas en la referencia 94. Como se observa en las tablas siguientes los triazoles ligados en N en la presente se identifican como los grupos mas preferidos que muestran una superioridad sorprendente especialmente en términos de desplegar una potencia máxima, estabilidad metabólica equivalente a los mejores en su clase y únicamente una alta AUC (exposición) y una baja depuración en ratas que se determina por una dosificación oral e iv a 5 mg/kg y 1 mg/kg respectivamente. El modelo de rata es un modelo inicial usado para evaluar el potencial para exposición en el hombre.

La utilidad de compuestos en la clase triazol es sorprendentemente muy independiente de los patrones de sustitución como se detallan. Por ejemplo los 1,2,3 -triazoles colocados en el átomo de nitrógeno en la posición 2, han mostrado a la fecha una AUC significativamente reducida (exposición) en ratas en comparación con los compuestos detallados. Además al mover el grupo E cuando E es metilo en el triazol ligado en N 1,2,4- de la posición 3 a la 5 proporciona compuestos con una potencia significativamente reducida. Como se puede observar en la tabla A2, los triazoles ligados en N especificados, muestran una gran potencia en un ensayo antiviral inicial.

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Como es evidente de las tablas A3-A8 de los compuestos en comparación, la estabilidad metabólica de los compuestos de triazol ligados en N Ia de la invención es sorprendentemente equivalente o mejor que cualquiera de los compuestos cubiertos en la serie de solicitudes publicadas del azaindol (esto es, referencias 94 y 106).

Como se muestra dramáticamente en la tablas, la baja depuración y alta exposición observada en las ratas para los compuestos en la tabla A2 fue sorprendente e inesperada ya que el arte previo enseña compuestos que no mostraron estas propiedades como se esperaría.

En la tablas que siguen estos términos tienen los siguientes significados:

"NT" significa no probado.

"Dificultades" significa resultados que n9 se puede interpretar (esto es en la prueba HLM).

Resultados

Tabla A1. Datos biológicos clave para EC_{50} en la tabla A2-A7.

Compuestos* Con EC_{50} >1μM	Compuestos Con EC_{50} >0.2 nM pero <1μM	Compuestos con EC50 ≤ 0.20 nM
Grupo 3	Grupo 2	Grupo 1

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TABLA A2. Triazoles enlazados a N como R4 con propiedades superiores sorprendentes.

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
216	1	Si	Bajo	32 ± 12	1.6 ± 0.2
188	1	Si	Bajo	20 ± 4.6	2.4 ± 0.08
187	1	Si	Bajo	22.4 ± 7.2	2.4 ± 0.5
215, 303	1	Si	Bajo	83.7 ± 9.8	0.7 ± 0.12
245	1	Si	Bajo	12.1 ± 1.3	5.6 ± 1.8
313	1	Si	Bajo		
316	1	Si	Bajo	52 ± 12	1.3 ± 0.19
317	1	Si	Bajo	43 ± 12	1.9 ± 0.26
306	1	Si	Bajo	160 ± 11	0.39 ± 0.07
321	1	Si	Bajo		
322	1	Si	Bajo	82 ± 23	1.8 ± 0.4
314	1	Si	Bajo		
315	1	Si	Bajo		
352	1	Si	Bajo		
325	1	Si	Bajo		
326	1	Si	Bajo	9.8 ± 2.9	8.3
274	1	Si	bajo		
273	1	Si	Bajo		
324	1	Si	Bajo		
275	1	Si	bajo		

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TABLA A3. Algunos otros Triazoles enlazados a N substituidos alternativamente a R4 como comparación.

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
217	2	Si	NT	NT	NT
307	2	Si	NT	NT	NT
256	2	Si	NT	NT	NT
350	2	Si	Bajo	NT	NT
327	2	Si	Bajo	NT	NT
328	1	Si	Bajo	NT	NT
351	NT	NT	Bajo	1.5 $\pm$ 0.14	16.6 $\pm$ 1.4

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TABLA A4. Algunos otros Heteroarilos enlazados a N relevante a R4 como comparación.

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
139	2	Si	Alto	32 ± 12	1.6 ± 0.2
219, 305	1	Si	Alto	20 ± 4.6	2.4 ± 0.08
193	1	No	Bajo	14 ± 8	4.5 ± 0.4
189	2	Si	Bajo		
222	2	Si	Bajo		
221	2	Si	Bajo		
220	2	Si	NT		
218, 304	2	Si	Bajo		
190	1	Si	Bajo	7.4 ± 3.4*	3.7 ± 1.0
191	2	Si	NT		
309	1	Si	Bajo	0.09 ± 0.05	34.3 ± 2.6
318	2	Si	Bajo		
310	1	Si	Bajo	2.1 ± 0.4*	16.5 ± 3.3
241	1	Si	Bajo	6.4 ± 4.2*	11.2 ± 0.9
312	2	Si	Bajo		
241	1	Si	Bajo	0.0086 ± 0.005**	131 ± 4.3

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Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
236	1	Si	bajo	0.56 ± 0.25	29 ± 6.7
251	1	Si	Bajo		
230	1	Si	Intermedio		
343	1	Si	Bajo		
344	1	Si	Bajo		
276	1	Si	NT		
255	1	Si	Intermedio		
258	1	Si	Bajo		
314	1	Si	Bajo		
315	1	Si	Bajo		
352	1	Si	Bajo		
326	1	Si	Bajo	9.8 ± 2.9	8.3
274	1	Si			
273	1	Si			
275	1	Si			

TABLA A5. Algunos Heteroarilos enlazados a C relevantes en comparación

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
40	2	No	Bajo		
42	2	Si	Bajo		
22	1	No	Intermedio		
35	1	Si	Intermedio		
37	1	Nq	NT		
38	1	No	Bajo		
39	2	No	Intermedio		
28	3	No	NT		
29	2	No	Alto		
22	2	No	Alto		
74	2	No	Intermedio		
71	1	Si	Intermedio		
73	1	Si	Intermedio		
78	2	Si	Intermedio		
94	1	Si	NT		
102	2	Si	NT	6.9 $\pm$ 1.3	12 $\pm$ 5.5
163	2	Si	dificultades		
95	1	Si	Intermedio		

1018

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
140	2	Si	Intermedio		
146	2	Si	Intermedio		
145	1	Si	Dificultades	12 ± 3.8	1.4 ± 0.29
148	2	Si	NT		
210	1	Si	Intermedio		
211	1	No	Intermedio		
212	1	Si	Bajo		
223	2	Si	Bajo		
224	2	Si	Bajo		
225	2	Si	NT		
227	2	Si	bajo	3.8 ± 0.83	8.8 ± 3.7
226	1	Si	bajo	0.5 ± 0.13*	24.5 ± 3
299	1	No	Bajo		
300	2	Si	Bajo		
266	1	Si	bajo	0.16 ± 0.04*	37.4 ± 3.2
345	2	Si	bajo		
301	2	Si	NT		
346	2	Si	NT		
347	2	Si	Bajo		

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
334	2	Si	NT		
348	2	Si	Bajo		
349	2	Si	NT		
342	1	Si	Bajo		

TABLA A6. Algunos 4-azaindol relevantes en comparación y datos

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
204	2	Si	bajo	12 ± 1.4	10 ± 1.3
161	1	Si	Alto		
205	2	Si	bajo	9.6 ± 1.2	5.4 ± 0.4
207	2	Si	Bajo		
206	2	Si	NT		
208	2	Si	NT		
353	2	Si	bajo	1363 ± 307	5.6 ± 1.1*
354	2	Si	bajo	1.26 0.18*	11.2 ± 0.8
355	2	Si	bajo	3.3 ± 0.77*	13.9 ± 5.3

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
356	2	Si	Bajo		
357	2	Si	Intermedio		
358	2	Si	Alto		
359	2	Si	NT		
360	2	Si	bajo		
361	2	Si	NT		

TABLA A7. Algunas comparaciones relevantes y datos de la patente de E.U.A.6476034 (Referencia 94)

Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
1	2	Si	bajo	0.5	32 $\pm$ 1.8
2	2	Si	Intermedio		
3	2	Si	Bajo	6.3 $\pm$ 2.7	01.3 $\pm$ 4.0
4	2	Si	Bajo		
5	1	Si	Intermedio		
6	2	Si	Bajo	1.7 $\pm$ 0.58	31 $\pm$ 5.9

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Número de Ejemplo	Categoría EC_{50}	CC50 >100uM	Clase de depuración humana predicha por HLM	AUC 24h (ug.hr/ml)	CL, iv (mL/min/kg)
7	1	Si	Bajo	2.6 ± 0.12*	19.3 ± 0.65
8	1	Si	Bajo	1.03 ± 0.07	47.2 ± 11.5
9	2	Si	bajo	5.9 ± 2.2	5.9 ± 2.2
10	2	Si	bajo	2.9 ± 0.3	11.7 ± 1.0
11	1	Si		1.4 ± 0.2*	24.8 + 0.41
12	1	Si	bajo	4.7 ± 1.1	11.9 ± 1.8
13	2	Si	NT		

Estructuras de compuestos de referencia como una clave para la tabla A7

Compuesto de referencia 1

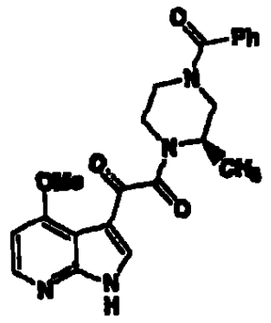
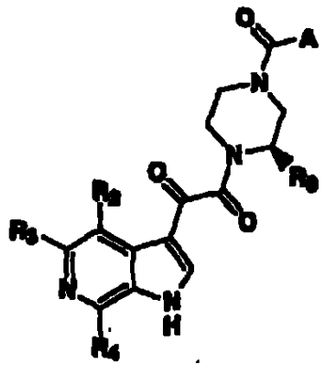


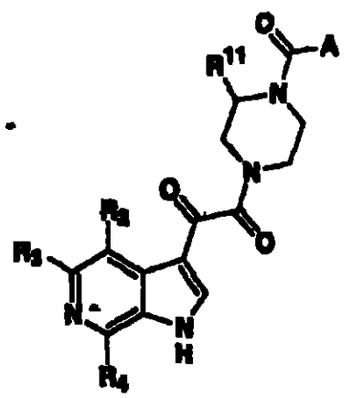
Tabla A8 (estructuras de los compuestos de referencia 2-9)



Número de compuesto de referencia	R2	R3	R4	R9	A
2	OMe	H	X_2—OMe	(R)-Me	X_5
3	OMe	H	X_2—OMe	H	X_5
4	OMe	H	X_2—OH	H	X_5
5	Cl	H	X_2	H	X_5
6	F	H	X_2	H	X_5
7	F	H	X_2	H	X_5
8	MeO	H	X_2	H	X_5
9	MeO	H	X_2	H	X_5

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Tabla A9 (compuestos de referencia 10-12)



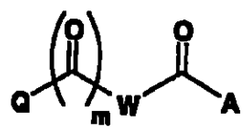
Número de compuesto de referencia	R2	R3	R4	R11	A
10	MeO	H	X_2—OMe	(R)-Me	X_4
11	MeO	H	X_2 (NH$_2$, O)	(R)-Me	X_4
12	MeO	H	X_2 (NHCH$_3$, O)	(R)-Me	X_4

En la tablas A8 y A9, X_2 y X_4 se refieren a el punto de enlace.

