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División de Nuevas Creaciones

SOLICITUD

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ENTRAJA EN FASE NACIONAL

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06-49957

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AGENTES ANTIVIRALES DE DIAZAINDOL-DICARBONIL-PIPERAZINILO

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107D487/04, A61K31/5025,

A61K31/519, A61P31/12, 31/18

71. SOLICITANTE

BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO

PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. APODERADO

1 JUAN PABLO CADENA SARMENTO

22. SANTAFE DE BOGOTA, D.C.

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1

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**Industria y Comercio**  
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## FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

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## SOLICITUD DE:

☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☒ Capítulo I.☐ Capítulo II.

2

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(71)

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## IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual \_\_\_\_\_

Número \_\_\_\_\_

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Cual \_\_\_\_\_

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Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)

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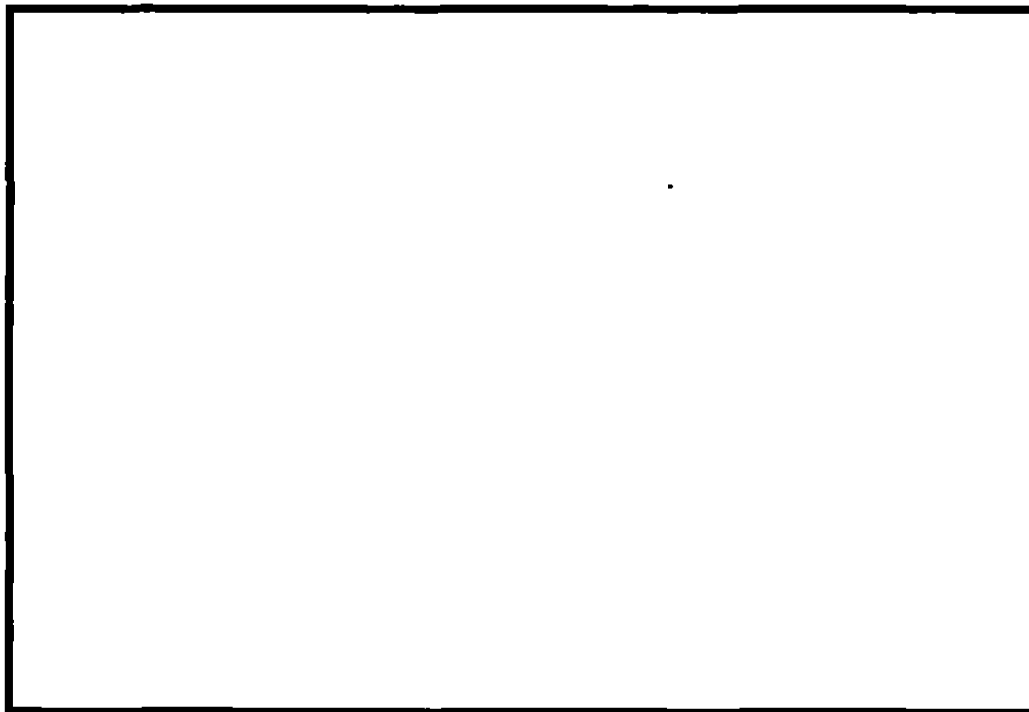
60/525,624

9 Comprobante de pago No. 06-24,289Fecha 24-05-2006

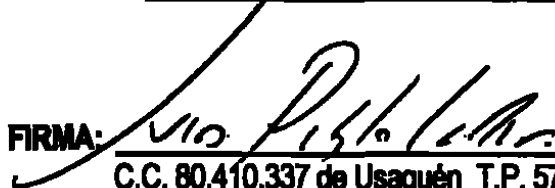
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$463.000
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- ☒ Documento de cesión del inventor al solicitante o a su causante.
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- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
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- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Extracto para publicación y tarjeta de archivo temático.  
Tarjeta de Propietarios

## 11 FIGURA CARACTERÍSTICA:



## 12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTOFIRMA:   
C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE           | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO      |
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| BRIGARD & CASTRO LTDA | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 44793612 | 27/03/2006 | 21,060,000.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. RENTISTICO          | CONCEPTO                            | TOTAL CONCEPTO |
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| 1 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 463,000.00     |
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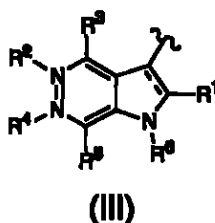
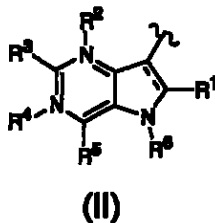
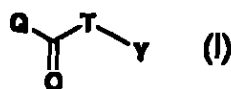
(74) Agents: DUBOFF, Samuel et al.; Bristol-Myers Squibb  
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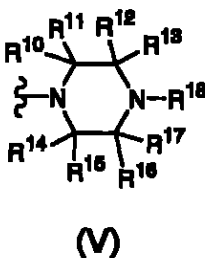
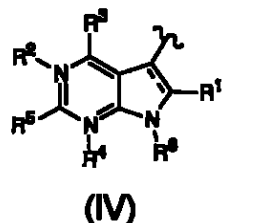
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[Continued on next page]

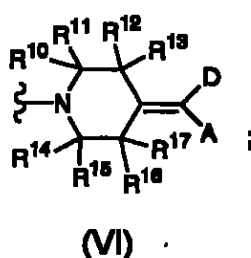
(54) Title: DIAZAINDOLE-DICARBONYL-PIPERAZINYL ANTIVIRAL AGENTS



and



and



(57) Abstract: The invention comprises substituted diazaindole-dicarbonyl-piperaziny derivatives of general Formula (I) wherein: Q is selected from the group consisting of Formulas (II), (III) and (IV) may represent a bond; T is -C(O)- or -CH(CN)-; and -Y- is selected from the group consisting of Formulas (V) and (VI) compositions thereof and their use for treating HIV infection.

Folia 4 y 5 depicts 6 examples

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FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, 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, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW,

BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, 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, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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DIAZAINDOLE-DICARBONYL-PIPERAZINYL ANTIVIRAL AGENTS 96

## CROSS-REFERENCE TO RELATED APPLICATIONS

5           This application claims the benefit of U.S. Provisional Application Serial Number 60/525,624 filed November 26, 2003.

## BACKGROUND OF THE INVENTION

## Field of the Invention

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

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## 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 ten nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations (zidovudine or AZT (or Retrovir<sup>®</sup>), didanosine (or Videx<sup>®</sup>), stavudine (or Zerit<sup>®</sup>), lamivudine (or 3TC or Epivir<sup>®</sup>), zalcitabine (or DDC or Hivid<sup>®</sup>), abacavir succinate (or Ziagen<sup>®</sup>), Tenofovir disoproxil fumarate salt (or Viread<sup>®</sup>), Combivir<sup>®</sup> (contains -3TC plus AZT), Trizivir<sup>®</sup> (contains abacavir, lamivudine, and zidovudine) and Emtriva<sup>®</sup> (emtricitabine); three non-nucleoside reverse transcriptase inhibitors: nevirapine (or Viramune<sup>®</sup>), delavirdine (or Rescriptor<sup>®</sup>) and efavirenz (or Sustiva<sup>®</sup>), nine peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra<sup>®</sup> (lopinavir and

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Ritonavir), Atazanavir (Reyataz<sup>®</sup>), Fosamprenavir<sup>®</sup> and one fusion inhibitor which targets viral gp41 T-20 (FUZEON<sup>®</sup>). 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). A recent overview of non-nucleoside

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reverse transcriptase inhibitors: perspectives on novel therapeutic compounds and strategies for the treatment of HIV infection. has appeared (Buckheit, reference 99). A review covering both NRTI and NNRTIs has appeared (De Clercq, reference 100). An overview of the current state of the HIV drugs has been published (De Clercq, reference 101).

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 transcriptase 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). 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).

Structurally related aza-indole amide derivatives have been disclosed previously (Kato et al, Ref. 23(a); Levacher et al, Ref. 23(b); 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 monoaza-indole mono-amide rather than oxoacetamide derivatives, and there is no mention of the use of these compounds for treating viral infections, particularly HIV.

New drugs for the treatment of HIV are needed for the treatment of patients who become resistant to the currently approved drugs described above which target reverse transcriptase or the protease. One approach to obtaining these drugs is to find molecules which inhibit new and different targets of the virus. A general class of inhibitors which are under active study are HIV entry inhibitors. This general classification includes drugs aimed at several targets which include chemokine receptor (CCR5 or CXCR4) inhibitors, fusion inhibitors targeting viral gp41, and inhibitors which prevent attachment of the viral envelope, gp120, to its human cellular target CD4. A number of reviews or general papers on viral entry inhibitors

have recently appeared and some selected references are:

*Chemokine receptor antagonists as HIV entry inhibitors. Expert Opinion on Therapeutic Patents* (2004), 14(2), 251-255.

5

*Inhibitors of the entry of HIV into host cells. Meanwell, Nicholas A.; Kadow, John F. Current Opinion in Drug Discovery & Development* (2003), 6(4), 451-461.

*Virus entry as a target for anti-HIV intervention. Este, Jose A. Retrovirology Laboratory irsiCaixa, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain. Current Medicinal Chemistry* (2003), 10(17), 1617-1632.

*New antiretroviral agents. Rachline, A.; Joly, V. Service de Maladies Infectieuses et Tropicales A, Hopital Bichat-Claude Bernard, Paris, Fr. Antibiotiques* (2003), 5(2), 77-82.

*New antiretroviral drugs. Gulick, R. M. Cornell HIV Clinical Trials Unit, Division of International Medicine and Infectious Diseases, Weill Medical College of Cornell University, New York, NY, USA. Clinical Microbiology and Infection* (2003), 9(3), 186-193.

*Sensitivity of HIV-1 to entry inhibitors correlates with envelope/coreceptor affinity, receptor density, and fusion kinetics. Reeves, Jacqueline D.; Gallo, Stephen A.; Ahmad, Navid; Miamidian, John L.; Harvey, Phoebe E.; Sharron, Matthew; Pohlmann, Stefan; Sfakianos, Jeffrey N.; Derdeyn, Cynthia A.; Blumenthal, Robert; Hunter, Eric; Doms, Robert W. Department of Microbiology, University of Pennsylvania, Philadelphia, PA, USA. Proceedings of the National Academy of Sciences of the United States of America* (2002), 99(25), 16249-16254. CODEN: PNASA6 ISSN: 0027-8424.

*Opportunities and challenges in targeting HIV entry. Biscone, Mark J.; Pierson, Theodore C.; Doms, Robert W. Department of Microbiology, University of*

Pennsylvania, Philadelphia, PA, USA. *Current Opinion in Pharmacology* (2002), 2(5), 529-533.

7/10

*HIV entry inhibitors in clinical development.* O'Hara, Bryan M.; Olson, William C.  
5 Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA. *Current Opinion in Pharmacology* (2002), 2(5), 523-528.

*Resistance mutation in HIV entry inhibitors.* Hanna, Sheri L.; Yang, Chunfu; Owen, Sherry M.; Lal, Renu B. HIV Immunology and Diagnostics Branch, Division of  
10 AIDS, STD, Atlanta, GA, USA. *AIDS* (London, United Kingdom) (2002), 16(12), 1603-1608.

*HIV entry: are all receptors created equal?* Goldsmith, Mark A.; Doms, Robert W. Genencor International, Inc., Palo Alto, CA, USA. *Nature Immunology* (2002),  
15 3(8), 709-710. CODEN: NIAMCZ ISSN: 1529-2908.

*Peptide and non-peptide HIV fusion inhibitors.* Jiang, Shibo; Zhao, Qian; Debnath, Asim K. The New York Blood Center, Lindale F. Kimball Research Institute, New York, NY, USA. *Current Pharmaceutical Design* (2002), 8(8), 563-580.

20

A series of recent publications and disclosures characterize and describe a compound labelled as BMS-806, an initial member of a class of viral entry inhibitors which target viral gp-120 and prevent attachment of virus to host CD4.

25 *A small molecule HIV-1 inhibitor that targets the HIV-1 envelope and inhibits CD4 receptor binding.* Lin, Pin-Fang; Blair, Wade; Wang, Tao; Spicer, Timothy; Guo, Qi; Zhou, Nannan; Gong, Yi-Fei; Wang, H. -G. Heidi; Rose, Ronald; Yamanaka, Gregory; Robinson, Brett; Li, Chang-Ben; Fridell, Robert; Deminie, Carol; Demers, Gwendeline; Yang, Zheng; Zadjura, Lisa; Meanwell, Nicholas; Colonna, Richard.  
30 *Proceedings of the National Academy of Sciences of the United States of America* (2003), 100(19), 11013-11018.



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*Biochemical and genetic characterizations of a novel human immunodeficiency virus type 1 inhibitor that blocks gp120-CD4 interactions.* Guo, Qi; Ho, Hsu-Tso; Dicker, Ira; Fan, Li; Zhou, Nannan; Friberg, Jacques; Wang, Tao; McAuliffe, Brian V.; Wang, Hwei-gene Heidi; Rose, Ronald E.; Fang, Hua; Scarnati, Helen T.; Langley, David R.; Meanwell, Nicholas A.; Abraham, Ralph; Colonna, Richard J.; Lin, Pin-fang. *Journal of Virology* (2003), 77(19), 10528-10536.

*Method using small heterocyclic compounds for treating HIV infection by preventing interaction of CD4 and gp120.* Ho, Hsu-Tso; Dalterio, Richard A.; Guo, Qi; Lin, Pin-Fang. *PCT Int. Appl.* (2003), WO 2003072028A2.

*Discovery of 4-benzoyl-1-[(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)oxoacetyl]-2-(R)-methylpiperazine (BMS-378806): A Novel HIV-1 Attachment Inhibitor That Interferes with CD4-gp120 Interactions.* Wang, Tao; Zhang, Zhongxing; Wallace, Owen B.; Deshpande, Milind; Fang, Haiquan; Yang, Zheng; Zadjura, Lisa M.; Tweedie, Donald L.; Huang, Stella; Zhao, Fang; Ranadive, Sunanda; Robinson, Brett S.; Gong, Yi-Fei; Riccardi, Keith; Spicer, Timothy P.; Deminie, Carol; Rose, Ronald; Wang, Hwei-Gene Heidi; Blair, Wade S.; Shi, Pei-Yong; Lin, Pin-fang; Colonna, Richard J.; Meanwell, Nicholas A. *Journal of Medicinal Chemistry* (2003), 46(20), 4236-4239.

Indole, azaindole and other oxo amide containing derivatives have been disclosed in a number different PCT and issued U.S. patent applications (Reference 93-95, 106, 108, 109, 110, 111, 112, 113, and 114). None of these applications discloses diazindole compounds such as described in this invention. The extra nitrogen of the diazaindole class of molecules provides altered properties especially in combination with specific substituents that are advantageous and not available from the azaindoles. The diazaindoles are easier to access and thus offer the potential to provide patients with lower cost treatments. A series of PCT International Patent applications Bernd Nickel et.al. (reference 107a,b, and c) describes N-indolylglyoxamides for the treatment of cancer. Although some of these compounds contain N-heteroaryl or N-aryl piperazines, the substitution patterns at the other positions are outside the scope of this invention.

Structurally similar diazaindoles with a C-3 oxoacetyl group have also been previously disclosed (Hutchison et al, Ref 5(d); Resnyanskaya et al, Ref 24 (a); Cook et al, Ref 24(b)). However, these molecules differ from those claimed in that they do not contain the piperazine or piperidine moieties and there is no mention of the use of these molecules as antiviral agents, particularly against HIV.

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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## REFERENCES CITED

Patent documents

1. Greenlee, W.J.; Srinivasan, P.C. Indole reverse transcriptase inhibitors. U.S. Patent 5,124,327.

2. Williams, T.M.; Ciccarone, T.M.; Saari, W. S.; Wai, J.S.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Theohrides, A.D. Indoles as inhibitors of HIV reverse transcriptase. European Patent 530907.

20

3. Romero, D.L.; Thomas, R.C.; Preparation of substituted indoles as anti-AIDS pharmaceuticals. PCT WO 93 / 01181.

4. Boschelli, D.H.; Connor, D.T.; Unangst, P.C. Indole-2-carboxamides as inhibitors of cell adhesion. U.S. Patent 5,424,329.

5. (a) Mantovanini, M.; Melillo, G.; Daffonchio, L. Tropol 7-azaindol-3-ylcarboxyamides as antitussive agents. PCT WO 95/04742 (Dompe Spa). (b) Cassidy, F.; Hughes, I.; Rahman, S.; Hunter, D. J. Bisheteroaryl-carbonyl and carboxamide derivatives with 5HT 2C/2B antagonists activity. PCT WO 96/11929. (c) Scherlock, M. H.; Tom, W. C. Substituted 1H-pyrrolopyridine-3-carboxamides. U. S. Patent 5,023,265. (d) Hutchison, D. R.; Martinelli, M. J.; Wilson, T. M. Preparation of pyrrolo[2,3-d]pyrimidines as sPLA2 inhibitors PCT WO 00/00201.

30

4/13

Other Publications

6. Larder, B.A.; Kemp, S.D. Multiple mutations in the HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science*, 1989,  
5 246,1155-1158.
7. Gulick, R.M. Current antiretroviral therapy: An overview. *Quality of Life Research*, 1997, 6, 471-474.
- 10 8. Kuritzkes, D.R. HIV resistance to current therapies. *Antiviral Therapy*, 1997,  
2 (Supplement 3), 61-67.
9. Morris-Jones, S.; Moyle, G.; Easterbrook, P.J. Antiretroviral therapies in HIV-1 infection. *Expert Opinion on Investigational Drugs*, 1997, 6(8),1049-1061.  
15
10. Schinazi, R.F.; Larder, B.A.; Mellors, J.W. Mutations in retroviral genes associated with drug resistance. *International Antiviral News*, 1997, 5,129-142.
11. Vacca, J.P.; Condra, J.H. Clinically effective HIV-1 protease inhibitors.  
20 *Drug Discovery Today*, 1997, 2, 261-272.
12. Flexner, D. HIV-protease inhibitors. *Drug Therapy*, 1998, 338, 1281-1292.
13. Berkhout, B. HIV-1 evolution under pressure of protease inhibitors:  
25 Climbing the stairs of viral fitness. *J. Biomed. Sci.*, 1999, 6, 298-305.
14. Ren, S.; Lien, E. J. Development of HIV protease inhibitors: A survey. *Prog. Drug Res.*, 1998, 51, 1-31.
- 30 15. Pedersen, O.S.; Pedersen, E.B. Non-nucleoside reverse transcriptase inhibitors: the NNRTI boom. *Antiviral Chem. Chemother.* 1999, 10, 285-314.

16. (a) De Clercq, E. The role of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 infection. *Antiviral Research*, 1998, 38, 153-179.
- (b) De Clercq, E. Perspectives of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV infection. *IL Farmaco*, 1999, 54, 26-45.

5

17. Font, M.; Monge, A.; Cuartero, A.; Elorriaga, A.; Martinez-Irujo, J.J.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J.J.; Sarobe, P. and Borras, F. Indoles and pyrazino[4,5-*b*]indoles as nonnucleoside analog inhibitors of HIV-1 reverse transcriptase. *Eur. J. Med. Chem.*, 1995, 30, 963-971.

10

18. Romero, D.L.; Morge, R.A.; Genin, M.J.; Biles, C.; Busso, M.; Resnick, L.; Althaus, I.W.; Reusser, F.; Thomas, R.C and Tarpley, W.G.
- Bis(heteroaryl)piperazine (BHAP) reverse transcriptase inhibitors: structure-activity relationships of novel substituted indole analogues and the identification of 1-[(5-methanesulfonamido-1H-indol-2-yl)-carbonyl]-4-[3-[1-methylethyl)amino]-pyridinyl]piperazine momomethansulfonate (U-90152S), a second generation clinical candidate. *J. Med. Chem.*, 1993, 36, 1505-1508.

15

19. Young, S.D.; Amblard, M.C.; Britcher, S.F.; Grey, V.E.; Tran, L.O.; Lumma, W.C.; Huff, J.R.; Schleif, W.A.; Emmini, E.E.; O'Brien, J.A.; Pettibone, D.J. 2-Heterocyclic indole-3-sulfones as inhibitors of HIV-reverse transcriptase. *Bioorg. Med. Chem. Lett.*, 1995, 5, 491-496.

20

20. Genin, M.J.; Poel, T.J.; Yagi, Y.; Biles, C.; Althaus, I.; Keiser, B.J.; Kopta, L.A.; Friis, J.M.; Reusser, F.; Adams, W.J.; Olmsted, R.A.; Voorman, R.L.; Thomas, R.C. and Romero, D.L. Synthesis and bioactivity of novel bis(heteroaryl)piperazine (BHAP) reverse transcriptase inhibitors: structure-activity relationships and increased metabolic stability of novel substituted pyridine analogs. *J. Med. Chem.*, 1996, 39, 5267-5275.

25

30

21. Silvestri, R.; Artico, M.; Bruno, B.; Massa, S.; Novellino, E.; Greco, G.; Marongiu, M.E.; Pani, A.; De Montis, A and La Colla, P. Synthesis and biological evaluation of 5H-indolo[3,2-*b*][1,5]benzothiazepine derivatives, designed as

conformationally constrained analogues of the human immunodeficiency virus type 1 reverse transcriptase inhibitor L-737,126. *Antiviral Chem. Chemother.* 1998, 9, 139-148.