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Reivindicaciones:

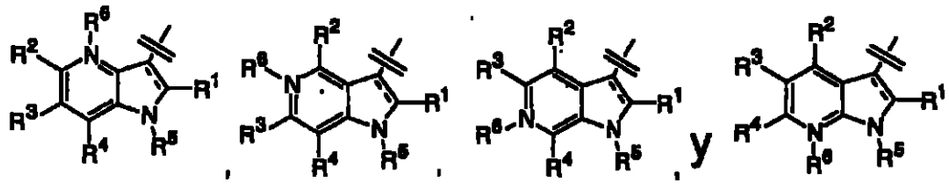
1. Un compuesto de la fórmula I, incluyendo sales farmacéuticamente aceptables del mismo,



I

caracterizado porque:

Q se selecciona del grupo que consiste de:



R^1, R^2, R^3, y R^4, son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, ciano, nitro, $COOR^{56}$, XR^{57}, $C(O)R^7$, $C(O)NR^{55}R^{56}$, B, D, y E con la condición de que al menos uno de R^1-R^4 se selecciona de B o E;

En donde - representa un enlace carbono-carbono o no existe;

m es 1 ó 2;

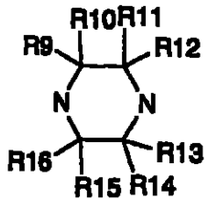
R^5 es hidrógeno o $(CH_2)_nCH_3$, $-C(O)(CH_2)_nCH_3$, $-C(O)O(CH_2)_nCH_3$, $-C(O)(CH_2)_nN(CH_3)_2$ en donde n es 0-5;

R^6 es O o no existe;

A se selecciona del grupo que consiste de C_{1-6}alcoxi,

arilo y heteroarilo; en los cuales arilo es fenilo o naftilo; el heteroarilo se selecciona del grupo que consiste de piridinilo, pirimidinilo, pirazinilo, triazinilo, furanilo, tienilo, pirrolilo, imidazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, quinolinilo, isoquinolinilo, benzofuranilo, benzotienilo, benzoimidazolilo y benzotiazolilo; y el arilo o heteroarilo es opcionalmente substituido con uno o dos de los mismos o diferentes miembros seleccionados del grupo que consiste de amino, nitro, ciano, hidroxi, C_{1-6}alcoxi, $-C(O)NH_2$, C_{1-6}alquilo, $-NHC(O)CH_3$, halógeno y trifluorometilo;

-W- es



;

B se selecciona del grupo que consiste de $-C(=NR^{45})(R^{47})$, $C(O)NR^{40}R^{41}$, arilo, heteroarilo, heteroalicíclico, $S(O)_2R^8$, $C(O)R^7$, XR^{8a}, (C_{1-6})alquilo$NR^{40}R^{41}$, (C_{1-6})alquil$COOR^{8b}$; en donde el arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o de uno hasta tres iguales o diferentes substituyentes seleccionados del grupo F; en donde arilo es naftilo o fenilo substituido; en donde heteroarilo es un sistema mono o bicíclico el cual contiene desde 3 hasta 7

átomos en el anillo por un sistema monocíclico y hasta 12 átomos en un sistema bicíclico fusionado, incluyendo desde 1 hasta 4 heteroátomos; en donde heteroalicíclico es un anillo monocíclico de 3 hasta 7 miembros los cuales pueden contener desde 1 hasta 2 heteroátomos en la estructura del anillo y el cual puede ser fusionado a un anillo de benceno o piridina;

q es 0, 1, ó 2;

D se selecciona del grupo que consiste de (C_{1-6})alquilo y (C_{2-6})alquenilo; en donde el (C_{1-6})alquilo y (C_{2-6})alquenilo son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o de uno hasta tres iguales o diferentes substituyentes seleccionados del grupo que consiste de $C(O)NR^{55}R^{56}$, hidroxi, ciano y XR^{57};

E se selecciona del grupo que consiste de (C_{1-6})alquilo y (C_{2-6})alquenilo; en donde el (C_{1-6})alquilo y (C_{2-6})alquenilo son independientemente opcionalmente substituidos con un miembro seleccionado del grupo que consiste de fenilo, heteroarilo, SMe, SPh, $-C(O)NR_{56}R_{57}$, $C(O)R^{57}$, $SO_2(C_{1-6})$alquilo y SO_2Ph; en donde heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 7 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos;

F se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-7})cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, (C_{1-6})alcoxi, ariloxi, (C_{1-6})tioalcoxi, ciano, halógeno, nitro, $-C(O)R^{57}$, bencilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, -

$NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR_{42}C(O)$-heteroalicíclico, un anillo cíclico de N-lactama de 4, 5, ó 6 miembros, $-NR^{42}S(O)_2-(C_{1-6})$alquilo,, $-NR^{42}S(O)_2-(C_{3-6})$cicloalquilo, $-NR^{42}S(O)2$-arilo, $-NR^{42}S(O)_2$-heteroarilo, $-NR^{42}S(O)2$-heteroalicíclico, $S(O)_2(C_{1-6})$alquilo, $S(O)_2$arilo, $-S(O)_2NR^{42}R^{43}$, $NR^{42}R^{43}$, (C_{1-6})alquiloC(O)$NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$, $NHC(O)NR^{42}R^{43}$, $OC(O)NR^{42}R^{43}$, $NHC(O)OR^{54}$, (C_{1-6})alquil$NR^{42}R^{43}$, $COOR^{54}$ y (C_{1-6})alquil$COOR^{54}$; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, arilo, heteroarilo, heteroalicíclico, (C_{1-6})alcoxi, y ariloxi, son opcionalmente substituidos con uno hasta nueve halógenos iguales o diferentes o desde uno hasta cinco substituyentes iguales o diferentes seleccionados del grupo que consiste de G; en donde arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 7 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina;

G se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-7})cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, (C_{1-6})alcoxi, ariloxi, ciano, halógeno, nitro, $-C(O)R^{57}$, bencilo, $-NR^{48}C(O)-(C_{1-6})$alquilo, $-NR^{48}C(O)-(C_{3-6})$cicloalquilo, $-NR^{48}C(O)$-arilo, $-NR^{48}C(O)$-heteroarilo, $-NR^{48}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de

4, 5, ó 6 miembros, $-NR^{48}S(O)_2-(C_{1-6})$alquilo, $-NR^{48}S(O)_2-(C_{3-6})$cicloalquilo, $-NR^{48}S(O)_2$-arilo, $-NR^{48}S(O)_2$-heteroarilo, $-NR^{48}S(O)_2$-heteroalicíclico, sulfinilo, sulfonilo, sulfonamida, $NR^{48}R^{49}$, (C_{1-6})alquil $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$, $NHC(O)NR^{48}R^{49}$, $OC(O)NR^{48}R^{49}$, $NHC(O)OR^{54}$, (C_{1-6})alquil$NR^{48}R^{49}$, $COOR^{54}$, y (C_{1-6})alquil$COOR^{54}$; en donde arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 7 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina;

R^7 se selecciona del grupo que consiste de arilo, heteroarilo, y heteroalicíclico; en donde el arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o con desde uno hasta tres substituyentes iguales o diferentes seleccionados del grupo F;

en donde R^7, R^8, R^{8a}, R^{8b} arilo es fenilo; heteroarilo es un sistema mono o bicíclico el cual contiene desde 3 hasta 7 átomos en el anillo por el sistema monocíclico y hasta 10 átomos en un sistema bicíclico, incluyendo desde 1 hasta 4 heteroátomos; en donde heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano,

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tetrahidropirano, azepina, y morfolina;

R^8 se selecciona del grupo que consiste de hidrógeno, (C_{1-6})alquilo, (C_{3-7})cicloalquilo, (C_{2-6})alquenilo, (C_{3-7})cicloalquenilo, (C_{2-6})alquinilo, arilo, heteroarilo, y heteroalicíclico; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, (C_{2-6})alquenilo, (C_{3-7})cicloalquenilo, (C_{2-6})alquinilo, arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta seis halógenos iguales o diferentes o desde uno hasta cinco substituyentes iguales o diferentes seleccionados del grupo F;

R^{8a} es un miembro seleccionado del grupo que consiste de arilo, heteroarilo, y heteroalicíclico; en donde cada uno de los miembros es independientemente opcionalmente substituido con uno hasta seis halógenos iguales o diferentes o desde uno hasta cinco substituyentes iguales o diferentes seleccionados del grupo F;

R^{8b} se selecciona del grupo que consiste de hidrógeno, (C_{1-6})alquilo y fenilo;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, son cada uno independientemente seleccionados del grupo que consiste de hidrógeno y (C_{1-6})alquilo; en donde el (C_{1-6})alquilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes;

X se selecciona del grupo que consiste de NH o NCH_3, O, y S;

R^{40} y R^{41} son independientemente seleccionados del grupo

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que consiste de (a) hidrógeno; (b) (C_{1-6})alquilo o (C_{3-7})cicloalquilo substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes seleccionados del grupo F; y (c) (C_{1-6})alcoxi, arilo, heteroarilo o heteroalicíclico; o R^{40} y R^{41} se toman junto con el nitrógeno al cual se enlazan para formar un miembro seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, 4-NMe piperazina, piperidina, azepina, y morfolina; y en donde el arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres substituyentes iguales o diferentes seleccionados del grupo F; en donde R^{40} y R^{41} arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 6 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico se selecciona del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina; con la condición que cuando B es $C(O)NR^{40}R^{41}$, al menos uno de R^{40} y R^{41} no se seleccionan de grupos (a) o (b);

R^{42} y R^{43} son independientemente seleccionados del grupo que consiste de hidrógeno, (C_{1-6})alquilo, alilo, (C_{1-6})alcoxi, (C_{3-7})cicloalquilo, arilo, heteroarilo y heteroalicíclico; o R^{42} y R^{43} se toman juntos con el nitrógeno al cual se enlazan para formar un miembro

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seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, 4-NMe piperazina, piperidina, azepina, y morfolina; y en donde el (C_{1-6})alquilo, (C_{1-6})alcoxi, (C_{3-7})cicloalquilo, arilo, heteroarilo, y heteroalicíclico son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo G; en donde para R^{42} y R^{43} arilo es fenilo; heteroarilo es un sistema monocíclico el cual contiene desde 3 hasta 6 átomos en el anillo, incluyendo desde 1 hasta 4 heteroátomos; heteroalicíclico es un miembro seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, piperidina, tetrahidrofurano, tetrahidropirano, azepina, y morfolina;

R_a y R_b son cada uno independientemente H, (C_{1-6})alquilo o fenilo;

R^{46} se selecciona del grupo que consiste de H, OR^{57}, y $NR^{55}R^{56}$;

R^{47} se selecciona del grupo que consiste de H, amino, halógeno, fenilo, y (C_{1-6})alquilo;

R^{48} y R^{49} son independientemente seleccionados del grupo que consiste de hidrógeno, (C_{1-6})alquilo y fenilo;

R^{50} se selecciona del grupo que consiste de H, (C_{1-6})alquilo, (C_{3-6})cicloalquilo, y bencilo; en donde cada uno de los (C_{1-6})alquilo, (C_{3-7})cicloalquilo y bencilo son opcionalmente substituidos con uno hasta tres halógenos

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iguales o diferentes, amino, OH, CN o NO_2;

R^{54} se selecciona del grupo que consiste de hidrógeno y (C_{1-6})alquilo;

$R^{54'}$ es (C_{1-6})alquilo;

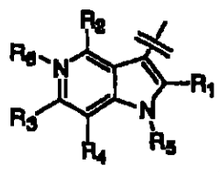
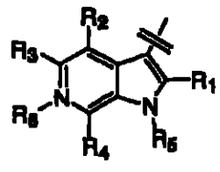
R^{55} y R^{56} son independientemente seleccionados del grupo que consiste de hidrógeno y (C_{1-6})alquilo; y

R^{57} se selecciona del grupo que consiste de hidrógeno, (C_{1-6})alquilo y fenilo.

2. El compuesto de conformidad con la reivindicación 1, que incluye sales farmacéuticamente aceptables del mismo caracterizado porque:

R^1 es hidrógeno;

Q es ya sea:

(a)  o  ;

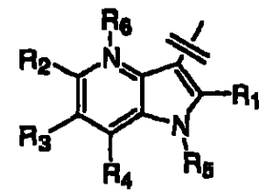
en donde R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, hidroxi, $-O(C_{1-6})$alquilo, ciano, nitro y XR^{57};

en donde R^3 se selecciona del grupo que consiste de hidrógeno, halógeno, hidroxi, $-O(C_{1-6})$alquilo, ciano, $-COOR^{56}$, nitro, XR^{57}; fenilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o uno de metoxi, hidroxi o XR^{57}; furilo, oxazolilo, o pirazolilo, independientemente

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opcionalmente substituido con halógeno, metoxi, (C_{1-3})alquilo o XR^{57}; o

(b) Q es:



en donde R^2 y R^3 son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, hidroxi, $-O(C_{1-6})$alquilo, ciano, nitro, $-COOR^{56}$, XR^{57}, $-C(O)NR^{55}R^{56}$; fenilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o uno de metoxi, hidroxi o XR^{57}; furilo, oxazolilo o pirazolilo, independientemente opcionalmente substituido con (C_{1-3})alquilo, halógeno, metoxi o XR^{57};

y para ambos (a) y (b):

m es 2;

R^5 es hidrógeno;

R^6 no existe;

A se selecciona del grupo que consiste de C_{1-6}alcoxi, arilo y heteroarilo; en donde el arilo es fenilo; heteroarilo se selecciona del grupo que consiste de piridinilo, pirimidinilo, pirazinilo, triazinilo, furanilo, tienilo, pirrolilo, imidazolilo, tiazolilo, oxazolilo e isoxazolilo; y el arilo o heteroarilo es opcionalmente substituido con uno ó dos de los mismos o

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diferentes miembros seleccionados del grupo que consiste de amino, ciano, hidroxi, C_{1-6}alcoxi, C_{1-6}alquilo, $-NHC(O)CH_3$, halógeno y trifluorometilo;

--- representa un enlace carbono-carbono;

X es NH o NCH_3;

R^{57} es H o (C_{1-3})alquilo; y

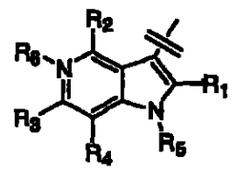
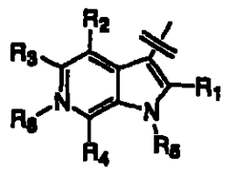
R^{55} y R^{56} son independientemente H o (C_{1-6})alquilo.