- 5 22. Fredenhagen, A.; Petersen, F.; Tintelnot-Blomley, M.; Rosal, J.; Mett, H and Hug, P. J. Semicochliodinol A and B: Inhibitors of HIV-1 protease and EGF-R protein Tyrosine Kinase related to Asterriquinones produced by the fungus *Chrysosporium nardarium*. *Antibiotics*, 1997, 50, 395-401.
- 10 23. (a) Kato, M.; Ito, K.; Nishino, S.; Yamakuni, H.; Takasugi, H. New 5-HT<sub>3</sub> (Serotonin-3) receptor antagonists. IV. Synthesis and structure-activity relationships of azabicycloalkaneacetamide derivatives. *Chem. Pharm. Bull.*, 1995, 43, 1351-1357. (b) Levacher, V.; Benoit, R.; Duflos, J; Dupas, G.; Bourguignon, J.; Queguiner, G. Broadening the scope of NADH models by using chiral and non
- 15 chiral pyrrolo [2,3-*b*] pyridine derivatives. *Tetrahedron*, 1991, 47, 429-440.
24. (a) Reanyanskaya, E. V.; Tverdokhlebov, A. V.; Volovenko, Y. M.; Shishkin, O. V.; Zubatyuk, R. I. A simple synthesis of 1-acyl-3-aryl-3H-pyrrolo[2',3':4,5]pyrimido[6,1-*b*]benzothiazol-6-ium-2-olates: Betainic derivatives
- 20 of a novel heterocyclic system. *Synthesis*, 2002, 18, 2717-2724. (b) Cook, P. D.; Castle, R. N. Pyrrolopyridazines. 1. Synthesis and reactivity of [2,3-*d*]pyridazine 5-oxides. *J. Het. Chem.* 1973, 10(4), 551-557.
- 25 25. Shadrina, L.P.; Dormidontov, Yu.P.; Ponomarev, V.G.; Lapkin, I.I. Reactions of organomagnesium derivatives of 7-aza- and benzoindoles with diethyl oxalate and the reactivity of ethoxalylindoles. *Khim. Geterotsikl. Soedin.*, 1987, 1206-1209.
- 30 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-azaindoles. *Khim. Geterotsikl. Soedin.*, 1987, 100-106.

+4  
16

27. (a) Desai, M.; Watthey, J.W.H.; Zuckerman, M. A convenient preparation of 1-arylpiperazines. *Org. Prep. Proced. Int.*, 1976, 8, 85-86. (b) Adamczyk, M.; Fino, J.R. Synthesis of procainamide metabolites. N-acetyl desethylprocainamide and desethylprocainamide. *Org. Prep. Proced. Int.* 1996, 28, 470-474. (c) Rossen, K.; Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. Asymmetric Hydrogenation of tetrahydropyrazines: Synthesis of (*S*)-piperazine 2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor Indinavir. *Tetrahedron Lett.*, 1995, 36, 6419-6422. (d) Wang, T.; Zhang, Z.; Meanwell, N.A. Benzoylation of Dianions: Preparation of mono-Benzoylated Symmetric Secondary Diamines. *J. Org. Chem.*, 1999, 64, 7661-7662.
28. Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT): A new coupling reagent with remarkable resistance to racemization. *Organic Lett.*, 1999, 1, 91-93.
29. Harada, N.; Kawaguchi, T.; Inoue, I.; Ohashi, M.; Oda, K.; Hashiyama, T.; Tsujihara, K. Synthesis and antitumor activity of quaternary salts of 2-(2'-oxoalkoxy)-9-hydroxyellipticines. *Chem. Pharm. Bull.*, 1997, 45, 134-137.
30. Schneller, S. W.; Luo, J.-K. Synthesis of 4-amino-1*H*-pyrrolo[2,3-*b*]pyridine (1,7-Dideazaadenine) and 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (1,7-Dideazahypoxanthine). *J. Org. Chem.*, 1980, 45, 4045-4048.
31. Shiotani, S.; Tanigochi, K. Furopyridines. XXII [1]. Elaboration of the C-substituents *alpha* to the heteronitrogen atom of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine. *J. Het. Chem.*, 1997, 34, 901-907.
32. Minakata, S.; Komatsu, M.; Ohshiro, Y. Regioselective functionalization of 1*H*-pyrrolo[2,3-*b*]pyridine via its N-oxide. *Synthesis*, 1992, 661-663.
33. Klemm, L. H.; Hartling, R. Chemistry of thienopyridines. XXIV. Two transformations of thieno[2,3-*b*]pyridine 7-oxide (1). *J. Het. Chem.*, 1976, 13, 1197-1200.

20  
17

34. Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Crifantini, M.; Martelli, S. Synthesis of 4-amino-1- $\beta$ -D-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1-Deazatubercidin) as a potential antitumor agent. *J. Med. Chem.*, 1982, 25, 1258-1261.
- 5
35. (a) Regnouf De Vains, J.B.; Papet, A.L.; Marsura, A. New symmetric and unsymmetric polyfunctionalized 2,2'-bipyridines. *J. Het. Chem.*, 1994, 31, 1069-1077. (b) Miura, Y.; Yoshida, M.; Hamana, M. Synthesis of 2,3-fused quinolines from 3-substituted quinoline 1-oxides. Part II, *Heterocycles*, 1993, 36, 1005-1016.
- 10 (c) Profft, V.B.; Rolle, W. Uber 4-merkaptoverbindungendes 2-methylpyridins. *J. Prakt. Chem.*, 1960, 283 (11), 22-34.
36. Nesi, R.; Giomi, D.; Turchi, S.; Tedeschi, P.; Ponticelli, F. A new one step synthetic approach to the isoxazolo[4,5-*b*]pyridine system. *Synth. Comm.*, 1992, 22,
- 15 2349-2355.
37. (a) Walser, A.; Zenchoff, G.; Fryer, R.L. Quinazolines and 1,4-benzodiazepines. 75. 7-Hydroxyaminobenzodiazepines and derivatives. *J. Med. Chem.*, 1976, 19, 1378-1381. (b) Barker, G.; Ellis, G.P. Benzopyrone. Part I. 6-
- 20 Amino- and 6-hydroxy-2-substituted chromones. *J. Chem. Soc.*, 1970, 2230-2233.
38. Ayyangar, N.R.; Lahoti, R.J.; Daniel, T. An alternate synthesis of 3,4-diaminobenzophenone and mebendazole. *Org. Prep. Proced. Int.*, 1991, 23, 627-631.
- 25
39. Mahadevan, I.; Rasmussen, M. Ambident heterocyclic reactivity: The alkylation of pyrrolopyridines (azaindoles, diazaindenes). *Tetrahedron*, 1993, 49, 7337-7352.
- 30 40. Chen, B.K.; Saksela, K.; Andino, R.; Baltimore, D. Distinct modes of human immunodeficiency type 1 proviral latency revealed by superinfection of nonproductively infected cell lines with recombinant luciferase-encoding viruses. *J. Virol.*, 1994, 68, 654-660.

2718

41. Bodanszky, M.; Bodanszky, A. *"The Practice of Peptide Synthesis"* 2<sup>nd</sup> Ed., Springer-Verlag: Berlin Heidelberg, Germany, 1994.
42. Albericio, F. *et al. J. Org. Chem.* 1998, 63, 9678.
- 5
43. Knorr, R. *et al. Tetrahedron Lett.* 1989, 30, 1927.
44. (a) Jaszay Z. M. *et al. Synth. Commun.*, 1998 28, 2761 and references cited therein; (b) Bernasconi, S. *et al. Synthesis*, 1980, 385.
- 10
45. (a) Jaszay Z. M. *et al. Synthesis*, 1989, 745 and references cited therein; (b) Nicolaou, K. C. *et al. Angew. Chem. Int. Ed.* 1999, 38, 1669.
46. Ooi, T. *et al. Synlett.* 1999, 729.
- 15
47. Ford, R. E. *et al. J. Med. Chem.* 1986, 29, 538.
48. (a) Yeung, K.-S. *et al. Bristol-Myers Squibb Unpublished Results.* (b) Wang, W. *et al. Tetrahedron Lett.* 1999, 40, 2501.
- 20
49. Brook, M. A. *et al. Synthesis*, 1983, 201.
50. Yamazaki, N. *et al. Tetrahedron Lett.* 1972, 5047.
- 25
51. Barry A. Bunin *"The Combinatorial Index"* 1998 Academic Press, San Diego / London pages 78-82.
52. Richard C. Larock *Comprehensive Organic Transformations* 2nd Ed. 1999, John Wiley and Sons New York.
- 30
53. M.D. Mullican *et al. J. Med. Chem.* 1991, 34, 2186-2194.



72  
19

54. Protective groups in organic synthesis 3rd ed. / Theodora W. Greene and Peter G.M. Wuts. New York : Wiley, 1999.
55. Katritzky, Alan R. Lagowski, Jeanne M. The principles of heterocyclic  
5 Chemistry New York : Academic Press, 1968.
56. Paquette, Leo A. Principles of modern heterocyclic chemistry New York: Benjamin.
- 10 57. Katritzky, Alan R.; Rees, Charles W.; Comprehensive heterocyclic chemistry: the structure, reactions, synthesis, and uses of heterocyclic compounds 1st ed. Oxford (Oxfordshire); New York: Pergamon Press, 1984. 8 v.
58. Katritzky, Alan R. Handbook of heterocyclic 1st ed Oxford (Oxfordshire); New  
15 York: Pergamon Press, 1985.
59. Davies, David I Aromatic Heterocyclic Oxford; New York: Oxford University Press, 1991.
- 20 60. Ellis, G. P. Synthesis of fused Chichester [Sussex]; New York: Wiley, c1987-c1992. Chemistry of heterocyclic compounds; v. 47.
61. Joule, J. A Mills, K., Smith, G. F. Heterocyclic Chemistry, 3rd ed  
London; New York Chapman & Hall, 1995.
- 25 62. Katritzky, Alan R., Rees, Charles W., Scriven, Eric F. V. Comprehensive heterocyclic chemistry II: a review of the literature 1982-1995.
63. The structure, reactions, synthesis, and uses of heterocyclic compounds 1st  
30 ed. Oxford; New York: Pergamon, 1996. 11 v. in 12: ill.; 28 cm.