3. El compuesto de conformidad con la reivindicación 2, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; y el fenilo o el heteroarilo son opcionalmente substituidos con uno hasta dos amino iguales o diferentes, C_{1-6}alquilo, hidroxi, o halógeno;

-- R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} y R^{16} son cada uno independientemente hidrógeno o metilo con la condición de que al menos uno es metilo;

Q es ya sea:

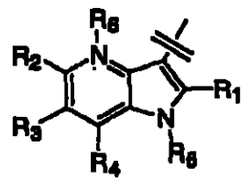
(a)  o 

y luego R^2 se selecciona del grupo que consiste de hidrógeno, halógeno y metoxi; y

R^3 es hidrógeno; o

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(b) Q es:



;

y R^2 es halógeno o hidrógeno y R^3 es hidrógeno;

y para ambos (a) y (b):

R4 se selecciona del grupo que consiste de B;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido, heteroarilo, oxazolina, pirazinona y metilen dioxi o etilen dioxi fusionado a benceno o piridina; en donde el heteroarilo o fenilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

4. El compuesto de conformidad con la reivindicación 3, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido y heteroarilo; en donde el fenilo es substituido y heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F;

F se selecciona del grupo que consiste de (C_{1-6})alquilo,

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(C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, (C_{1-6})alcoxi, (C_{1-6})tioalcoxi, ciano, halógeno, $-C(O)R^{57}$, bencilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR^{42}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{42}S(O)_2-(C_{1-6})$alquilo, $-NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ y $COOR^{54}$; en donde el (C_{1-6})alquilo, (C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, (C_{1-6})alcoxi, son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo G;

G se selecciona del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, halógeno, $-NR^{48}C(O)-(C_{1-6})$alquilo, $-NR^{48}C(O)-(C_3)$cicloalquilo, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{48}S(O)_2-(C_{1-6})$alquilo, $NR^{48}R^{49}$, (C_{1-6})alquilo$C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ y (C_{1-6})alquilo$NR^{48}R^{49}$;

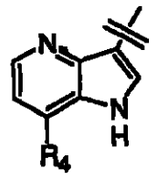
R^{40} es hidrógeno; y

R^{41} se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo y heteroarilo; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo, o heteroarilo son substituidos con uno hasta tres halógenos iguales o diferentes o uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de metilo, (C_{1-3})alcoxi, heteroarilo y arilo; en donde el

arilo o heteroarilo son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, $-NR^{42}C(O)-(C_{1-6})$alquilo, $NR^{42}R^{43}$ y $C(O)NR^{42}R^{43}$.

5. El compuesto de conformidad con la reivindicación 4, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

Q es



;

A es fenilo, 2-piridilo, o 3-piridilo;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$ o heteroarilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de F.

6. El compuesto de conformidad con la reivindicación 5, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

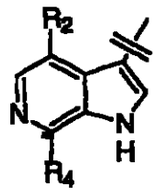
B es heteroarilo, en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos

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iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

7. El compuesto de conformidad con la reivindicación 4, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

Q es



;

R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, y metoxi;

R^4 es B;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$ o heteroarilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

8. El compuesto de conformidad con la reivindicación 7, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

A es fenilo, 2-piridilo, o 3-piridilo.

9. El compuesto de conformidad con la reivindicación 8, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

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B es $-C(O)NR^{40}R^{41}$.

10. El compuesto de conformidad con la reivindicación 8, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

B es heteroarilo, en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes seleccionados del grupo F.

11. El compuesto de conformidad con la reivindicación 4, caracterizado porque:

F se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-6})cicloalquilo, (C_{1-6})alcoxi, hidroxi, heteroarilo, heteroalicíclico, metoxi, $-S(C_{1-3})$alquilo, halógeno, $-C(O)R^{57}$, $C(O)NR^{42}R^{43}$, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR^{42}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{42}S(O)_2-(C_{1-6})$alquilo, $-NR^{42}S(O)_2-(C_{3-6})$cicloalquilo, $-NR^{42}S(O)_2$-arilo, $-NR^{42}S(O)_2$-heteroarilo, $-NR^{42}S(O)_2$-heteroalicíclico, $NR^{42}R^{43}$, $NR^{55}(C_{1-3})$alquil$NR^{55}R^{56}$ y $COOR^{54}$.

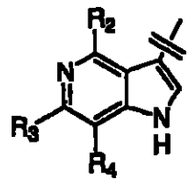
12. El compuesto de conformidad con la reivindicación 11, caracterizado porque:

A es fenilo, 2-piridilo, o 3-piridilo.

13. El compuesto de conformidad con la reivindicación 4, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

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Q es



;

R^2 se selecciona del grupo que consiste de hidrógeno y metoxi;

R^3 es hidrógeno; y

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$ y heteroarilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

14. El compuesto de conformidad con la reivindicación 8, caracterizado porque R^2 es fluoro.

15. El compuesto de conformidad con la reivindicación 8, caracterizado porque R^2 es metoxi.

16. El compuesto de conformidad con la reivindicación 8, caracterizado porque:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos

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iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

17. El compuesto de conformidad con la reivindicación 5, caracterizado porque:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

18. El compuesto de conformidad con la reivindicación 13, caracterizado porque:

-- B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

19. El compuesto de conformidad con la reivindicación 7, caracterizado porque:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol, piridilo, indol, azaindol, y diaza-indol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes seleccionados del grupo F.

20. El compuesto de conformidad con la reivindicación 6, caracterizado porque:

B es heteroarilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 -alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), -C(O)-NH_2, C(O)NHMe, $C(O)NMe_2$, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, -tiazol, pirrol, piperazina, pirrolidina y N-pirrolidona.

21. El compuesto de conformidad con la reivindicación 7, caracterizado porque:

B es -C(O)NH-heteroarilo en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-

C_6 alquilo), -metoxi, -NHC(C_1-C_6 alquilo) y -N(C_1-C_6 alquilo)$_2$.

22. El compuesto de conformidad con la reivindicación 10, caracterizado porque:

B es heteroarilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -NHC(C_1-C_6 alquilo), -N(C_1-C_6 alquilo)$_2$, -heteroarilo y una N-lactama cíclica de 4, 5, ó 6 miembros.

23. El compuesto de conformidad con la reivindicación 9, caracterizado porque:

B es -C(O)NH-heteroarilo en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -metoxi, -NHC(C_1-C_6 alquilo) y -N(C_1-C_6 alquilo)$_2$.

24. El compuesto de conformidad con la reivindicación 16, caracterizado porque:

B es heteroarilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -COOC_1-C_6

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alquilo, -NHC(O)-(C_{1-6}alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, -tiazol, pirrolo, piperazina, pirrolidina y N-pirrolidona.

25. El compuesto de conformidad con la reivindicación 13, caracterizado porque:

B es -C(O)NH-heteroarilo en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), --metoxi, -NHC(C_1-C_6 alquilo) y -N(C_1-C_6 alquilo)$_2$.

26. El compuesto de conformidad con la reivindicación 5, caracterizado porque:

B es tienilo.

27. El compuesto de conformidad con la reivindicación 24, caracterizado porque:

B es tienilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -COOC_1-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y

trifluorometilo.

28. El compuesto de conformidad con la reivindicación 10, caracterizado porque:

B es tienilo.

29. El compuesto de conformidad con la reivindicación 27, caracterizado porque:

B es tienilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, amino, -NHC(O)-(C_1-C_6 alquilo), -C(O)-NH_2, C(O)NHMe, C(O)NMe_2 y -$NR^{55}R^{56}$.

30. El compuesto de conformidad con la reivindicación 10, caracterizado porque:

B es tienilo opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

31. El compuesto de conformidad con la reivindicación 16, caracterizado porque:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol,

imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol y piridilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquil), -$NHS(O)_2$-(C_1-C_6 alquil), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

32. El compuesto de conformidad con la reivindicación 17, caracterizado porque:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol y piridilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquilo)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y

trifluorometilo.

33. El compuesto de conformidad con la reivindicación 18, caracterizado porque:

B es heteroarilo seleccionado del grupo que consiste de tiazol, piridazina, pirazina, pirazol, isoxazol, isotiazol, imidazol, furilo, tienilo, oxazol, oxadiazol, tiadiazol, pirimidina, pirazol, triazina, triazol, tetrazol y piridilo; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de hidroxi, C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_3 tioalcoxi, amino, -C(O)H, -COOH, -$COOC_1$-C_6 alquilo, -NHC(O)-(C_1-C_6 alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -$NR^{55}R^{56}$, $NR^{55}R^{56}$-(C_1-C_6 alquil)-$NR^{55}R^{56}$, heteroarilo, piperazina, pirrolidina, N-pirrolidona y trifluorometilo.

34. El compuesto de conformidad con la reivindicación 3, caracterizado porque se describe en la tabla 2.

35. El compuesto de conformidad con la reivindicación 3, caracterizado porque se describe en la tabla 2-1.

36. El compuesto de conformidad con la reivindicación 3, caracterizado porque se describe en la tabla 3.

37. El compuesto de conformidad con la reivindicación 3, caracterizado porque se describe en la tabla 4

38. El compuesto de conformidad con la reivindicación 3, caracterizado porque se describe en la tabla 5

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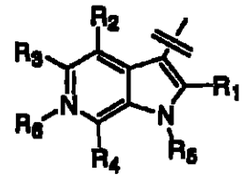
39. El compuesto de conformidad con la reivindicación 1, caracterizado porque:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; en donde el fenilo o heteroarilo es independientemente opcionalmente substituido con uno hasta dos de los mismos o diferentes amino, C_{1-6}alquilo, o halógeno;

- - representa un enlace carbono-carbono;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, y R^{16} son cada uno independientemente hidrógeno o metilo, con la condición de que solamente cero, uno, o dos es metilo;

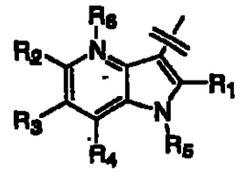
Q es ya sea:

(a)  ;

-- R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, y metoxi; y

R^3 es hidrógeno; o

(b) Q es:

 ;

R^2 y R^3 son hidrógeno;

y para ambos (a) y (b):

R^4 se selecciona del grupo que consiste de B;

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B es heteroarilo seleccionado del grupo que consiste de triazol, pirazol, oxazol, pirazina, pirimidina y oxadiazol; en donde el heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o de uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F;

F se selecciona del grupo que consiste de (C_{1-6})alquilo, heteroarilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}R^{43}$ y $C(O)NR^{42}R^{43}$;

R^5 es hidrógeno;

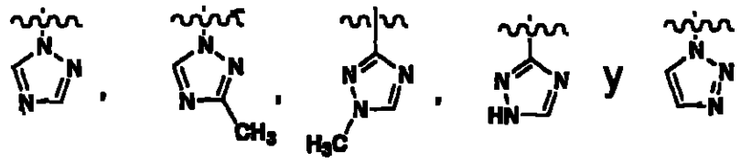
R^6 no existe; y

R^{42} y R^{43} son independientemente seleccionados del grupo que consiste de hidrógeno y (C_{1-6})alquilo; o R^{42} y R^{43} se toman juntos con el nitrógeno al cual se enlazan para formar un heteroalicíclico seleccionado del grupo que consiste de aziridina, azetidina, pirrolidina, piperazina, tetrahidrofurano, tetrahidropirano, azepina y morfolina.

40. El compuesto de conformidad con la reivindicación 39, caracterizado porque:

R^2 es H, Cl, F, o metoxi; y

R^4 se selecciona del grupo que consiste de



41. El compuesto de conformidad con la reivindicación 40, caracterizado porque:

R^2 es metoxi o fluoro; y

Uno de R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, ó R^{16} es metilo y los otros son hidrógeno.

42. El compuesto de conformidad con la reivindicación 40, caracterizado porque:

R^2 es metoxi; y

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, y R^{16} cada uno son hidrógeno.

43. El compuesto de conformidad con la reivindicación 41, caracterizado porque:

uno de R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, ó R^{16} es (R)-metilo y los otros son hidrógeno.

44. El compuesto de conformidad con la reivindicación 41, caracterizado porque:

uno de R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, ó R^{16} es (S)-metilo y los otros son hidrógeno.

45. El compuesto de conformidad con la reivindicación 39, caracterizado porque:

R^2 es metoxi, hidrógeno, cloro, o fluoro; y

R^4 es oxadiazol.

46. El compuesto de conformidad con la reivindicación 54, caracterizado porque:

R^2 es metoxi, hidrógeno, cloro o fluoro; y

R^4 es oxadiazol substituido con un grupo simple fluoro, cloro, amino o metilo.