2720

64. Eicher, Theophil, Hauptmann, Siegfried. The chemistry of heterocycles : structure, reactions, syntheses, and applications Stuttgart; New York: G. Thieme, 1995.
- 5 65. Grimmett, M. R. Imidazole and benzimidazole Synthesis London; San Diego: Academic Press, 1997.
66. Advances in heterocyclic chemistry. Published in New York by Academic Press, starting in 1963-present.
- 10 67. Gilchrist, T. L. (Thomas Lonsdale) Heterocyclic chemistry 3rd ed. Harlow, Essex: Longman, 1997, 414 p: ill.; 24 cm.
68. Farina, Vittorio; Roth, Gregory P. Recent advances in the Stille reaction; 15 *Adv. Met.-Org. Chem.* 1996, 5, 1-53.
69. Farina, Vittorio; Krishnamurthy, Venkat; Scott, William J. The Stille reaction ; *Org. React. (N. Y.)* (1997), 50, 1-652.
- 20 70. Stille, J. K. *Angew. Chem. Int. Ed. Engl.* 1986, 25, 508-524.
71. Norio Miyaura and Akio Suzuki *Chem Rev.* 1995, 95, 2457.
72. Home, D.A. *Heterocycles* 1994, 39, 139.
- 25 73. Kamitori, Y. et.al. *Heterocycles*, 1994, 37(1), 153.
74. Shawali, J. *Heterocyclic Chem.* 1976, 13, 989.
- 30 75. a) Kende, A.S.et al. *Org. Photochem. Synth.* 1972, 1, 92. b) Hanks, L.V.; *Biochem. Prep.* 1966, 11, 63. c) *Synth. Meth.* 22, 837.
76. Hulton et. al. *Synth. Comm.* 1979, 9, 789.

2/21

77. Pattanayak, B.K. et.al. *Indian J. Chem.* 1978, 16, 1030.
78. *Chemische Berichte* 1902, 35, 1545.
- 5 79. *Chemische Berichte* Ibid 1911, 44, 493.
80. Moubarak, I., Vessiere, R. *Synthesis* 1980, Vol. 1, 52-53.
81. *Ind J. Chem.* 1973, 11, 1260.
- 10 82. Roomi et.al. *Can J. Chem.* 1970, 48, 1689.
83. Sorrel, T.N. *J. Org. Chem.* 1994, 59, 1589.
- 15 84. Nitz, T.J. et. al. *J. Org. Chem.* 1994, 59, 5828-5832.
85. Bowden, K. et.al. *J. Chem. Soc.* 1946, 953.
86. Nitz, T.J. et. al. *J. Org. Chem.* 1994, 59, 5828-5832.
- 20 87. Scholkopf et. al. *Angew. Int. Ed. Engl.* 1971, 10(5), 333.
88. (a) Behun, J. D.; Levine, R. *J. Org. Chem.* 1961, 26, 3379. (b) Rossen, K.; Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J.
- 25 Asymmetric Hydrogenation of tetrahydropyrazines: Synthesis of (*S*)-piperazine 2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor Indinavir. *Tetrahedron Lett.*, 1995, 36, 6419-6422. (c) Jenneken, L. W.; Mahy, J.; den Berg, E. M. M. de B.-v.; Van der Hoef, I.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* 1995, 114, 97.
- 30 89. Wang, T.; Zhang, Z.; Meanwell, N.A. Benzoylation of Dianions: Preparation of mono-Benzoylated Symmetric Secondary Diamines. *J. Org. Chem.*, 1999, 64, 7661-7662.

7/22

90. (a) Adamczyk, M.; Fino, J.R. Synthesis of procainamide metabolites. N-acetyl desethylprocainamide and desethylprocainamide. *Org. Prep. Proced. Int.* 1996, 28, 470-474. (b) Wang, T.; Zhang, Z.; Meanwell, N.A. Regioselective mono-Benzoylation of Unsymmetrical Piperazines. *J. Org. Chem.*, in press.
- 5
91. Masuzawa, K.; Kitagawa, M.; Uchida, H. *Bull Chem. Soc. Jpn.* 1967, 40, 244-245.
92. Furber, M.; Cooper, M. B.; Donald, D. K. *Tetrahedron Lett.* 1993, 34, 1351-1354.
- 10
93. Blair, Wade S.; Deshpande, Milind; Fang, Haiquan; Lin, Pin-fang; Spicer, Timothy P.; Wallace, Owen B.; Wang, Hui; Wang, Tao; Zhang, Zhongxing; Yeung, Kap-sun. Preparation of antiviral indoleoxoacetyl piperazine derivatives US patent 6,469,006. Preparation of antiviral indoleoxoacetyl piperazine derivatives. PCT Int. Appl. (PCT/US00/14359), WO 0076521 A1, filed May 24, 2000, published December 21, 2000.
- 15
94. Wang, Tao; Wallace, Owen B.; Zhang, Zhongxing; Meanwell, Nicholas A.; Bender, John A. Antiviral azaindole derivatives. U.S. patent 6,476,034 and Wang, Tao; Wallace, Owen B.; Zhang, Zhongxing; Meanwell, Nicholas A.; Bender, John A. Preparation of antiviral azaindole derivatives. PCT Int. Appl. (PCT/US01/02009), WO 0162255 A1, filed January 19, 2001, published August 30, 2001.
- 20
95. Wallace, Owen B.; Wang, Tao; Yeung, Kap-Sun; Pearce, Bradley C.; Meanwell, Nicholas A.; Qiu, Zhilei; Fang, Haiquan; Xue, Qiufen May; Yin, Zhiwei. Composition and antiviral activity of substituted indoleoxoacetic piperazine derivatives. U.S. Patent 6,573,262 which is a continuation-in-part application of U.S. Serial Number 09/888,686 filed June 25, 2001 (corresponding to PCT Int. Appl. (PCT/US01/20300), WO 0204440 A1, filed June 26, 2001, published January 17, 2002.
- 25
- 30

23

96. J. L. Marco, S. T. Ingate, and P. M. Chinchon Tetrahedron 1999, 55, 7625-7644.
97. C. Thomas, F. Orecher, and P. Grmeiner Synthesis 1998, 1491.
- 5
98. M. P. Pavia, S. J. Lobbestael, C. P. Taylor, F. M. Hershenson, and D. W. Miskell.
99. Buckheit, Robert W., Jr. Expert Opinion on Investigational Drugs 2001, 10(8), 1423-1442.
- 10
100. Balzarini, J.; De Clercq, E.. Antiretroviral Therapy 2001, 31-62.
101. E. De clercq Journal of Clinical Virology, 2001, 22, 73-89.
- 15
102. Merour, Jean-Yves; Joseph, Benoit. Curr. Org. Chem. (2001), 5(5), 471-506.
103. T. W. von Geldern et al. J. Med. Chem 1996, 39, 968.
- 20
104. M. Abdaoui et al. Tetrahedron 2000, 56, 2427.
105. W. J. Spillane et al. J. Chem. Soc., Perkin Trans. 1, 1982, 3, 677.
- 25
106. Wang, Tao; Zhang, Zhongxing; Meanwell, Nicholas A.; Kadow, John F.; Yin, Zhiwei; Xue, Qiu fen May. (USA). *Composition and antiviral activity of substituted azaindoleoxoacetic piperazine derivatives*. U.S. Pat. Appl. Publ. (2003), US 20030207910 A1 published Nov 6, 2003 which is 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.
- 30

24

107. a) Nickel, Bernd; Szelenyi, Istvan; Schmidt, Jurgen; Emig, Peter; Reichert, Dietmar; Gunther, Eckhard; Brune, Kay. *Preparation of indolylglyoxylamides as antitumor agents*. PCT Int. Appl. (1999), 47 pp. CODEN: PIXXD2 WO 9951224, b) Emig, Peter; Bacher, Gerald; Reichert, Dietmar; Baasner, Silke; Aue, Beate; 5 Nickel, Bernd; Guenther, Eckhard. *Preparation of N-(6-quinolinyl)-3-indolylglyoxylamides as antitumor agents*. PCT Int. Appl. (2002), 4WO 2002010152A2, c) Nickel, Bernd; Klenner, Thomas; Bacher, Gerald; Beckers, Thomas; Emig, Peter; Engel, Juergen; Bruyneel, Erik; Kamp, Guenter; Peters, Kirsten. *Indolyl-3-glyoxylic acid derivatives comprising therapeutically valuable 10 properties*. PCT Int. Appl. (2001), WO 2001022954A2.
108. Wang, Tao; Wallace, Owen B.; Meanwell, Nicholas A.; Zhang, Zhongxing; Bender, John A.; Kadow, John F.; Yeung, Kap-Sun. *Preparation of indole, azaindole, and related heterocyclic piperazinecarboxamides for treatment of AIDS*. 15 PCT Int. Appl. WO 2002085301A2, published October 31, 2002; corresponding to U.S. Patent Publication U.S. 20030096825A1, published May 22, 2003.
109. Kadow, John F.; Xue, Qiufen May; Wang, Tao; Zhang, Zhongxing; Meanwell, Nicholas A. *Preparation of indole, azaindole and related heterocyclic 20 pyrrolidine derivatives as antiviral agents*. PCT Int. Appl. WO 2003068221A1, published August 21, 2003; corresponding to U.S. Patent Publication U.S. 20030236277A1.
110. Wang, Tao; Wallace, Owen B.; Meanwell, Nicholas A.; Kadow, John F.; 25 Zhang, Zhongxing; Yang, Zhong. *Preparation of piperazine derivatives as antiviral agents*. PCT Int. Appl. (2003), WO 2003092695 A1; corresponding to U.S. Patent Publication U.S. 20040009985A1, published January 15, 2004.
111. Kadow, John F.; Regueiro-Ren, Alicia; Xue, Qiufen May. *Preparation of 30 indolyl-, azaindolyl-, and related heterocyclic sulfonylureidopiperazines for treatment of HIV and AIDS*. PCT Int. Appl. (2003), WO 2004000210 A2; corresponding to U.S. Patent Publication U.S. 20040006090A1, published January 8, 2004.

112. Regueiro-Ren, Alicia; Xue, Qiufen May; Kadow, John F.; Taylor, Malcolm. *Preparation of indolyl-, azaindolyl-, and related heterocyclic ureido and thioureido piperazines for treatment of HIV and AIDS*. PCT Int. Appl. (2004), WO 2004011425 A2; corresponding to U.S. Patent Publication U.S. 20040063746A1, published April 1, 2004.
113. Wang, Tao; Zhang, Zhongxing; Meanwell, Nicholas A.; Kadow, John F.; Yin, Zhiwei; Xue, Qiufen May; Regueiro-Ren, Alicia; Matiskella, John D.; Ueda, Yasutsugu. *Composition and antiviral activity of substituted azaindolesoxoacetic piperazine derivatives*. U.S. Pat. Appl. Publ. (2004), US 2004110785 A1; published June 10, 2004.
114. Wang, Tao; Kadow, John F.; Meanwell, Nicholas A.; Yeung, Kap-Sun; Zhang, Zhongxing; Yin, Zhiwei; Qiu, Zhilei; Deon, Daniel H.; James, Clint A.; Ruediger, Edward H.; Bachand, Carol. *Preparation and pharmaceutical compositions of indole, azaindole and related heterocyclic 4-alkenyl piperidine amides*. U.S. Pat. Appl. Publ. (2004), US 20040063744 A1; published April 1, 2004; corresponding to PCT Intl. Appln. (2004), WO 2004/04337.