47. El compuesto de conformidad con la reivindicación 2, que incluye sales farmacéuticamente aceptables del mismo,

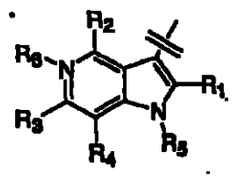
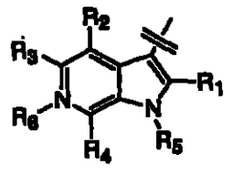
caracterizado porque:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde el heteroarilo es piridinilo, furanilo o tienilo; y el fenilo o el heteroarilo es opcionalmente substituido con uno hasta dos de los mismos o diferentes amino, C_{1-6}alquilo, hidroxi, o halógeno;

R^9, R^{10}, R^{11}, R^{12}, R^{15}, y R^{16} son cada uno hidrógeno;

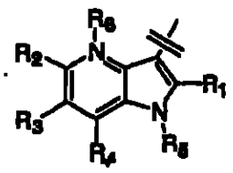
R^{13} y R^{14} son cada uno independientemente hidrógeno o metilo con la condición de que solamente uno es metilo;

Q es ya sea:

(a)  o  ;

R^2 se selecciona del grupo que consiste de hidrógeno, halógeno y metoxi; y

R^3 es hidrógeno; o

(b) Q es:  ;

y R^2 es halógeno o hidrógeno y R^3 es hidrógeno;

y para ambos (a) y (b):

R^4 se selecciona del grupo que consiste de B; y

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido, heteroarilo, oxazolina, pirazinona, metilen dioxi o etilen dioxi se fusionan a un benceno o piridina; en donde el heteroarilo o fenilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

48. El compuesto de conformidad con la reivindicación 47, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido y heteroarilo; en donde el fenilo es substituido y heteroarilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F;

F se selecciona del grupo que consiste de (C_{1-6})alquilo, (C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, hidroxi, (C_{1-6})alcoxi, (C_{1-6})tioalcoxi, ciano, halógeno, $-C(O)R^{57}$, bencilo, $-NR^{42}C(O)-(C_{1-6})$alquilo, $-NR^{42}C(O)-(C_{3-6})$cicloalquilo, $-NR^{42}C(O)$-arilo, $-NR^{42}C(O)$-heteroarilo, $-NR^{42}C(O)$-heteroalicíclico, una N-lactama de anillo cíclico de

4, 5, ó 6 miembros, $-NR^{42}S(O)_2-(C_{1-6})$alquilo, $-NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ y $COOR^{54}$; en donde el (C_{1-6})alquilo, (C_{3-6})cicloalquilo, arilo, heteroarilo, heteroalicíclico, (C_{1-6})alcoxi, son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo G;

G se selecciona del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, halógeno, $-NR^{48}C(O)-(C_{1-6})$alquilo, $-NR^{48}C(O)-(C_3)$cicloalquilo, una N-lactama de anillo cíclico de 4, 5, ó 6 miembros, $-NR^{48}S(O)_2-(C_{1-6})$alquilo, $NR^{48}R^{49}$, (C_{1-6})alquilo $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$ y (C_{1-6})alquilo$NR^{48}R^{49}$;

R^{40} es hidrógeno;

R^{41} es (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo, o heteroarilo; en donde el (C_{1-6})alquilo, (C_{3-7})cicloalquilo, fenilo, o heteroarilo son substituidos con uno hasta tres halógenos iguales o diferentes o uno hasta dos metilo, (C_{1-3})alcoxi, heteroarilo o arilo iguales o diferentes; en donde el arilo o heteroarilo son opcionalmente substituidos con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo que consiste de (C_{1-6})alquilo, hidroxi, (C_{1-6})alcoxi, $-NR^{42}C(O)-(C_{1-6})$alquilo, $NR^{42}R^{43}$ y $C(O)NR^{42}R^{43}$.

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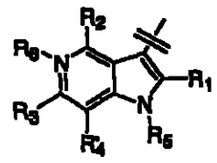
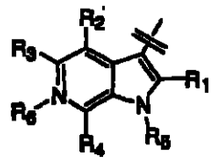
49. El compuesto de conformidad con la reivindicación 2, que incluye sales farmacéuticamente aceptables del mismo,

caracterizado porque:

A se selecciona del grupo que consiste de fenilo y heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; y el fenilo o el heteroarilo es opcionalmente substituido con uno hasta dos de los mismos o diferentes amino, C_{1-6} alquilo, hidroxi, o halógeno;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, y R^{16} son cada uno independientemente hidrógeno o metilo con la condición de que solo uno es metilo;

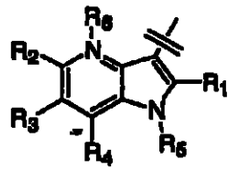
Q es ya sea:

(a)  o  ;

en donde R^2 se selecciona del grupo que consiste de hidrógeno, halógeno y metoxi; y

R_3 es hidrógeno; o

(b) Q es:

 ;

en donde R^2 es halógeno o hidrógeno; y R^3 es

hidrógeno;

y para ambos (a) y (b):

R^4 se selecciona del grupo que consiste de B;

B se selecciona del grupo que consiste de $-C(O)NR^{40}R^{41}$, fenilo substituido, heteroarilo, oxazolina, pirazinona, metilen dioxi o etilen dioxi fusionado a un benceno o piridina; en donde el heteroarilo o fenilo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o desde uno hasta dos substituyentes iguales o diferentes seleccionados del grupo F.

50. El compuesto de conformidad con la reivindicación 49, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

B se selecciona del grupo que consiste de pirazinona y metilen dioxi o etilen dioxi fusionado a un anillo de benceno; en donde el grupo es opcionalmente substituido con uno hasta tres halógenos iguales o diferentes o un substituyente seleccionado del grupo F que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -$NHS(O)_2$-(C_1-C_6 alquilo), metoxi, $-C(O)-NH_2$, C(O)NHMe, C(O)NMe2, trifluorometilo, -NHC(C_1-C_6 alquilo), -N(C_1-C_6 alquilo)$_2$, -heteroarilo y una N-lactama cíclica de 4, 5, ó 6 miembros.

51. El compuesto de conformidad con la reivindicación 49, que incluye sales farmacéuticamente

aceptables del mismo,

caracterizado porque:

B se selecciona del grupo que consiste de oxadiazol, triazol, pirazol, pirazina y pirimidina; en donde el grupo es opcionalmente substituido con uno hasta tres iguales o diferentes halógenos o un substituyente seleccionado del grupo F que consiste de (C_1-C_6 alquilo), amino, -NHC(O)-(C_1-C_6 alquilo), -NHS(O)$_2$-(C_1-C_6 alquilo), metoxi, -C(O)-NH_2, C(O)NHMe, C(O)NMe2, trifluorometilo, -NHC(C_1-C_6 alquilo), -N(C_1-C_6 alquilo)$_2$, -heteroarilo, una N-lactama cíclica de 4, 5, ó 6 miembros y (C_1-$_6$)alquil$NR^{48}R^{49}$.

52. El compuesto de conformidad con la reivindicación 49, que incluye sales farmacéuticamente aceptables del mismo,

caracterizado porque:

-- heteroarilo en B se selecciona del grupo que consiste de pirazina y pirimidina.

53. El compuesto de conformidad con la reivindicación 50, que incluye sales farmacéuticamente aceptables del mismo,

caracterizado porque:

heteroarilo en B se selecciona del grupo que consiste de pirazina y pirimidina.

54. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^9, R^{10}, R^{15} y R^{16} son cada uno hidrógeno; y R^{11}, R^{12}, R^{13}, y R^{14} son cada uno

independientemente hidrógeno o metil con la condición de que hasta uno puede ser metilo.

55. El compuesto de conformidad con la reivindicación 54, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque uno de R^{11}, R^{12}, R^{13}, y R^{14} es metilo.

56. El compuesto de conformidad con la reivindicación 55, caracterizado porque el átomo de carbono del anillo de piperazina al cual el grupo metilo de R^{11}, R^{12}, R^{13}, y R^{14} se enlazan tiene una configuración (R).

57. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^{11}, R^{12}, R^{13}, y R^{14} son cada uno hidrógeno; y R^9, R^{10}, R^{15} y R^{16} son cada uno independientemente hidrógeno o metilo con la condición de que hasta uno puede ser metilo.

58. El compuesto de conformidad con la reivindicación 57, caracterizado porque uno de R^9, R^{10}, R^{15} y R^{16} es metilo.

59. El compuesto de conformidad con la reivindicación 58, caracterizado porque el átomo de carbono del anillo de piperazina al cual el grupo metilo de R^9, R^{10}, R^{15} y R^{16} se enlazan tiene una configuración (R).

60. El compuesto de conformidad con la reivindicación 1, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^1 es hidrógeno;

m es 2;

R^5 es hidrógeno;

R^6 no existe;

A se selecciona del grupo que consiste de C_{1-6}alcoxi, arilo y heteroarilo; en donde arilo es fenilo; heteroarilo se selecciona del grupo que consiste de piridinilo, pirimidinilo, pirazinilo, triazinilo, furanilo, tienilo, pirrolilo, imidazolilo, tiazolilo, oxazolilo e isoxazolilo; y el arilo o heteroarilo es opcionalmente substituido con uno o dos de los mismos o diferentes amino, ciano, hidroxi C_{1-6}alcoxi, C_{1-6}alquilo, $-NHC(O)CH_3$, halógeno y trifluorometilo; y

- - representa un enlace carbono-carbono.

61. Una formulación farmacéutica caracterizada porque comprende una cantidad efectiva antiviral de un compuesto de la fórmula I, incluyendo sales farmacéuticamente aceptables de los mismos, como los reivindicados en la reivindicación 1, y un portador farmacéuticamente aceptable.

62. La formulación farmacéutica de conformidad con la reivindicación 61, que es útil para el tratamiento de la infección por VIH, caracterizada porque comprende adicionalmente una cantidad efectiva antiviral de un agente del tratamiento del SIDA seleccionado del grupo que consiste de:

(a) Un agente antiviral del SIDA;

(b) Un agente anti-infeccioso;

(c) un immunomodulador; y

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(d) inhibidores de entrada del VIH.

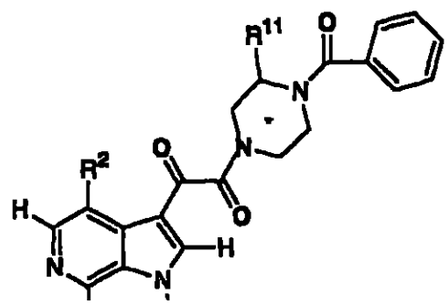
63. Un método para el tratamiento de mamíferos infectados con un virus, caracterizado porque comprende administrar al mamífero una cantidad efectiva antiviral de un compuesto de la fórmula I, incluyendo sales farmacéuticamente aceptables del mismo, como se reivindica en la reivindicación 1.

64. El método de conformidad con la reivindicación 63, caracterizado porque comprende administrar al mamífero una cantidad efectiva antiviral de un compuesto de la fórmula I en combinación con una cantidad efectiva antiviral de un agente de tratamiento del SIDA seleccionado del grupo que consiste de: un agente antiviral del SIDA; un agente anti-infeccioso; un immunomodulador e inhibidores de entrada del VIH.

65. El método de conformidad con la reivindicación 63, caracterizado porque el virus es VIH.

66. El método de conformidad con la reivindicación 64, caracterizado porque el virus es VIH.

67. El método de conformidad con la reivindicación 1, que tiene la fórmula Ia, incluyendo sales farmacéuticamente aceptables de los mismos,

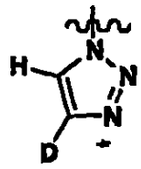


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caracterizado porque:

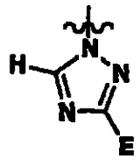
R^2 es metoxi, fluoro o cloro.

R^4 se selecciona del grupo que consiste de un grupo 1,2,3-triazolilo que tiene la fórmula



, o

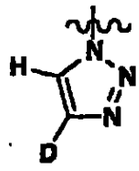
un grupo 1,2,4-triazolilo que tiene la fórmula



D es hidrógeno o C_1-C_3 alquilo.

E se selecciona del grupo que consiste de hidrógeno, (C_1-C_3)alquilo, O(C_1-C_3)alquilo o CH_2OCH_3 y

R^{11} es ya sea hidrógeno o metilo en el cual la configuración a la cual el metilo se enlazó es (R) con la condición de que cuando R^4 es



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, luego R^{11} es hidrógeno.

68. El compuesto de conformidad con la reivindicación 67, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^2 es metoxi o flúor;

D es hidrógeno o metilo; y

E es hidrógeno, metilo o etilo.

69. El compuesto de conformidad con la reivindicación 68, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^2 es metoxi;

D es hidrógeno o metilo; y

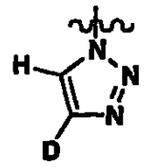
E es hidrógeno, metilo o etilo.

70. El compuesto de conformidad con la reivindicación 69, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^{11} es hidrógeno.

71. El compuesto de conformidad con la reivindicación 70, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^4 es



; y

R^{11} es hidrógeno.

72. El compuesto de conformidad con la reivindicación 71, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

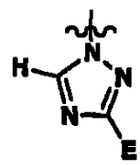
D es hidrógeno.

73. El compuesto de conformidad con la reivindicación 71, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

D es metilo.

74. El compuesto de conformidad con la reivindicación 70, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^4 es



75. El compuesto de conformidad con la reivindicación 74, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es hidrógeno.

76. El compuesto de conformidad con la reivindicación 74, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es metilo.

77. El compuesto de conformidad con la reivindicación

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74, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es etilo.

78. El compuesto de conformidad con la reivindicación 68, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

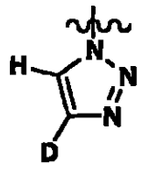
R^2 es fluoro,

D es hidrógeno o metilo; y

E es hidrógeno o metilo.

79. El compuesto de conformidad con la reivindicación 78, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^4 es



; y

R^{11} es hidrógeno.

80. El compuesto de conformidad con la reivindicación 79, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

D es hidrógeno.

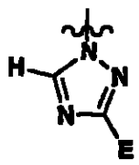
81. El compuesto de conformidad con la reivindicación 79, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

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D es metilo.

82. El compuesto de conformidad con la reivindicación 78, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^4 es



83. El compuesto de conformidad con la reivindicación 82, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es hidrógeno.

84. El compuesto de conformidad con la reivindicación 82, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es metilo.

85. El compuesto de conformidad con la reivindicación 68, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^2 es metoxi;

D es hidrógeno o metilo;

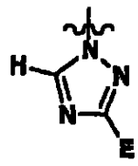
E es hidrógeno, metilo o etilo; y

R^{11} es (R)-metilo.

86. El compuesto de conformidad con la reivindicación 85, que incluye sales farmacéuticamente aceptables del mismo,

caracterizado porque

R^4 es



87. El compuesto de conformidad con la reivindicación 86, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es hidrógeno.

88. El compuesto de conformidad con la reivindicación 86, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es metilo.

89. El compuesto de conformidad con la reivindicación 86, que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

E es etilo.

90. Una formulación farmacéutica, caracterizada porque comprende una cantidad efectiva antiviral de un compuesto de la fórmula Ia, incluyendo sales farmacéuticamente aceptables del mismo, como se reivindica en la reivindicación 67 y un portador farmacéuticamente aceptable.

91. La formulación farmacéutica de conformidad con la reivindicación 90, caracterizada porque es útil para el

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tratamiento de la infección por VIH, la cual comprende adicionalmente una cantidad efectiva antiviral de un agente del tratamiento del SIDA seleccionado del grupo que consiste de:

(a) un agente antiviral del SIDA;

(b) un agente anti-infeccioso;

(c) un immunomodulador; e

(d) inhibidores de entrada del VIH.

92. Un método para tratar mamíferos infectados con el virus del VIH, caracterizado porque comprende administrar al mamífero una cantidad efectiva antiviral de un compuesto de la fórmula Ia, incluyendo sales farmacéuticamente aceptables del mismo, de conformidad con la reivindicación 67.

93. El método de conformidad con de la reivindicación 92, caracterizado porque comprende administrar al mamífero una cantidad efectiva antiviral de un compuesto de la fórmula Ia en combinación con una cantidad efectiva antiviral de un agente de tratamiento del SIDA seleccionado del grupo que consiste de: un agente antiviral del SIDA; un agente anti-infeccioso; un immunomodulador; e inhibidores de entrada del VIH.

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RESUMEN DE LA INVENCIÓN

Esta invención proporciona compuestos que tienen propiedades bioafectadoras y de fármacos; sus composiciones farmacéuticas y método de uso. En particular, la invención se refiere a derivados de azaindoloxoacetil piperazina. Estos compuestos poseen actividad antiviral única, ya sea al usarse solos o en combinación con otros antivirales, anti-infecciosos, inmunomoduladores o inhibidores de la entrada del VIH. Más particularmente, la presente invención se refiere al tratamiento del VIH y SIDA.

1068 AJ:96.302

GY0085A - PC

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SAMUEL J. DUBOFF
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (*day/month/year*)	22 JUL 2004
Applicant's or agent's file reference GY85A CIP2	IMPORTANT NOTIFICATION

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US03/24415	04 August 2003 (04.08.2003)	07 August 2002 (07.08.2002)

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

RECEIVED
AUG 02 2004
BRISTOL-MYERS SQUIBB CO.
PATENT DEPARTMENT
WALLINGFORD, CT

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Emily Bernhardt
Facsimile No. (703) 872-9306	Telephone No. (571) 272-1600

Form PCT/IPEA/416 (July 1992)

RECEIVED
KMS PATENT LAW
JUL 26 2004

Docketed Item
Due Date
Attorney DuBOFF

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference GY85A CIP2	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/24415	International filing date *(day/month/year)* 04 August 2003 (04.08.2003)	Priority date *(day/month/year)* 07 August 2002 (07.08.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/496, 31/497, 31/506; C07D 487/04. and US Cl.: 514/252.11, 252.18, 253.04; 544/295, 357, 362.		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20 February 2004 (20.02.2004)	12 July 2004 (12.07.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 872-9306	Authorized officer Emily Bernhardt J. Roberts for Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

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PATENT COOPERATION TREATY

PCT

NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No.	Applicant's or agent's file reference	Date of informal communication *(day/month/year)*
PCT/US03/24415	GYBSA CIP2	29 June 2004 (29.06.2004)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

Communication	Participants			
☒ by telephone	☒ Applicant:	BRISTOL-MYERS SQUIBB COMPANY	☐ Identity checked	☐ authorization checked
☐ personal	☒ Agent:	Mr. DuBoff		☒ personally known
	☒ Examiner(s):	Emily Bernhardt		

Summary of communication:

The examiner requested permission to go directly to a 409 despite the presence of an "X" reference and thus need to make a negative statement in view of the lateness in submitting an opinion. Mr. DuBoff authorized permission to proceed to a 409.

☐ ~~An extension of time limit is granted (Form PCT/IPEA/427.~~

☒ A copy of this note is being sent to the applicant with Form ~~PCT/IPEA/429.~~ PCT/IPEA/434. 416 & 409

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Emily Bernhardt F. Roberts for
Facsimile No. (703) 872-9306	Telephone No. (571) 272-1600

Form PCT/IPEA/428 (July 1992)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/24415

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-578 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 579-612, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/24415

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	10,16-46,50-53,67-93	YES
	Claims	1-9,11-15,47-49,54-66	NO
Inventive Step (IS)	Claims	10,16-46,50-53,67-93	YES
	Claims	1-9,11-15,47-49,54-66	NO
Industrial Applicability (IA)	Claims	1-93	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 10,16-46,50-53,67-93 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the type of choices permitted at "B" embraced by these claims.

Claims 1-9, 11-15,47-49 and 54-66 lack novelty and thus an inventive step under PCT Articles 33(2)-(3) as being anticipated and rendered obvious by Wang (US'892). The published patent application describes similar compounds within the instant scope for use in treating HIV either alone or coadministered with other HIV agents. See pages 4-7 and species on p.34, left column.

Claims 1-93 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry. Compounds are particularly described for treating HIV and AIDS.

TRATADO DE CO PERACI N EN MATERIA DE PATENTES
P C T
REPORTE DE EXAMEN PRELIMINAR INTERNACI NAL
(Artículo 36 y Regla 70 del PCT)

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Archivo de referencia del solicitante o agente	PARA TOMAR ACCION ADICIONAL	Véase la Notificación de la Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416)
GY85A CIP2		
Solicitud Internacional No.	**Fecha de Presentación Internacional**	**Fecha de Prioridad**
PCT/US 03/24415	4 Agosto2003 (04.08.2003)	7 Agosto 2002 (07.08.2002)

Clasificación de Patente Internacional (IPC) o Clasificación nacional e IPC
IPC(7): A61K 31/496, 31/497, 31/506; C07D 487/04 y US CL: 514/252.11, 252.18, 253.04; 544/295, 357, 362.

Solicitante
BRISTOL-MYERS SQUIBB COMPANY

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Examinación Preliminar Internacional y es transmitido al solicitante de acuerdo con el Artículo 36.

2. Este reporte consiste de 3 hojas.

☐ Este reporte también está acompañado por ANEXOS, es decir, hojas de la descripción, las reivindicaciones y/o los dibujos, los cuales han sido enmendados y son la base para este reporte y/o las hojas que contienen las rectificaciones hechas antes de esta Autoridad. (Véase la Regla 70.16 y la Sección 607 de las Instrucciones Administrativa bajo el PCT).

Estos anexos consisten de un total de _____ Hojas.

3. Este reporte contiene las indicaciones que están relacionadas con los siguientes puntos:

I ☒ Base del reporte
II ☐ Prioridad
III ☐ Ningún establecimiento del reporte con respecto a la novedad, paso de la invención, o aplicabilidad industrial
IV ☐ Carencia de unidad de la invención
V ☒ Establecimiento razonado bajo el Artículo 35(2) con respecto a la novedad, paso de la invención o Aplicabilidad industrial; las citas y explicaciones que soportan tal establecimiento o fundamento.
VI ☐ Ciertos documentos citados
VII ☐ Ciertos defectos en la solicitud internacional
VIII ☐ Ciertas observaciones en la solicitud internacional.

Fecha de presentación de la solicitud	Fecha en la que se completa este reporte
20 de Febrero del 2004 (20.02.2004)	12 de Julio del 2004 (12.07.2004)

Nombre y dirección del envío IPERA/US	Oficial Autorizado
Mail Stop PCT, Attn: ISA/US Comisionado para Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Fax. No.: (703) 305-3230	Rúbrica Emily Bernhardt Teléfono No. (571) 272-1600

Forma PCT/IPEA/409 (hoja de cubierta) (Enero de 1994) *

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REPORTE DE EXAMEN PRELIMINAR INTERNACI NAL

Solicitud Internacional No.
PCT/US03/24415

I.Bases del Reporte

1. Con respecto a los elementos de la solicitud internacional:

☒ la solicitud internacional como se presentó originalmente.

☒ la descripción, páginas 1-578, como se presentó originalmente.

páginas NINGUNA, presentadas con la solicitud.

páginas NINGUNA, presentadas con la carta de _____.

☒ las reivindicaciones, páginas, 579-612, como se presentó originalmente.

páginas NINGUNA, como se enmendó bajo el Artículo 19

páginas NINGUNA, presentada con la solicitud

páginas NINGUNA, presentada con la carta de _____.

☒ los dibujos, páginas. NINGUNO, como se presentaron originalmente.

páginas NINGUNO, Presentada con la demanda

páginas NINGUNO, presentada con la carta de

☐ parte del listado de secuencias de la descripción:

páginas NINGUNA, como se presentó originalmente.

páginas NINGUNA, presentadas con la solicitud.

páginas NINGUNA, presentadas con la carta de _____.

2. Con respecto al lenguaje, todos los elementos marcados arriba están disponibles o se proporcionan por esta Autoridad en el lenguaje en el cual se presentó la solicitud internacional, salvo que se indique lo contrario bajo este punto

Estos elementos están disponibles o se proporcionan por esta Autoridad en el siguiente lenguaje: , que es:

☐ el lenguaje de una traducción proporcionada para los propósitos de la búsqueda internacional (bajo la Regla 23.1 (b))

☐ el lenguaje de la publicación internacional (bajo la Regla 48.3(b))

☐ el lenguaje de la publicación para los propósitos del examen preliminar internacional (bajo la regla 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia de nucleótido o aminoácido descrita en la solicitud internacional, el examen preliminar internacional se lleva a cabo en base al listado de secuencia:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentado junto con la solicitud internacional en forma para leer en computadora.

☐ proporcionado subsecuentemente por esta Autoridad en forma escrita.

☐ proporcionado subsecuentemente por esta Autoridad en forma para leer en computadora

☐ se proporciona la declaración de que el listado de secuencia subsecuentemente proporcionado no va más allá de la descripción en la solicitud internacional como se presentó.

☐ se proporciona la declaración de que la información registrada en forma que se puede leer en computadora es idéntica al listado de secuencia como se presentó.

4. [ ]Las enmiendas han dado por resultado la cancelación de:

[ ] la descripción, páginas NINGUNA.
[ ] las reivindicaciones, Nos. NINGUNA.
[ ] los dibujos, hojas/fig. NINGUNA.

5. [ ] Este reporte se ha establecido como si (alguna de) las enmiendas no se han hecho, puesto que se han considerado que van más allá de la descripción como se presentó (Regla 70.2(c)):

** Las hojas de reemplazo que se han presentado en la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se refieren a este reporte como "presentadas originalmente" y no se anexan a este reporte ya que no contienen enmiendas (Reglas 70.16 y 70.17).*
*** Cualquier hoja de reemplazo que contenga tales enmiendas, deberá referirse bajo el punto I y anexarse a este reporte.*

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/US03/24415

V. Declaración razonada bajo el Artículo 35(2) con respecto a la novedad, etapa inventiva o la aplicabilidad industrial; citas y explicaciones que soportan tal declaración

1. DECLARACION.

Novedad (N)	Reivindicaciones	10, 16-46, 50-53, 67-93
	Reivindicaciones	1-9, 11-15, 47-49, 54-66
Etapa Inventiva (EI)	Reivindicaciones	10, 16-46, 50-53, 67-93
	Reivindicaciones	1-9, 11-15, 47-49, 54-66
Aplicación Industrial (AI)	Reivindicaciones	1-93
	Reivindicaciones	NINGUNA

2. CITAS Y EXPLICACIONES

Las reivindicaciones 10, 16-46, 50-53, 67-93 cumplen con el criterio establecido en el Artículo 33(2)-(3) del PCT, ya que el arte previo no enseña o sugiere razonablemente el tipo de elecciones permitidas en "B" abarcadas por estas reivindicaciones.