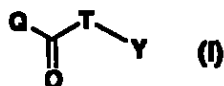
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## SUMMARY OF THE INVENTION

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formula I, which include nontoxic pharmaceutically acceptable salts thereof, have the formula and meaning as described below.

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

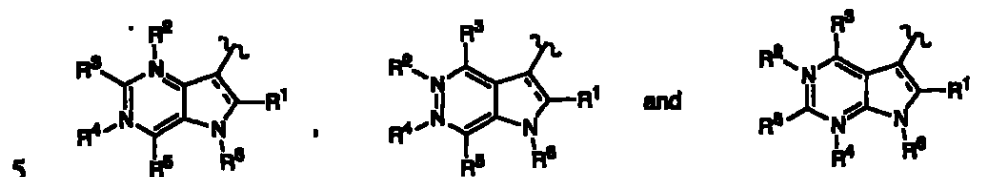
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26

wherein:

Q is selected from the group consisting of



T is  $-\text{C}(\text{O})-$  or  $-\text{CH}(\text{CN})-$ ;

$\text{R}^1$  is hydrogen or methyl;

10

$\text{R}^3$  and  $\text{R}^5$  are independently selected from the group consisting of hydrogen, halogen, cyano, nitro,  $\text{COOR}^8$ ,  $\text{XR}^9$  and B;

$\text{R}^2$  and  $\text{R}^4$  are independently O or do not exist with the proviso that only one of  $\text{R}^2$  and

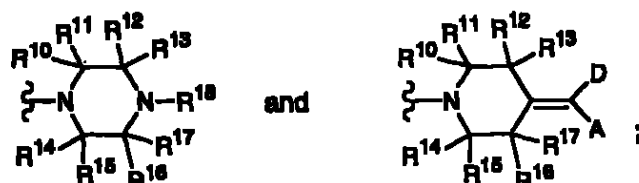
15  $\text{R}^4$  are O;

$\text{R}^6$  is  $(\text{CH}_2)_n\text{H}$ , wherein n is 0-1;

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

20

-Y- is selected from the group consisting of



25  $\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $\text{R}^{13}$ ,  $\text{R}^{14}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  are each independently H or  $(\text{C}_{1-6})$ alkyl; wherein said  $(\text{C}_{1-6})$ alkyl may optionally be substituted with one to three same or different halogen, OH or CN;



27

**R<sup>18</sup>** is a member selected from the group consisting of C(O)-phenyl, C(O)-heteroaryl, pyridinyl, pyrimidinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalinyl, naphthyridinyl, pthalazinyl, azabenzofuryl and azaindolyl; wherein said member is optionally substituted with from one to two substituents selected from the group consisting of methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl and halogen;

**D** is selected from the group consisting of hydrogen, cyano, S(O)<sub>2</sub>R<sup>24</sup>, halogen, COOR<sup>20</sup>, C(O)NR<sup>21</sup>R<sup>22</sup>, phenyl and heteroaryl; wherein said phenyl or heteroaryl is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F (as defined below);

**A** is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

**B** is selected from the group consisting of (C<sub>1-6</sub>)alkyl, C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)CH<sub>3</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NC(O)pyrazolyl, phenyl and heteroaryl; wherein said (C<sub>1-6</sub>)alkyl, phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl and triazolyl;

**F** is selected from the group consisting of (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkenyl, phenyl, pyridinyl, hydroxy, (C<sub>1-6</sub>)alkoxy, halogen, benzyl, -NR<sup>23</sup>C(O)-(C<sub>1-6</sub>)alkyl, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, and -CONR<sup>24</sup>R<sup>25</sup>; wherein said (C<sub>1-6</sub>)alkyl or phenyl are each optionally substituted with hydroxy, (C<sub>1-6</sub>)alkoxy, (C<sub>1-6</sub>)alkyl, CF<sub>3</sub>, dimethylamino or from one to three same or different halogen;

329

$R^8$ ,  $R^9$  and  $R^{26}$  are each independently selected from the group consisting of hydrogen and  $(C_{1-6})$ alkyl;

$X$  is selected from the group consisting of  $NR^{26}$ , O and S;

5

$R^{20}$ ,  $R^{21}$ ,  $R^{22}$ ,  $R^{23}$ ,  $R^{24}$  and  $R^{25}$  are independently selected from the group consisting of hydrogen,  $(C_{1-6})$ alkyl, phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different halogen or methyl; and

10

$R^{27}$  is piperazinyl, N-methyl piperazinyl, or 3-pyrazolyl.

A preferred embodiment includes compounds where T is  $\text{---}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{---}$ .

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

wherein:

20  $R^1$  is hydrogen;

-- represents a carbon-carbon bond; and

$R^2$  and  $R^4$  do not exist.

25

D is selected from the group consisting of hydrogen, cyano,  $S(O)_2R^{24}$ , halogen,  $COOR^{20}$ ,  $C(O)NH_2$ , phenyl and heteroaryl; wherein said phenyl or heteroaryl is independently optionally substituted with one to three same or different halogens or a member selected from the group consisting of  $(C_{1-6})$ alkyl,  $(C_{1-6})$ alkenyl, hydroxy,  $(C_{1-6})$ alkoxy, halogen,  $-NR^{24}R^{25}$ ,  $-S(O)_2NR^{24}R^{25}$ ,  $COOR^{26}$  and  $-CONR^{24}R^{25}$ ; wherein  
30 said  $(C_{1-6})$ alkyl is optionally substituted with one to three same or different halogen or a hydroxy; and

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29

- A is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole are independently optionally substituted with one to three same or different halogens or a member selected from the group consisting of (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkenyl, (C<sub>1-3</sub>)alkoxy, halogen and -NH<sub>2</sub>; wherein said (C<sub>1-3</sub>)alkyl is optionally substituted with one to three same or different halogens.

Another preferred embodiment are compounds I wherein:

- R<sup>6</sup> is hydrogen; and

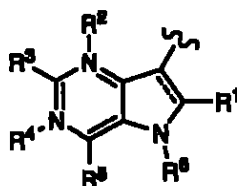
R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> are each independently H or methyl with the proviso that a maximum of two of R<sup>10</sup>-R<sup>17</sup> is a methyl.

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

wherein:

- Q is a member selected from groups (A), (B), and (C) consisting of

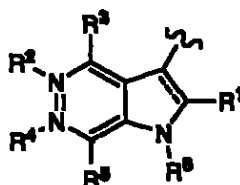
(A)



- wherein R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub> alkoxy, -NR<sup>26</sup>R<sup>9</sup> or halogen;

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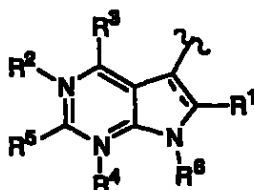
(B)



wherein R<sup>3</sup> is hydrogen, methoxy or halogen; and

5

(C)



wherein R<sup>3</sup> is hydrogen, methoxy or halogen.

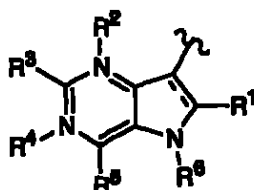
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Another preferred embodiment of the invention are compounds of Formula I, as above including pharmaceutically acceptable salts thereof, wherein:

group(A) of Q is:

15

(A)

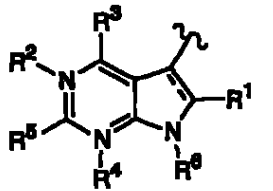


wherein R<sup>3</sup> is hydrogen; and

20

group (C) of Q is:

26



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wherein:

5  $R^5$  is hydrogen.

In another preferred embodiment of the invention, Q is selected from group (A) or (B), and

10  $R^5$  is selected from the group consisting of hydrogen, halogen, heteroaryl, phenyl, cyano, methoxy,  $\text{COOR}^8$ ,  $\text{C(O)NH}_2$ ,  $\text{C(O)NHheteroaryl}$ , and  $\text{C(O)NHCH}_3$ ; wherein said  $\text{C(O)NHheteroaryl}$ , phenyl, and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F.

15

Other preferred embodiments are compounds I:

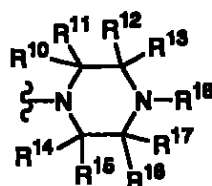
wherein heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl and triazolyl; wherein said heteroaryl is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

20  $R^{18}$  is  $\text{-C(O)phenyl}$  or  $\text{-C(O)heteroaryl}$ ; wherein said heteroaryl is pyridinyl, furanyl or thienyl; wherein heteroaryl is independently optionally substituted with a member selected from the group consisting of halogen, methyl, -amino,  $\text{-NHMe}$ ,  $\text{NMe}_2$  and hydroxymethyl;

-W- is

30

27



$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or methyl with the proviso that not more than one is methyl; and

5

$R^{18}$  is selected from the group consisting of C(O)-phenyl or C(O)-heteroaryl wherein each of C(O)-phenyl or -C(O)-heteroaryl may be optionally substituted with from one to two methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl or halogen groups; or

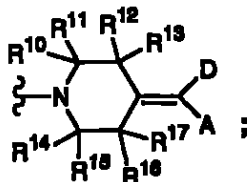
10

$R^{18}$  is selected from the group consisting of pyridyl, pyrimidinyl, quinolyl, isoquinolyl, quinazolyl, quinoxaliny, naphthyridinyl, pthalazinyl, azabenzofuryl and azaindolyl, each of which may be optionally substituted with from one to two methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl or halogen groups.

15

In another preferred embodiment:

-W- is selected from the group consisting of



20

$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or methyl, with the proviso that one is methyl;

25

D is selected from the group consisting of hydrogen, cyano, S(O)<sub>2</sub>R<sup>24</sup>, halogen, COOR<sup>20</sup>, C(O)NH<sub>2</sub>, phenyl, or heteroaryl; wherein said phenyl or heteroaryl is independently optionally substituted with one to three same or different halogens or

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from one to three same or different substituents selected from the group consisting of (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkenyl, hydroxy, (C<sub>1-6</sub>)alkoxy, halogen, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup> and -CONR<sup>24</sup>R<sup>25</sup>; wherein said (C<sub>1-6</sub>)alkyl is optionally substituted with one to three same or different halogen or a hydroxy; and

5

A is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole is independently 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<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkenyl, (C<sub>1-3</sub>)alkoxy, halogen and -NH<sub>2</sub>; wherein said (C<sub>1-4</sub>)alkyl is optionally substituted with one to three same or different halogens.

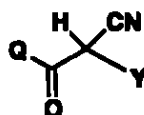
10

In another preferred embodiment:

15 Q is selected from Group (A).

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

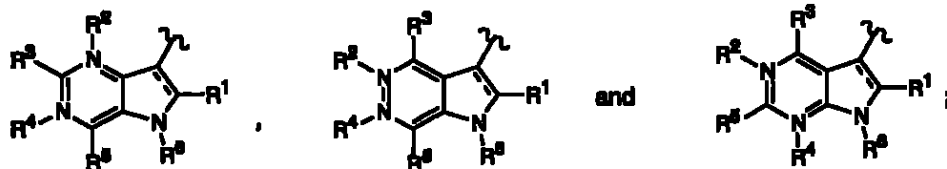
20



wherein:

25

Q is selected from the group consisting of



R<sup>1</sup> is hydrogen or methyl;

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$R^3$  and  $R^5$  are independently selected from the group consisting of hydrogen, halogen, cyano, nitro,  $\text{COOR}^8$ ,  $\text{XR}^9$  and B;

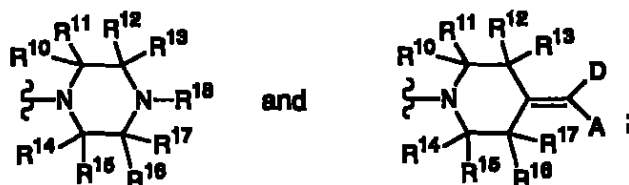
5  $R^2$  and  $R^4$  are independently O or do not exist, with the proviso that only one of  $R^2$  and  $R^4$  are O;

$R^6$  is  $(\text{CH}_2)_n\text{H}$ , wherein n is 0-1;

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

10

-Y- is selected from the group consisting of



15  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or  $(\text{C}_{1-6})$ alkyl; wherein said  $(\text{C}_{1-6})$ alkyl may optionally be substituted with one to three same or different halogen, OH or CN;

20  $R^{18}$  is a member selected from the group consisting of  $\text{C}(\text{O})$ -phenyl,  $\text{C}(\text{O})$ -heteroaryl, pyridinyl, pyrimidinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalinyl, naphthyridinyl, pthalazinyl, azabenzofuryl and azaindolyl; wherein said member is optionally substituted with from one to two substituents selected from the group consisting of methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl and halogen;

25 D is selected from the group consisting of hydrogen, cyano,  $\text{S}(\text{O})_2\text{R}^{24}$ , halogen,  $\text{COOR}^{20}$ ,  $\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$ , phenyl and heteroaryl; wherein said phenyl or heteroaryl is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;



2639

A is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

5

B is selected from the group consisting of (C<sub>1-6</sub>)alkyl, (C<sub>3-6</sub>)cycloalkyl, C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)CH<sub>3</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NC(O)pyrazolyl, phenyl and heteroaryl; wherein said (C<sub>1-6</sub>)alkyl, phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

10

heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl and triazolyl;

15

F is selected from the group consisting of (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkenyl, phenyl, pyridinyl, hydroxy, (C<sub>1-6</sub>)alkoxy, halogen, benzyl, -NR<sup>23</sup>C(O)-(C<sub>1-6</sub>)alkyl, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, and -CONR<sup>24</sup>R<sup>25</sup>; wherein said (C<sub>1-6</sub>)alkyl or phenyl are each optionally substituted with hydroxy, (C<sub>1-6</sub>)alkoxy, dimethylamino or from one to three same or different halogen;

20

R<sup>8</sup>, R<sup>9</sup> and R<sup>26</sup> are each independently selected from the group consisting of hydrogen and (C<sub>1-6</sub>)alkyl;

25 X is selected from the group consisting of NR<sup>26</sup>, O and S;

R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup> and R<sup>25</sup> are independently selected from the group consisting of hydrogen, (C<sub>1-6</sub>)alkyl, phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different halogen or methyl; and

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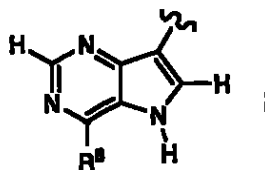
R<sup>27</sup> is piperazinyl, N-methylpiperazinyl or 3-pyrazolyl.

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In another embodiment are Compounds I, including pharmaceutically acceptable salts, wherein:

Q is

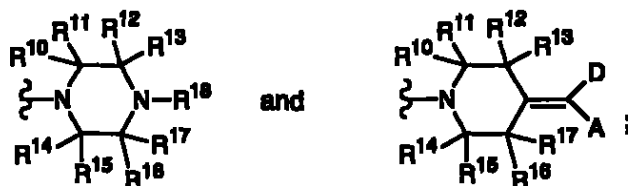
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10  $R^8$  is selected from the group consisting of hydrogen, halogen, cyano,  $XR^9$ , heteroaryl,  $-N(CH_2CH_2)_2NC(O)pyrazolyl$ , and  $-C(O)CH_3$ , wherein said heteroaryl is optionally substituted with one substituent selected from F;

heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, isoxazolyl, pyrazolyl, and triazolyl;

15 -Y- is selected from the group consisting of



20  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each hydrogen;

A is phenyl or pyridinyl;

$R^{18}$  is  $C(O)$ -phenyl, isoquinolyl or quinazolyl;

25 D is cyano or oxadiazolyl;

LD  
37

F is selected from the group consisting of (C<sub>1-6</sub>)alkyl, phenyl, pyridinyl, (C<sub>1-2</sub>)alkoxy, -COOR<sup>26</sup>, -COR<sup>27</sup> and -CONR<sup>24</sup>R<sup>25</sup>; wherein said phenyl is optionally substituted with one group selected from methyl, methoxy, fluoro, or trifluoromethyl;

5 X is selected from the group consisting of O;

R<sup>9</sup> is (C<sub>1-2</sub>)alkyl;

R<sup>26</sup> is hydrogen, methyl, or ethyl;

10

R<sup>24</sup> and R<sup>25</sup> are independently selected from the group consisting of hydrogen and methyl; and

R<sup>27</sup> is piperazinyl, N-methyl piperazinyl, or 3-pyrazolyl.

15

Another embodiment of the present invention is a method for treating mammals infected with the HIV virus, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, excipients or diluents; optionally the compound of Formula I can be administered 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.

20

25

Another embodiment of the present invention is a pharmaceutical composition comprising an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, excipients, diluents and 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.

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## DETAILED DESCRIPTION OF THE INVENTION

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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<sub>1-6</sub> 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.

15

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, naphthalenyl 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<sup>x</sup>R<sup>y</sup>, wherein R<sup>x</sup> and R<sup>y</sup> 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

5 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

10 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

15  $R^x$  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. Rings are selected from those which provide stable

20 arrangements of bonds and are not intended to encompass systems which would not exist. 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 azetidiny, piperidyl, piperazinyl, imidazoliny, thiazolidiny, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl.

25 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,

30 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.

40

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, cyclopentane, 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<sup>x</sup>R<sup>y</sup> with R<sup>x</sup> and R<sup>y</sup> 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.

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

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

10 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.

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

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

20 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.

25

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

30 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.

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

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

10 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 heteroalicyclic group.

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

15

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

20 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.

25 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.

30

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



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

5 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.

10 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.

15 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.

20

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.

25

A "C-amido" group refers to a  $-C(=O)NR^XR^Y$  group with  $R^X$  and  $R^Y$  as defined herein.

30 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.

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

An "thioureido" group refers to a  $-NR^x C(=S)NR^y R^{y2}$  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  $-R^x NC(=N)NR^y R^{y2}$  group, with  $R^x$ ,  $R^y$  and  $R^{y2}$  as defined herein.

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

A "cyano" group refers to a  $-CN$  group.

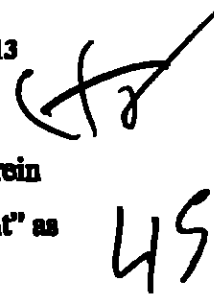
A "silyl" group refers to a  $-Si(R'')_3$ , with  $R''$  as defined herein.

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

A "hydrazino" group refers to a  $-NR^x NR^y R^{y2}$  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 nitrogen 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  
5 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  
10 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  
15 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  
20 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  
25 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  
30 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

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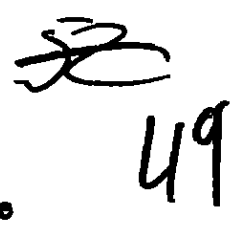
|    | <u>Drug Name</u>                | <u>Manufacturer</u>                             | <u>Indication</u>                                                                               |
|----|---------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 5  | 097                             | Hoechst/Bayer                                   | HIV infection,<br>AIDS, ARC<br>(non-nucleoside<br>reverse trans-<br>criptase (RT)<br>inhibitor) |
| 10 |                                 |                                                 |                                                                                                 |
|    | Amprenivir<br>141 W94<br>GW 141 | Glaxo Wellcome                                  | HIV infection,<br>AIDS, ARC<br>(protease inhibitor)                                             |
| 15 |                                 |                                                 |                                                                                                 |
|    | Abacavir (1592U89)<br>GW 1592   | Glaxo Wellcome                                  | HIV infection,<br>AIDS, ARC<br>(RT inhibitor)                                                   |
| 20 |                                 |                                                 |                                                                                                 |
|    | Acomannan                       | Carrington Labs<br>(Irving, TX)                 | ARC                                                                                             |
|    |                                 |                                                 |                                                                                                 |
|    | Acyclovir                       | Burroughs Wellcome                              | HIV infection, AIDS,<br>ARC, in combination<br>with AZT                                         |
| 25 |                                 |                                                 |                                                                                                 |
|    | AD-439                          | Tanox Biosystems                                | HIV infection, AIDS,<br>ARC                                                                     |
|    |                                 |                                                 |                                                                                                 |
| 30 | AD-519                          | Tanox Biosystems                                | HIV infection, AIDS,<br>ARC                                                                     |
|    |                                 |                                                 |                                                                                                 |
|    | Adefovir dipivoxil<br>AL-721    | Gilead Sciences<br>Ethigen<br>(Los Angeles, CA) | HIV infection<br>ARC, PGL<br>HIV positive, AIDS                                                 |
| 35 |                                 |                                                 |                                                                                                 |
|    | Alpha Interferon                | Glaxo Wellcome                                  | Kaposi's sarcoma,<br>HIV in combination<br>w/Retrovir                                           |
| 40 |                                 |                                                 |                                                                                                 |

|           |                                                                                   |                                                                            |                                                              |
|-----------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------|
|           | <b>Ansamycin<br/>LM 427</b>                                                       | <b>Adria Laboratories<br/>(Dublin, OH)<br/>Erbamont<br/>(Stamford, CT)</b> | <b>ARC</b>                                                   |
| <b>5</b>  |                                                                                   |                                                                            |                                                              |
|           | <b>Antibody which<br/>Neutralizes pH<br/>Labile alpha aberrant<br/>Interferon</b> | <b>Advanced Biotherapy<br/>Concepts<br/>(Rockville, MD)</b>                | <b>AIDS, ARC</b>                                             |
| <b>10</b> |                                                                                   |                                                                            |                                                              |
|           | <b>AR177</b>                                                                      | <b>Aronex Pharm</b>                                                        | <b>HIV infection, AIDS,<br/>ARC</b>                          |
| <b>15</b> |                                                                                   |                                                                            |                                                              |
|           | <b>Beta-fluoro-ddA</b>                                                            | <b>Nat'l Cancer Institute</b>                                              | <b>AIDS-associated<br/>diseases</b>                          |
|           |                                                                                   |                                                                            |                                                              |
|           | <b>BMS-232623<br/>(CGP-73547)</b>                                                 | <b>Bristol-Myers Squibb/<br/>Novartis</b>                                  | <b>HIV infection,<br/>AIDS, ARC<br/>(protease inhibitor)</b> |
| <b>20</b> |                                                                                   |                                                                            |                                                              |
|           | <b>BMS-234475<br/>(CGP-61755)</b>                                                 | <b>Bristol-Myers Squibb/<br/>Novartis</b>                                  | <b>HIV infection,<br/>AIDS, ARC<br/>(protease inhibitor)</b> |
| <b>25</b> |                                                                                   |                                                                            |                                                              |
|           | <b>CI-1012</b>                                                                    | <b>Warner-Lambert</b>                                                      | <b>HIV-1 infection</b>                                       |
|           |                                                                                   |                                                                            |                                                              |
|           | <b>Cidofovir</b>                                                                  | <b>Gilead Science</b>                                                      | <b>CMV retinitis,<br/>herpes, papillomavirus</b>             |
| <b>30</b> |                                                                                   |                                                                            |                                                              |
|           | <b>Curdian sulfate</b>                                                            | <b>AJI Pharma USA</b>                                                      | <b>HIV infection</b>                                         |
|           |                                                                                   |                                                                            |                                                              |
|           | <b>Cytomegalovirus<br/>Immune globin</b>                                          | <b>MedImmune</b>                                                           | <b>CMV retinitis</b>                                         |
| <b>35</b> |                                                                                   |                                                                            |                                                              |
|           | <b>Cytovene</b>                                                                   | <b>Syntex</b>                                                              | <b>Sight threatening</b>                                     |
|           |                                                                                   |                                                                            |                                                              |
|           | <b>Ganciclovir</b>                                                                |                                                                            | <b>CMV<br/>peripheral CMV<br/>retinitis</b>                  |
| <b>40</b> |                                                                                   |                                                                            |                                                              |

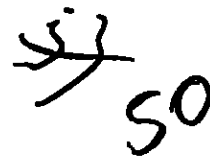
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|    |                                                                                                    |                                                         |                                                                               |
|----|----------------------------------------------------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------------------------------------|
|    | <b>Delaviridine</b>                                                                                | <b>Pharmacia-Upjohn</b>                                 | <b>HIV infection,<br/>AIDS, ARC<br/>(RT inhibitor)</b>                        |
| 5  | <b>Dextran Sulfate</b>                                                                             | <b>Ueno Fine Chem.<br/>Ind. Ltd. (Osaka,<br/>Japan)</b> | <b>AIDS, ARC, HIV<br/>positive<br/>asymptomatic</b>                           |
| 10 | <b>ddC<br/>Dideoxycytidine</b>                                                                     | <b>Hoffman-La Roche</b>                                 | <b>HIV infection, AIDS,<br/>ARC</b>                                           |
| 15 | <b>ddI<br/>Dideoxyinosine</b>                                                                      | <b>Bristol-Myers Squibb</b>                             | <b>HIV infection, AIDS,<br/>ARC; combination<br/>with AZT/d4T</b>             |
|    | <b>DMP-450</b>                                                                                     | <b>AVID<br/>(Camden, NJ)</b>                            | <b>HIV infection,<br/>AIDS, ARC<br/>(protease inhibitor)</b>                  |
| 20 | <b>Efavirenz<br/>(DMP 266)<br/>(-)-6-Chloro-4-(S)-<br/>cyclopropylethynyl-<br/>4(S)-trifluoro-</b> | <b>DuPont Merck</b>                                     | <b>HIV infection,<br/>AIDS, ARC<br/>(non-nucleoside RT<br/>inhibitor)</b>     |
| 25 | <b>methyl-1,4-dihydro-<br/>2H-3,1-benzoxazin-<br/>2-one, STOCRINE</b>                              |                                                         |                                                                               |
| 30 | <b>EL10</b>                                                                                        | <b>Elan Corp, PLC<br/>(Gainesville, GA)</b>             | <b>HIV infection</b>                                                          |
|    | <b>Famciclovir</b>                                                                                 | <b>Smith Kline</b>                                      | <b>herpes zoster,<br/>herpes simplex</b>                                      |
| 35 | <b>FTC</b>                                                                                         | <b>Emory University</b>                                 | <b>HIV infection,<br/>AIDS, ARC<br/>(reverse transcriptase<br/>inhibitor)</b> |
| 40 | <b>GS 840</b>                                                                                      | <b>Gilead</b>                                           | <b>HIV infection,<br/>AIDS, ARC<br/>(reverse transcriptase<br/>inhibitor)</b> |

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|           |                                              |                                             |                                                                                                                  |
|-----------|----------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------|
|           | <b>HB Y097</b>                               | <b>Hoechst Marion<br/>Roussel</b>           | <b>HIV infection,<br/>AIDS, ARC<br/>(non-nucleoside<br/>reverse transcriptase<br/>inhibitor)</b>                 |
| <b>5</b>  |                                              |                                             |                                                                                                                  |
|           | <b>Hypericin</b>                             | <b>VIMRx Pharm.</b>                         | <b>HIV infection, AIDS,<br/>ARC</b>                                                                              |
| <b>10</b> | <b>Recombinant Human<br/>Interferon Beta</b> | <b>Triton Biosciences<br/>(Alameda, CA)</b> | <b>AIDS, Kaposi's<br/>sarcoma, ARC</b>                                                                           |
|           | <b>Interferon alfa-n3</b>                    | <b>Interferon Sciences</b>                  | <b>ARC, AIDS</b>                                                                                                 |
| <b>15</b> | <b>Indinavir</b>                             | <b>Merck</b>                                | <b>HIV infection, AIDS,<br/>ARC, asymptomatic<br/>HIV positive, also in<br/>combination with<br/>AZT/ddI/ddC</b> |
| <b>20</b> |                                              |                                             |                                                                                                                  |
|           | <b>ISIS 2922</b>                             | <b>ISIS Pharmaceuticals</b>                 | <b>CMV retinitis</b>                                                                                             |
|           | <b>KNI-272</b>                               | <b>Nat'l Cancer Institute</b>               | <b>HIV-assoc. diseases</b>                                                                                       |
| <b>25</b> | <b>Lamivudine, 3TC</b>                       | <b>Glaxo Wellcome</b>                       | <b>HIV infection,<br/>AIDS, ARC<br/>(reverse<br/>transcriptase<br/>inhibitor); also<br/>with AZT</b>             |
| <b>30</b> |                                              |                                             |                                                                                                                  |
|           | <b>Lobucavir</b>                             | <b>Bristol-Myers Squibb</b>                 | <b>CMV infection</b>                                                                                             |
| <b>35</b> | <b>Nelfinavir</b>                            | <b>Agouron<br/>Pharmaceuticals</b>          | <b>HIV infection,<br/>AIDS, ARC<br/>(protease inhibitor)</b>                                                     |
|           | <b>Nevirapine</b>                            | <b>Boehringer<br/>Ingelheim</b>             | <b>HIV infection,<br/>AIDS, ARC<br/>(RT inhibitor)</b>                                                           |
| <b>40</b> |                                              |                                             |                                                                                                                  |



|    |                                                |                                      |                                                          |
|----|------------------------------------------------|--------------------------------------|----------------------------------------------------------|
|    | Novapren                                       | Novaferon Labs, Inc.<br>(Akron, OH)  | HIV inhibitor                                            |
| 5  | Peptide T<br>Octapeptide<br>Sequence           | Peninsula Labs<br>(Belmont, CA)      | AIDS                                                     |
| 10 | Trisodium<br>Phosphonoformate                  | Astra Pharm.<br>Products, Inc.       | CMV retinitis, HIV<br>infection, other CMV<br>infections |
| 15 | PNU-140690                                     | Pharmacia Upjohn                     | HIV infection,<br>AIDS, ARC<br>(protease inhibitor)      |
|    | Probucol                                       | Vyrex                                | HIV infection, AIDS                                      |
| 20 | RBC-CD4                                        | Sheffield Med.<br>Tech (Houston, TX) | HIV infection,<br>AIDS, ARC                              |
|    | Ritonavir                                      | Abbott                               | HIV infection,<br>AIDS, ARC<br>(protease inhibitor)      |
| 25 | Saquinavir                                     | Hoffmann-<br>LaRoche                 | HIV infection,<br>AIDS, ARC<br>(protease inhibitor)      |
| 30 | Stavudine; d4T<br>Didehydrodeoxy-<br>thymidine | Bristol-Myers Squibb                 | HIV infection, AIDS,<br>ARC                              |
| 35 | Valaciclovir                                   | Glaxo Wellcome                       | Genital HSV & CMV<br>infections                          |
|    | Virazole<br>Ribavirin                          | Viratek/ICN<br>(Costa Mesa, CA)      | asymptomatic HIV<br>positive, LAS, ARC                   |
| 40 | VX-478                                         | Vertex                               | HIV infection, AIDS,<br>ARC                              |



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|           |                                                      |                             |                                                                                        |
|-----------|------------------------------------------------------|-----------------------------|----------------------------------------------------------------------------------------|
|           | <b>Zalcitabine</b>                                   | <b>Hoffmann-LaRoche</b>     | <b>HIV infection, AIDS, ARC, with AZT</b>                                              |
| <b>5</b>  | <b>Zidovudine; AZT</b>                               | <b>Glaxo Wellcome</b>       | <b>HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies</b> |
| <b>10</b> | <b>Tenofovir disoproxil, fumarate salt (Viread®)</b> | <b>Gilead</b>               | <b>HIV infection, AIDS, (reverse transcriptase inhibitor)</b>                          |
| <b>15</b> | <b>Combivir®</b>                                     | <b>GSK</b>                  | <b>HIV infection, AIDS, (reverse transcriptase inhibitor)</b>                          |
| <b>20</b> | <b>abacavir succinate (or Ziagen®)</b>               | <b>GSK</b>                  | <b>HIV infection, AIDS, (reverse transcriptase inhibitor)</b>                          |
| <b>25</b> | <b>Reyataz® (or atazanavir)</b>                      | <b>Bristol-Myers Squibb</b> | <b>HIV infection AIDs, protease inhibitor</b>                                          |
| <b>30</b> | <b>Fuzeon® (or T-20)</b>                             | <b>Roche / Trimeris</b>     | <b>HIV infection AIDs, viral Fusion inhibitor</b>                                      |

**IMMUNOMODULATORS**

|           |                         |                            |                          |
|-----------|-------------------------|----------------------------|--------------------------|
| <b>35</b> | <u><b>Drug Name</b></u> | <u><b>Manufacturer</b></u> | <u><b>Indication</b></u> |
|           | <b>AS-101</b>           | <b>Wyeth-Ayerst</b>        | <b>AIDS</b>              |
|           | <b>Bropirimine</b>      | <b>Pharmacia Upjohn</b>    | <b>Advanced AIDS</b>     |

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|    |                                                                 |                                               |                                                                  |
|----|-----------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------|
|    | <b>Acemaman</b>                                                 | <b>Carrington Labs, Inc.<br/>(Irving, TX)</b> | <b>AIDS, ARC</b>                                                 |
| 5  | <b>CL246,738</b>                                                | <b>American Cyanamid<br/>Lederle Labs</b>     | <b>AIDS, Kaposi's<br/>sarcoma</b>                                |
|    | <b>EL10</b>                                                     | <b>Elan Corp, PLC<br/>(Gainesville, GA)</b>   | <b>HIV infection</b>                                             |
| 10 | <b>FP-21399</b>                                                 | <b>Fuki ImmunoPharm</b>                       | <b>Blocks HIV fusion<br/>with CD4+ cells</b>                     |
| 15 | <b>Gamma Interferon</b>                                         | <b>Genentech</b>                              | <b>ARC, in combination<br/>w/TNF (tumor<br/>necrosis factor)</b> |
| 20 | <b>Granulocyte<br/>Macrophage Colony<br/>Stimulating Factor</b> | <b>Genetics Institute<br/>Sandoz</b>          | <b>AIDS</b>                                                      |
|    | <b>Granulocyte<br/>Macrophage Colony<br/>Stimulating Factor</b> | <b>Hoechst-Roussel<br/>Immunex</b>            | <b>AIDS</b>                                                      |
| 25 | <b>Granulocyte<br/>Macrophage Colony<br/>Stimulating Factor</b> | <b>Schering-Plough</b>                        | <b>AIDS,<br/>combination<br/>w/AZT</b>                           |
| 30 | <b>HIV Core Particle<br/>Immunostimulant</b>                    | <b>Rorer</b>                                  | <b>Seropositive HIV</b>                                          |
|    | <b>IL-2<br/>Interleukin-2</b>                                   | <b>Cetus</b>                                  | <b>AIDS, in combination<br/>w/AZT</b>                            |
| 35 | <b>IL-2<br/>Interleukin-2</b>                                   | <b>Hoffman-LaRoche<br/>Immunex</b>            | <b>AIDS, ARC, HIV, in<br/>combination w/AZT</b>                  |

|           |                                                      |                                             |                                                 |
|-----------|------------------------------------------------------|---------------------------------------------|-------------------------------------------------|
|           | <b>IL-2<br/>Interleukin-2<br/>(aldeslulkin)</b>      | <b>Chiron</b>                               | <b>AIDS, increase in<br/>CD4 cell counts</b>    |
| <b>5</b>  | <b>Immune Globulin<br/>Intravenous<br/>(human)</b>   | <b>Cutter Biological<br/>(Berkeley, CA)</b> | <b>Pediatric AIDS, in<br/>combination w/AZT</b> |
| <b>10</b> | <b>IMREG-1</b>                                       | <b>Imreg<br/>(New Orleans, LA)</b>          | <b>AIDS, Kaposi's<br/>sarcoma, ARC, PGL</b>     |
|           | <b>IMREG-2</b>                                       | <b>Imreg<br/>(New Orleans, LA)</b>          | <b>AIDS, Kaposi's<br/>sarcoma, ARC, PGL</b>     |
| <b>15</b> | <b>Imuthiol Diethyl<br/>Dithio Carbamate</b>         | <b>Merieux Institute</b>                    | <b>AIDS, ARC</b>                                |
| <b>20</b> | <b>Alpha-2<br/>Interferon</b>                        | <b>Schering Plough</b>                      | <b>Kaposi's sarcoma<br/>w/AZT, AIDS</b>         |
|           | <b>Methionine-<br/>Enkephalin</b>                    | <b>TNI Pharmaceutical<br/>(Chicago, IL)</b> | <b>AIDS, ARC</b>                                |
| <b>25</b> | <b>MTP-PE<br/>Muramyl-Tripeptide</b>                 | <b>Ciba-Geigy Corp.</b>                     | <b>Kaposi's sarcoma</b>                         |
| <b>30</b> | <b>Granulocyte<br/>Colony Stimulating<br/>Factor</b> | <b>Amgen</b>                                | <b>AIDS, in combination<br/>w/AZT</b>           |
|           | <b>Remune</b>                                        | <b>Immune Response<br/>Corp.</b>            | <b>Immunotherapeutic</b>                        |
| <b>35</b> | <b>rCD4<br/>Recombinant<br/>Soluble Human CD4</b>    | <b>Genentech</b>                            | <b>AIDS, ARC</b>                                |
| <b>40</b> | <b>rCD4-IgG<br/>hybrids</b>                          |                                             | <b>AIDS, ARC</b>                                |
|           | <b>Recombinant<br/>Soluble Human CD4</b>             | <b>Biogen</b>                               | <b>AIDS, ARC</b>                                |



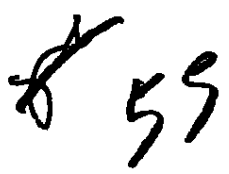
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|    |                               |                                                        |                                                        |
|----|-------------------------------|--------------------------------------------------------|--------------------------------------------------------|
|    | Interferon<br>Alfa 2a         | Hoffman-La Roche                                       | Kaposi's sarcoma<br>AIDS, ARC,<br>in combination w/AZT |
| 5  | SK&F106528<br>Soluble T4      | Smith Kline                                            | HIV infection                                          |
| 10 | Thymopentin                   | Immunobiology<br>Research Institute<br>(Annandale, NJ) | HIV infection                                          |
|    | Tumor Necrosis<br>Factor; TNF | Genentech                                              | ARC, in combination<br>w/gamma Interferon              |

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ANTI-INFECTIVES

|    | <u>Drug Name</u>                     | <u>Manufacturer</u>        | <u>Indication</u>                          |
|----|--------------------------------------|----------------------------|--------------------------------------------|
| 20 | Clindamycin with<br>Primaquine       | Pharmacia Upjohn           | PCP                                        |
| 25 | Fluconazole                          | Pfizer                     | Cryptococcal<br>meningitis,<br>candidiasis |
|    | Pastille<br>Nystatin Pastille        | Squibb Corp.               | Prevention of<br>oral candidiasis          |
| 30 | Ornidyl<br>Eflornithine              | Merrell Dow                | PCP                                        |
|    | Pentamidine<br>Isethionate (IM & IV) | LyphoMed<br>(Rosemont, IL) | PCP treatment                              |
| 35 | Trimethoprim                         |                            | Antibacterial                              |
|    | Trimethoprim/sulfa                   |                            | Antibacterial                              |
| 40 | Piritrexim                           | Burroughs Wellcome         | PCP treatment                              |



|    |                                              |                                  |                                                  |
|----|----------------------------------------------|----------------------------------|--------------------------------------------------|
|    | Pentamidine<br>Isethionate for<br>Inhalation | Fisons Corporation               | PCP prophylaxis                                  |
| 5  | Spiramycin                                   | Rhone-Poulenc<br>diarrhea        | Cryptosporidial                                  |
| 10 | Intraconazole-<br>R51211                     | Janssen-Pharm.                   | Histoplasmosis;<br>cryptococcal<br>meningitis    |
|    | Trimetrexate                                 | Warner-Lambert                   | PCP                                              |
| 15 | Daunorubicin                                 | NeXstar, Sequus                  | Kaposi's sarcoma                                 |
|    | Recombinant Human<br>Erythropoietin          | Ortho Pharm. Corp.               | Severe anemia<br>assoc. with AZT<br>therapy      |
| 20 | Recombinant Human<br>Growth Hormone          | Serono                           | AIDS-related<br>wasting, cachexia                |
| 25 | Megestrol Acetate                            | Bristol-Myers Squibb             | Treatment of<br>anorexia assoc.<br>W/AIDS        |
|    | Testosterone                                 | Alza, Smith Kline                | AIDS-related wasting                             |
| 30 | Total Enteral<br>Nutrition                   | Norwich Eaton<br>Pharmaceuticals | Diarrhea and<br>malabsorption<br>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 and  
*Inhibitors of the entry of HIV into host cells*. Meanwell, Nicholas A.; Kadow, John  
 F. Current Opinion in Drug Discovery & Development (2003), 6(4), 451-461.

Specifically the compounds can be utilized in combination with other attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor.

5 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.

10

Preferred combinations are simultaneous or alternating treatments 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 Reyataz<sup>®</sup> (active ingredient Atazanavir). Typically a dose of 300 to 600mg is administered once a day. This may be co-administered with a low dose of Ritonavir (50 to 500mgs). Another preferred inhibitor of HIV protease is Kaletra<sup>®</sup>. Another useful 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.

30

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).

5

## 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)                                                         |
|    | r.t.                            | = | room temperature                                                |
|    | mol                             | = | mole(s)                                                         |
| 15 | mmol                            | = | millimole(s)                                                    |
|    | g                               | = | gram(s)                                                         |
|    | mg                              | = | milligram(s)                                                    |
|    | mL                              | = | milliliter(s)                                                   |
|    | TFA                             | = | Trifluoroacetic Acid                                            |
| 20 | DCE                             | = | 1,2-Dichloroethane                                              |
|    | CH <sub>2</sub> Cl <sub>2</sub> | = | Dichloromethane                                                 |
|    | TPAP                            | = | tetrapropylammonium perruthenate                                |
|    | THF                             | = | Tetrahydrofuran                                                 |
|    | DEPBT                           | = | 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-             |
| 25 |                                 |   | one                                                             |
|    | DMAP                            | = | 4-dimethylaminopyridine                                         |
|    | P-EDC                           | = | Polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide |
|    | EDC                             | = | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide                   |
| 30 | DMF                             | = | <i>N,N</i> -dimethylformamide                                   |
|    | Hunig's Base                    | = | <i>N,N</i> -Diisopropylethylamine                               |
|    | MCPBA                           | = | <i>meta</i> -Chloroperbenzoic Acid                              |
|    | azaindole                       | = | 1 <i>H</i> -Pyrrolo-pyridine                                    |

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|    |                 |   |                                               |
|----|-----------------