Las Reivindicaciones 1-9, 11-15, 47-49 y 54-66 carecen de novedad y de esta manera una etapa inventiva bajo los artículos 33(2)-(3) del PCT como se anticipa y hace obvio por Wang (US'892). La solicitud de patente publicada describe compuestos similares dentro del alcance actual para usar en el tratamiento del VIH ya sea solos o coadministrados con otros agentes del VIH. Ver páginas 4-7 y especies en la p. 34, columna de la izquierda.

Las reivindicaciones 1-93 cumplen con el criterio establecido en el artículo 33(4) del PCT, y de esta manera poseen aplicación industrial debido a que la materia objeto reivindicada puede hacerse o usarse en la industria. Los compuestos se describen particularmente para el tratamiento del VIH y SIDA.

TRATAD DE CO PERACION EN MATERIA DE PATENTES

P C T

NOTA DE COMUNICACIÓN INFORMAL CON EL S LICITANTE

1036

(Regla 66.6 del PCT)

Solicitud Internacional No.	referencia de archivo del agente o solicitante	Fecha de comunicación informal
PCT/US 03/24415	GY85A CIP2	29 Junio 2004 (29.06.2004)

Solicitante

BRISTOL-MYERS SQUIBB COMPANY

Comunicación	Participantes [ ] Identidad revisada [ ]Autorización revisada [ ] Personalmente conocido
[X] por teléfono [ ] personal	[X] Solicitante: BRISTOL-MYERS SQUIBB COMPANY [X] Agente: Sr. DuBoff [X] Examinador(es): Emily Bernhardt

Resumen de la comunicación:
El examinador solicita permiso para dirigir a un 409 a pesar de la presencia de una referencia "X" y de esta manera necesita hacer una declaración negativa en vista de la demora en presentar la opinión. El Sr. DuBoff autoriza el permiso a que proceda un 409.

[ ] ~~Se otorga una extensión del límite de tiempo (Forma PCT/IPEA/427)~~
[X] Se manda una copia de esta nota al solicitante con la Forma ~~PCT/IPEA/420~~ PCT/IPEA/424 *416 y 409*

Nombre y dirección del envío IPERA/US	Oficial Autorizado
Mail Stop PCT, Attn: ISA/US Comisionado para Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Fax. No.: (703) 305-3230	Rúbrica Emily Bernhardt Teléfono No. (571) 272-1600

Forma PCT/IPEA/428 (Julio 1992)*

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PCT REQUEST

GY85CIP2 PCT

Original (for SUBMISSION) - printed on 05.08.2003 11:10:29 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	GY85CIP2 PCT
I	Title of invention	COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED AZAINDOLEOXOACETIC PIPERAZINE DERIVATIVES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	inventor only
III-1-4	Name (LAST, First)	WANG, Tao
III-1-5	Address:	1312 Town Brooke Middletown, CT 06457 United States of America
III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-4	Name (LAST, First)	ZHANG, Zhongxing
III-2-5	Address:	14 Martleshamheath Lane Madison, CT 06443 United States of America

III-3	Applicant and/or Inventor	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	MEANWELL, Nicholas, A.
III-3-5	Address:	15 Valli Drive East Hampton, CT 06424 United States of America
III-4	Applicant and/or Inventor	
III-4-1	This person is:	inventor only
III-4-4	Name (LAST, First)	KADOW, John, F.
III-4-5	Address:	9 Quarry Run Wallingford, CT 06492 United States of America
III-5	Applicant and/or Inventor	
III-5-1	This person is:	inventor only
III-5-4	Name (LAST, First)	YIN, Zhiwei
III-5-5	Address:	234 Sherman Avenue, Apt. 80 Meriden, CT 06450 United States of America
III-6	Applicant and/or Inventor	
III-6-1	This person is:	inventor only
III-6-4	Name (LAST, First)	XUE, Qiufen, May
III-6-5	Address:	75 Barrington Way Glastonbury, CT 06033 United States of America
III-7	Applicant and/or Inventor	
III-7-1	This person is:	inventor only
III-7-4	Name (LAST, First)	REGUEIRO-REN, Alicia
III-7-5	Address:	69 Greenview Terrace Middletown, CT 06457 United States of America
III-8	Applicant and/or Inventor	
III-8-1	This person is:	inventor only
III-8-4	Name (LAST, First)	MATISKELLA, John, D.
III-8-5	Address:	130 High Hill Road Wallingford, CT 06492 United States of America
III-9	Applicant and/or Inventor	
III-9-1	This person is:	inventor only
III-9-4	Name (LAST, First)	UEDA, Yasutsugu
III-9-5	Address:	46 Olde Orchard Road Clinton, CT 06413 United States of America

PCT REQUEST

GY85CIP2 PCT

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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)	DUBOFF, Samuel
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	203-677-7787
IV-1-4	Facsimile No.	203-677-6900
IV-1-5	Agent's registration No.	25,969
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BABAJKO, Suzanne(32,880); BAXAM, Deanna(45,266); BELFIELD, Jing(45,914); BUCHHOLZ, Briana(39,123); D'AMICO, Stephan, C.(46,652); DAVIS, Stephan(26,693); DUNCAN, Laurelee(44,096); GIBBONS, Maureen(44,121); GOLIAN, Paul, D.(42,591); KLEIN, Christopher(34,363); LANGE, Keith(44,201); O'BRIEN, Maureen(42,043); PATEL, Rena(41,412); PEIST, Kenneth(45,006); PROVOOST, Jonathan(44,292); RODNEY, Burton(22,076); SHER, Audrey(39,024); ALGIERI, Aldo(31,697); MAKUJINA, Shah(41,174); RYAN, Richard(30,491); VANATTEN, Mary, K.(39,408); VOLLES, Warren, K.(33,810); KORSEN, Elliott(32,705); LAMERDIN, John(44,858); DUNCAN, Sammy(46,675); EPPERSON, James(52,867); BOGIE, Terence, J.(44,544)

PCT REQUEST

GY85CIP2 PCT

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V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protoc l and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and f the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	07 August 2002 (07.08.2002)
VI-1-2	Number	10/214,982
VI-1-3	Country	US

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PCT REQUEST GY85CIP2 PCT

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VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	578	-
IX-3	Claims	34	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	619	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Post card receipt, Certificate of Express Mailing, Certification	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	Samuel H DuBoff	
X-1-1	Name (LAST, First)	DUBOFF, Samuel	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	

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10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

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PCT (ANNEX - FEE CALCULATION SHEET)

GY85CIP2 PCT

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(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared using		PCT-EASY Version 2.92 (updated 01.07.2003)		
0-9	Applicant's or agent's file reference		GY85CIP2 PCT		
2	Applicant		BRISTOL-MYERS SQUIBB COMPANY		
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee	T	⇨	240	
12-2-1	Search fee	S	⇨	700	
12-2-2	International search to be carried out by		US		
12-3	International fee				
	Basic fee				
	(first 30 sheets)	b1	476		
12-4	Remaining sheets		589		
12-5	Additional amount	(X)	12		
12-6	Total additional amount	b2	7,068		
12-7	b1 + b2 =	B	7,544		
12-8	Designation fees				
	Number of designations contained in international application		96		
12-9	Number of designation fees payable (maximum 5)		5		
12-10	Amount of designation fee	(X)	104		
12-11	Total designation fees	D	520		
12-12	PCT-EASY fee reduction	R	-148		
12-13	Total international fee (B+D-R)	I	⇨	7,916	
12-14	Fee for priority document				
	Number of priority documents requested		1		
12-15	Fee per document	(X)	20		
12-16	Total priority document fee	P	⇨	20	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	8,876	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions				
	The receiving Office:		United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.		✓		

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GY85CIP2.PCT

PCT (ANNEX - FEE CALCULATION SHEET)

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12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19-3880
12-22	Date	05 August 2003 (05.08.2003)
12-23	Name and signature	DUBOFF, Samuel

VALIDATION LOG AND REMARKS

13-2-2	Validation messages States	Green? More designations could be made. The following States have not been designated: US. Please verify.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

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0	Para uso de la Oficina receptora únicamente	
0-1	Solicitud internacional N°	
0-2	Fecha de presentación internacional	
0-3	Nombre de la oficina receptora y Solicitud internacional PCT	

0-4	Forma – PCT/RO/101 petitoria	
0-4-1	Preparado usando	PCT-EASY Versión 2.92 (actualizada 01.07.2003)
0-5	Petición El abajo firmante pide que la presente solicitud sea tramitada de conformidad con el Tratado de Cooperación en materia de Patentes.	
0-6	Oficina Receptora (especificada por el solicitante)	Oficina de Patentes y Marcas de los Estados Unidos (USPTO) (RO/US)
0-7	Referencia de archivo de solicitantes o agentes	GY85CIP2 PCT
I	TITULO DE LA INVENCION	COMPOSICIÓN Y ACTIVIDAD ANTIVIRAL DE DERIVADOS DE PIPERAZINA AZAINDOLOXOACÉTICO SUBSTITUIDOS
II	Solicitante	
II-1	Esta persona es:	Solicitante únicamente
II-2	Solicitante para	Todos los estados designados
II-4	Nombre	BRISTOL-MYERS SQUIBB COMPANY
II-5	Dirección:	P.O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 Estados Unidos de América
II-6	Estado de Nacionalidad	US
II-7	Estado de Residencia	US
II-8	Teléfono No.	609-252-4000
II-9	Fax No.	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	Inventor únicamente
III-1-4	Nombre (APELLIDO, Nombre)	WANG, Tao
III-1-5	Dirección	1312 Town Brooke Middletown, CT 06457 Estados Unidos de América
III-2	Solicitante y/o inventor	
III-2-1	Esta persona es:	Inventor únicamente
III-2-4	Nombre (APELLIDO, Nombre)	ZHANG, Zhongxing

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III-2-5	Dirección:	14 Martleshamheath Lane Madison, CT 06443 Estados Unidos de América
III-3	Solicitante y/o inventor	
III-3-1	Esta persona es:	Inventor únicamente
III-3-4	Nombre (APELLIDO, Nombre)	MEANWELL, Nicholas, A.
III-3-5	Dirección:	15 Valli Drive East Hampton, CT 06424 Estados Unidos de América
III-4	Solicitante y/o inventor	
III-4-1	Esta persona es:	Inventor únicamente
III-4-4	Nombre (APELLIDO, Nombre)	KADOW, John, F.
III-4-5	Dirección:	9 Quarry run Wallingford, CT 06492 Estados Unidos de América
III-5	Solicitante y/o inventor	
III-5-1	Esta persona es:	Inventor únicamente
III-5-4	Nombre (APELLIDO, Nombre)	YIN, Zhiwei
III-5-5	Dirección:	234 Sherman Avenue, Apt. 80 Meriden, CT 06450 Estados Unidos de América
III-6	Solicitante y/o inventor	
III-6-1	Esta persona es:	Inventor únicamente
III-6-4	Nombre (APELLIDO, Nombre)	XUE, Qiufen, May
III-6-5	Dirección:	75 Barrington Way Glastonbury, CT 06033 Estados Unidos de América
III-7	Solicitante y/o inventor	
III-7-1	Esta persona es:	Inventor únicamente
III-7-4	Nombre (APELLIDO, Nombre)	REGUEIRO-REN, Alicia
III-7-5	Dirección:	69 Greenview Terrace Middletown, CT 06457 Estados Unidos de América
III-8	Solicitante y/o inventor	
III-8-1	Esta persona es:	Inventor únicamente
III-8-4	Nombre (APELLIDO, Nombre)	MATISKELLA, John, D.
III-8-5	Dirección:	130 High Hill Road Wallingford, CT 06492 Estados Unidos de América
III-9	Solicitante y/o inventor	
III-9-1	Esta persona es:	Inventor únicamente
III-9-4	Nombre (APELLIDO, Nombre)	UEDA, Yasutsugu
III-9-5	Dirección:	46 Olde Orchard Road Clinton, CT 06413 Estados Unidos de América
IV-1	La persona abajo identificada se designa/ha sido designada para actuar en nombre del/ de los solicitante(s) ante las	Agente

	administraciones internacionales competentes como:	
IV-1-1	Nombre (APELLIDO, Nombre)	DUBOFF, Samuel
IV-1-2	Dirección	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No.	203-677-7787
IV-1-4	Fax No.	203-677-6900
IV-1-5	Numero de registro del agente	25,969
IV-2	Agentes adicionales	Agentes adicionales con la misma dirección como el primer agente nombrado
IV-2-1	Nombre (s)	BABAJKO, Suzanne (32,880); BAXAM, Deanna (45,266); BELFIELD, Jing (45,914), BUCHHOLZ, Briana (39,123); D'AMICO, Stephen, C. (46,652); DAVIS, Stephen (26,693); DUNCAN, Laurelee (44,096); GIBBONS, Maureen (44,121); GOLIAN, Paul, D. (42,591); KLEIN, christopher (34,363); LANGE, Keith (44,201); O'BRIEN, Maureen (42,043); PATEL, Rena (41,412), PEIST, Kenneth (45,006); PROVOOST, Jonathan (44,292); RODNEY, Burton (22,076); SHER, Audrey, (39,024); ALGIERI, Aldo (31,697); MAKUJINA, Shah (41.174); RYAN, Richard (30,491); VANATEEN, Mary, K. (39,408); VOLLES, Warren, K. (33,810); KORSEN, Elliott (32,705); LAMERDIN, John (44,858); DUNCAN, Sammy (46,675); EPPERSON, James (52,867); BOGIE, Terence, J. (44,544)
V	Designación de estados	
V-1	Patente Regional (otros tipos de protección si los hay se especifican entre paréntesis después de la designación concerniente)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW y cualquier otro estado que es un estado contratante del protocolo de Harare y del PCT. EA: AM AZ BY KG MD RU TJ TM y cualquier otro estado que es un estado contratante de la convención de patentes eurasiáticos y del PCT EP: AT BE BG CH&LI CY CZ DE

		DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR y cualquier otro estado que son un estado contratante de la convención de patentes Europea y del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro estado que son estados miembros de OAPI y un estado contratante del estado del PCT
V-2	Patente Nacional (otros tipos de protección si los hay se especifican entre paréntesis después de la designación concerniente)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
V-5	Declaración de Designación Precautoria Además de las designaciones hechas bajo los puntos V-1, V-2 y V-3, el solicitante también hace bajo la Regla 4.9(b) todas las designaciones que puedan permitirse bajo el PCT excepto cualquier designación de los Estados indicados bajo el punto V-6 siguiente. El solicitante declara que aquellas designaciones adicionales están sujetas a la confirmación y que cualquier designación que no se confirme antes de la expiración de 15 meses a partir de la fecha de prioridad serán apreciadas como retiradas por el solicitante en la expiración de este tiempo límite	
V-6	Exclusión(s) para designaciones preventivas	NINGUNO
VI-1	Solicitud de reivindicación de prioridad previa nacional	
VI-1-1	Fecha de presentación	7 Agosto 2002 (07.08.2002)
VI-1-2	Número	10/214,982
VI-1-3	País	US
VI-6	Solicitud de documento de prioridad Se ruega a la Oficina receptora que prepare y transmita a la Oficina Internacional una copia certificada de la	VI-1

	solicitud anterior/de las solicitudes anteriores identificada(s) supra como punto o punto(s)		
VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina de Patentes y Marcas de Estados Unidos de Norteamérica (USPTO) (ISA/US)	
VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración como para la identidad del inventor	-	
VIII-2	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para solicitar y garantizar una patente	-	
VIII-3	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para reivindicar la prioridad de la solicitud previa	-	
VIII-4	Declaración de los inventores (sólo para los propósitos de designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripciones o excepciones no perjudiciales para carecer de novedad	-	
IX	Lista de revisión	Número de hojas	Archivos electrónicos anexos
IX -1	Petitorio	6	-
IX -2	Descripción	578	-
IX-3	Reivindicaciones	34	-
IX -4	Resumen	1	EZABST00-TXT
IX -5	Dibujos	0	-
IX-7	Total	619	
	Puntos acompañantes	Papel de documento(s) anexo	Archivo(s) electrónico anexo
IX-8	Hoja de calculo de tasa	✔	
IX-16	Listado de secuencia en forma legible en computadora	✔	
IX-17	PCT-EASY disco	-	Disco
IX-16-(ii)	Copias adicionales que incluyen, donde aplica, la copia para los propósitos de la búsqueda internacional bajo la Regla 13ter	Postal de tarjeta de recepción, certificado de correo express, Certificación	
IX-19	Se sugiere la figura de los dibujos para acompañar el resumen en el momento de su publicación.		

IX-20	Idioma de presentación de la solicitud internacional de patente	INGLES
X-1	Firma del solicitante o del mandatario	Rúbrica
X-1-1	Nombre (primer, último)	DUBOFF, Samuel
	PARA LA OFICINA RECEPTORA ÚNICAMENTE	
10-1	Fecha efectiva de recepción de la pretendida solicitud internacional	
10-2 10-2-1 10-2-2	Dibujos Recibidos No recibidos	
10-3	Fecha efectiva de recepción, rectificada de la recepción ulterior pero dentro del plazo, de documentos o de dibujos que completa la pretendida solicitud internacional	
10-4	Fecha de recepción, dentro del plazo de las correcciones solicitadas según el Articulo 11(2) del PCT	
10-5	Autoridad de búsqueda internacional	ISA/US
10-6	Transmisión de la copia para la búsqueda diferida hasta que se pague la tasa de búsqueda	
	PARA USO UNICAMENTE DE LA OFICINA INTERNACIONAL	
11-1	Fecha de recepción del ejemplar Original por la Oficina Internacional	

GY0085A-WO-PCT
AM - file
never from abandon
- already ofed
in FDS.
SFB
1091

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED
BMS PATENT LAW
NOV 07 2003
Docketed Item US-IDS-CIP-GY0085A 7/5/04
Due Date US-IDS-CIP-GY0085A 7/5/04
Attorney

To:
SAMUEL DUBOFF
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION
(PCT Rule 44.1)

Applicant's or agent's file reference GY8SCIP2 PCT	Date of Mailing (day/month/year) 05 NOV 2003 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US03/24415	International filing date (day/month/year) 04 August 2003 (04.08.2003)
Applicant BRISTOL-MYERS SQUIBB COMPANY	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Emily Bernhardt Telephone No. (703) 308-1235

Form PCT/ISA/220 (April 2002) (*See notes on accompanying sheet*)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GY85CIP2 PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/24415	International filing date (*day/month/year*) 04 August 2003 (04.08.2003)	(Earliest) Priority Date (*day/month/year*) 07 August 2002 (07.08.2002)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.
   ☐ None of the figures

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GY85CIP2 PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/24415	International filing date (*day/month/year*) 04 August 2003 (04.08.2003)	(Earliest) Priority Date (*day/month/year*) 07 August 2002 (07.08.2002)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant. ☐ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/24415

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/496, 31/497, 31/506; C07D 487/04.
US CL : 514/252.11, 252.18, 253.04; 544/295, 357, 362.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/252.11, 252.18, 253.04; 544/295, 357, 362.

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/0061892 A1 (WANG et al.) 23 May 2002 (23.05.2002), see entire document especially pages 4-7 and page 34, left column.	1-9,11-15,47-49,54-66

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2003 (19.10.2003)	05 NOV 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Emily Bernhardt Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

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TRATADO DE COOPERACION EN MATERIA DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACI NAL
(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia al expediente del solicitante o del mandatario	PARA ACCION ADICIONAL	ver Notificación de la Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, en donde aplique el inciso 5 posterior
GY85CIP2 PCT		
No. de solicitud internacional	Fecha de presentación internacional (día/mes/año)	(Fecha de Prioridad) (La más cercana) (día/mes/año)
PCT/US 03/24415	4 Agosto 2003 (04.08.2003)	7 Agosto 2002 (07.08.2002)
Solicitante		
BRISTOL-MYERS SQUIBB COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de la Búsqueda Internacional y se transmite al solicitante de conformidad con el Artículo 18. Se transmite una copia a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 2 hojas

☒ También está acompañado de una copia de cada documento de la técnica anterior citado en este reporte.

1. Bases del reporte.

a. Con respecto al Lenguaje, la búsqueda internacional se ha llevado a cabo en base a la solicitud internacional en el lenguage en el que se presentó, salvo que se indique lo contrario bajo este punto.

☐ La búsqueda internacional se ha llevado a cabo en base a la traducción de la solicitud internacional presentada a esta autoridad (Regla 23.1(b)).

b. Con respecto a cualquier secuencia de aminoácido y/o nucleótido descrito en la solicitud internacional, el reporte internacional se llevó a cabo en base al listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentado junto con la solicitud internacional en forma leible en computadora.

☐ presentada posteriormente a esta Autoridad en forma escrita

☐ presentada posteriormente a esta Autoridad en forma leible en computadora

☐ la declaración de que el listado de secuencia presentado posteriormente no va más allá de la descripción en la solicitud internalconal como se presentó.

☐ la declaración de que la información registrada en la forma leible en computadora es idéntica al listado de secuencia escrito que se ha presentado

2. ☐ Ciertas reivindicaciones no son localizables (ver el Cuadro I).

3. ☐ La unidad de la invención es deficiente (ver el Cuadro II).

4. Con respecto al título,

☒ el texto se aprueba tal como lo presentó el solicitante,

☐ Esta Autoridad ha establecido que el texto sea como algue:

5. Con respecto al resumen, ☒ el texto se aprueba tal como lo presentó el solicitante.

☐ esta Autoridad ha establecido el texto, de acuerdo con la Regla 38.2(b), tal como aparece en el Cuadro III. El solicitante puede, dentro de un mes a partir de la fecha de envio por correo de este reporte de búsqueda internacional, proporcional comentarios a esta autoridad.

6. La figura de los dibujos que se va a publicar con el resumen es la Figura No. _____

☐ como lo sugirió el solicitante. ☐ Ninguna de las figuras

☐ porque al solicitante le faltó sugerir una figura.

☐ Porque esta figura caracteriza mejor la invención.

REPORTE DE BUSQUEDA INTERNACIONAL

No. de Solicitud Internacional
PCT /US 03/24415

A. CLASIFICACION DEL ASUNTO RELACIONADO
IPC(7) : A61K 31/496, 31/497, 31/506; C07D 487/04,
US CL: 514/252.11, 252.18, 253.04; 544/295, 357, 382,

De acuerdo con la Clasificación Internacional de Patentes (IPC) o tanto la clasificación nacional como la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación)
U.S.: 514/252.11, 252.18, 253.04; 544/295, 357, 382.

Documentación buscada diferente de la documentación mínima, al grado que estos documentos se incluyen en los campos buscados.

Base de datos, electrónica, consultada durante la búsqueda internacional (nombre de la base de datos, donde se puede practicar, términos de búsqueda usados).
BUSQUEDA DE ESTRUCTURAS EN LÍNEA CAS

C. DOCUMENTOS QUE SE CONSIDERAN PERTINENTES

Categoría*	Citación del documento, con indicación, donde es apropiado, de los pasajes pertinentes	Pertinente para la reivindicación No
X	US 2002/0061892 A1 (WANG et al.), 23 Mayo 2002 (23.05.2002), ver documento completo especialmente páginas 4-7 y página 34, de la columna de la izquierda	1-9, 11-15, 47-49, 54-66

☐ Documentos adicionales se listan en la continuación del cuadro C.

☐ Los miembros de la familia de patentes se listan en el anexo

* Categoría especial de los documentos citados:

"A" Documento que define el estado general de la técnica, que no se considera que es de pertinencia particular

"E" Documento anterior, pero publicado en o después de la fecha de presentación internacional

"L" Documento que puede crear dudas de la reivindicación(es) de prioridad o que se cita para establecer la fecha de publicación de otra situación u otra razón especial (como se especifique)

"O" Documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" Documento publicado antes de la fecha de presentación internacional, pero después de la fecha de prioridad reivindicada

"T" documento posterior publicado después de la fecha de presentación internacional o la fecha de prioridad, y que no provoca conflicto con la solicitud, pero se cita para entender el principio o teoría que trata la invención

"X" documento de pertinencia particular; la invención reivindicada no se puede considerar nueva o no se puede considerar que comprende un paso inventivo cuando el documento se toma solo

"Y" documento de pertinencia particular; la invención reivindicada no se puede considerar que comprende un paso inventivo cuando el documento se combina con uno o más de estos documentos, estas combinaciones son obvias para una persona experta en la técnica

"&" documento miembro de la familia de patentes

Fecha de la actual terminación de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
19 Octubre 2003 (19.10.2003)	5 Noviembre 2003

Nombre y dirección de envío ISA	Funcionario autorizado
Mail Stop PCT, Attn: ISA/US Comisionado para Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Fax. No.: (703) 305-3230	Rúbrica Emily Bernhardt Teléfono No. (703) 308-1235

Forma PCT/ISA/210 (hoja 2) (Julio 1992

PATENT COOPERATION TREATY

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10/4

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

DUBOFF, Samuel
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Date of mailing (day/month/year) 07 October 2003 (07.10.03)	
Applicant's or agent's file reference GY85CIP2 PCT	IMPORTANT NOTIFICATION
International application No. PCT/US03/24415	International filing date (day/month/year) 04 August 2003 (04.08.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 07 August 2002 (07.08.02)
Applicant BRISTOL-MYERS SQUIBB COMPANY	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
07 Augu 2002 (07.08.02)	10/214,982	US	03 Octo 2003 (03.10.03)

NOV - 4
RECEIVED
BMS PATENT LAW
OCT 24 2003
Docketed Item
Due Date

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Attorney A. LEDO PONTES
Facsimile No. (41-22) 338.89.95	Telephone No. (41-22) 338 7048

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

PTO-1382 (Rev. 04-2003) (Modified) PCTUS2.FRP /REV03

Date	20-02-04
International Application No.	PCT/US03/24415
Attorney Docket No.	GY85A CIP2

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I. Certification under 37 CFR 1.10 (If applicable)

EV 404516674US	20-02-04
Express Mail mailing number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Signature of person mailing correspondence	Samuel J. DuBoff
	Typed or printed name of person mailing correspondence

II. ☐ **New International Application**

TITLE		Earliest priority date (Day/Month/Year)

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was not made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).*

application no.		filed on	
application no.		filed on	

D. ☐ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages ____ and ☐ **DOES NOT ALTER** ☐ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15.

III. ☐ **A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:**

A. ☐ A Request for An Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

D. ☐ Submission of Priority Documents

Priority document		Priority document	

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ **A Request for Rectification under PCT 91** ☐ **A Petition** ☐ **A Sequence Listing Diskette**

V. ☒ **Other (please specify):** PCT Demand for International Preliminary Examination; PCT Demand Fee Calculation Sheet

The person signing this form is the:		
☐	Applicant	Samuel J. DuBoff
☒	Attorney/Agent (Reg. No.) 25,969	Typed name of signer
☐	Common Representative	Signature

U.S. Department of Commerce: Patent and Trademark Office

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The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference GY85A CIP2
International application No. PCT/US03/24415	International filing date *(day/month/year)* 05 August 2003 (05-08-03)	(Earliest) Priority date *(day/month/year)* 07 August 2002 (07-08-02)
Title of invention COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED AZAINDOLEOXOACETIC PIPERAZINE DERIVATIVES		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of*	Telephone No. 609-252-3414
BRISTOL-MYERS SQUIBB COMPANY P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America	Facsimile No. 609-252-4526
	Teleprinter No.
	Applicant's registration No. with the Office

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

3100

International application No.
PCT/US03/24415

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DUBOFF, Samuel J.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
United States of America

Telephone No.
203-677-7787

Facsimile No.
203-677-6900

Teleprinter No.

Agent's registration No. with the Office
25,969

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description
☐ as originally filed
☐ as amended under Article 34

the claims
☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings
☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d)).

4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☒ which is the language of a translation furnished for the purposes of international search.

☒ which is the language of publication of the international application.

☒ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

1101

Sheet No. .3.

International application No.
PCT/US03/24415

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ tables in computer readable form related to sequence listing
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Samuel J. DuBoff, Agent

Samuel J. DuBoff

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

— *deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Name: Samuel J. DuBoff

Signature:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No.	PCT/US03/24415
Applicant's or agent's file reference	GY85A CIP2

For International Preliminary Examining Authority use only

Date stamp of the IPEA

Applicant

BRISTOL-MYERS SQUIBB COMPANY

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	600.00 P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	148.00 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	748.00 TOTAL	

MODE OF PAYMENT

- ☒ authorization to charge deposit account with the IPEA (see below)
- ☐ cash
- ☐ cheque
- ☐ revenue stamps
- ☐ postal money order
- ☐ coupons
- ☐ bank draft
- ☐ other *(specify):*

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ US

☒ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 19-3880

Date: February 20, 2004

Name: Samuel J. DuBoff

Signature: Samuel J. DuBoff

Form PCT/IPEA/401 (Annex) (January 2004)
LegalStar 2004, Form PCTDFEE

See Notes to the fee calculation sheet

Brigard & Castro

SANTA FE DE BOGOTA - COLOMBIA

4103

PODER

Yo (nosotros)

C.C.

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA**, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de empresa, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, expedición de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) -faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia; con facultades para recibir notificaciones y designar apoderados judiciales y extrajudiciales.

Otorgado y firmado en

hoy de

Firma

Nombre

Cargo

PRESENTACION PERSONAL
El anterior escrito de esta Oficio se corresponde con el original que se ha tenido a la vista
27 ENE. 2005
NOTARIO CUARENTA Y SEIS
Luis [illegible]

POWER OF ATTORNEY

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciled in Princeton, New Jersey, USA

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, of Santafé de Bogotá, Colombia, my (our) true and lawfull attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Princeton, New Jersey, USA

this 14th day of April 1999

Signature BRISTOL-MYERS SQUIBB COMPANY

Name Stephen B. Davis

Title Associate Counsel Patents

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, es miembro y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (C RPORATION)

On this 14th day of April of 1998
personally appeared before me
Stephen.B. Davis
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the

Associate Counsel Patents

of BRISTOL-MYERS SQUIBB COMPANY

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to edifer this Power of Attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Delaware
under date of November 13, 1989

and that he (she) who grants the present power of attorney is its Representative.

Diane C. Bartram

Diane C. Bartram Public Notary (Seal)
Notary Public of New Jersey
My Commission Expires March 9, 2000

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this 14th day of April of 1999
personally appeared before me

Stephen B. Davis

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) said document(s) the uses and purposes therein expressed.

27 ENE

Diane C. Bartram

Notary Public (Seal)

Diane C. Bartram
Notary Public of New Jersey
My Commission Expires March 9, 2000

LEGALIZACION ANTE CONSUL COLOMBIANO ES REQUERIDA.

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED.

1104

1972

STATE OF NEW JERSEY, County of Mercer } ss.

I, CATHERINE DiCOSTANZO, Clerk of the County of Mercer,

Do Hereby Certify that Diane C. Bartus Esq., whose name is subscribed to the acknowledgment, proof or affidavit of the annexed instrument, and thereon written, is and was at the time of taking the same, a Notary Public in and for said State, dwelling in said County, commissioned and sworn and duly authorized by the laws thereof to take the proofs and acknowledgments of deeds or other instruments of writing, and affidavits to be recorded in said State, and that I am well acquainted with the handwriting of said official, and verily believe that the signature is genuine.

Further Certify that impression of Seal of Notaries Public not required by law be filed in my office.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of said County and Courts, at Trenton this 15th day of April A.D. nineteen hundred and ninety-one

Catherine DiCostanzo ..... Mercer County Clerk.

En la Notaría Cuarenta de este Círculo se protocolizó la presente fotocopia que coincide con el original que se tuvo a la vista.

27 ENE 2005

NOTARIO CUARENTA

1105

1099

EL SUSCRITO CONSUL DE COLOMBIA

VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

CERTIFICA

Que el Señor (a), **CATHERINE Dicostanzo** Clerck del condado de Mercer estado de New Jersey, autenticó la firma de la notario(a) publico(a) sr (a). **DIANE C. BARTRAN** del estado de New Jersey, Estados Unidos de América y quien ejercia las funciones antes expresadas, y que la firma y sello que en el documento aparecen como suyos, son los que usa y acostumbra en sus actos oficiales;

Que la notario(a) antes citada autenticó la firma del señor **STEPHEN B. DAVIS-** quien actua en calidad de Asesor de Patentes de la Compañia **BRISTOL-MEYERS SQUIBB COMPANY** sociedad que existe y esta legalmente organizada bajo las leyes del estado de Delaware U.S.A

Que ha tenido a la vista los documentos probatorios de los hechos citados y constatados por el notario público y el County Clerck del estado de New Jersey, los cuales forman parte integral del presente documento.

Se expide la presente certificación en cumplimiento de los artículos 259 del Código de Procedimiento Civil y 480 del Código de Comercio y a solicitud del interesado el 20 de Abril de 1999.

NO SE ASUME RESPONSABILIDAD POR EL CONTENIDO DEL DOCUMENTO ADJUNTO.

Se ha pagado IMPUESTO DE TIMBRE Y DERECHOS CONSULARES.

VALOR CUENTA Y SIETE DOLARES US$57.oo RECIBO No. 200283

Federico Mejía Mejía
Cónsul de Colombia

Ante la Notaría Cuarenta de esta ciudad se extendió la presente fotocopia que coincide con el original que se tuvo a la vista

27 ENE. 2004

NOTARIO CUARENTA (E)
Luis Alexander Ardila Betancourt
Bogotá, D.C., Colombia

MINISTERIO DE RELACIONES EXTERIORES

044498

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMP[illegible] LAS FUNCIONES INDICA[illegible]

NO SE AGUME RESPONSABILIDAD DEL TEXTO

99 APR 29 AM 9:43

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

NOTARIO CUARENTA (E)

27 ENE 2000

1106

TRADUCCION OFICIAL No. 260/99 de las Legalizaciones que se encuentran a continuación de un Poder otorgado por BRISTOL-MYERS SQUIBB COMPANY, una sociedad domiciliada en Princenton, New Jersey, Estados Unidos de América al doctor RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, D.C., Colombia, del inglés al español, las cuales para su identificación se sellan con el Sello del Traductor al mismo tiempo que la presente.-

++

ANEXOS: El Poder arriba mencionado, Certificaciones Notariales, Certificación de las Firmas Notariales, Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

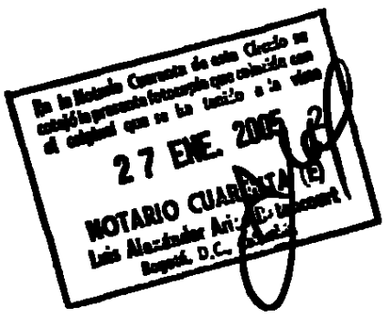
++

Diane C. Bartram (firmado)
Notario Público
HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

++

Diane C. Bartram (firmado)
Notario Público



HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

++

Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

HUGO NAVARRO ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL

1107

++

Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

++

Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

++

Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

++

En la Notaría Cuarenta de este Círculo se extendió la presente fotocopia que coincide con el original que se le mostró a la vista.
27 ENE. 2005
NOTARIO CUARENTA (40)
Luis Mauricio Ariza Montenegro
Bogotá, D.C., Colombia

ESTADO DE NEW JERSEY
Condado de Mercer

Yo, CATHERINE DiCOSTANZO, Escribano del Condado de Mercer,

Por Medio del Presente Certifico que Diane C. Bartram, cuyo nombre está suscrito al reconocimiento, prueba o declaración jurada del instrumento anexo, y en éste escrito, es y era en el momento de tomar el mismo, un NQtario Público en y para dicho Estado, residente en dicho Condado, comisionado y juramentado y debidamente autorizado por las leyes de éste para tomar las pruebas y recono-

HUGO NAVARRO ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL

1108

cimientos de escrituras u otros instrumentos escritos, y declaraciones juradas para ser registrados en dicho Estado, y que estoy familiarizado con la caligrafía de dicho funcionario, y de veras creo que la firma es genuina.
Además Certifico que la impresión del Sello de Notarios Públicos no está requerida por la ley para ser presentada en mi oficina.

En Testimonio de lo Cual, he firmado el presente de mi puño y letra y fijado el sello de dichos Condado y Tribunales, en Tranton este día 15 de Abril del A.D. de mil novecientos noventa y nueve.

Catherine DiConstanzo (fdo.) Escribano del Condado de Mercer.

SELLO EN RELIEVE.

++

EN ESPAÑOL: La Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América bajo el número 200283 de fecha 20 de Abril de 1999; Autenticación hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 044498 de fecha 29 de Abril de 1999.

(Pagado Impuesto de Timbre y Derechos Consulares por valor de $57.oo Dólares).

++

ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS.

ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL
Res. 1876 Diciembre 1997

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que coincide con el original que se le tuvo a la vista
27 ENE. 2005
NOTARIO CUARENTA (E)
Luis Alexander Ariza Betancourt
Bogotá D.C. Colombia

Resolución número 1876 del Ministerio de Justicia.

Fecha: Mayo 3 de 1999.

MINISTERIO DE RELACIONES EXTERIORES
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICA...
0 4 6 2 0 7

99 MAY -4 AM 11:09
JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.
NO SE ASUME RESPONSABILIDAD DEL TEXTO

REPÚBLICA DE COLOMBIA

GAVIRIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

Datos de la oficina de registro

Clase de oficina: Registraduría [ ] Notaría [X] Consulado [ ] Corregimiento [ ] Insp. de Policía [ ] Código 9995

País - Departamento - Municipio - Corregimiento o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C NOTARIA 32.

Datos del inscrito

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción	Hora	Número de certificado de defunción
Año 2004 Mes 10 Día 30	04:10 PM	A- 2094375.

Presunción de muerte

Juzgado que profirió la sentencia	Fecha de la sentencia
	Año Mes Día

Documento presentado

Autorización judicial [ ] Certificado Médico [X]

Nombre y cargo del funcionario

ANDRES DIAZ CAMPOS.
R.M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO II.

Documento de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	

Primer testigo

Apellidos y nombres completos

Documento de identificación (Clase y número)	Firma

Segundo testigo

Apellidos y nombres completos

Documento de identificación (Clase y número)	Firma

Fecha de inscripción	Nombre y firma del funcionario que autoriza
Año 2004 Mes 11 Día 02	BLANCA [illegible] RESTREPO NOTARIA

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGIST

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO TELEGRAFICO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO : QUE:

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: ST 62209
que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004

NOTARIA 32 DEL C...
DE BOGOTA D.C.
HELBON FLOREZ G.
SECRETARIO DELEGADO PARA COBRAR
DECRETO 1384 DE 1989

1104

1110

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificacion del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05010044 00000000 Folios: 1103
Fecha (mm): 2005-02-08 11:27:27
Tramite : 011 PCT-PATENT 379 FISL NAC1 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

[redacted]

Industria y Comercio
SUPERINTENDENCIA

. Folio 1185

2020
Bogotá, D.C.;

Doctor
HECTOR GOMEZ MEJIA
Apoderado
BRISTOL – MYERS SQUIBB COMPANY

Oficio N° 12304

12304

ASUNTO:	Radicación N°	05-10844
	Solicitud internacional	PCT/US2003/024415
	Fecha inicio fase nacional	07/03/2005
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 04 MAR. 2005.

202027

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia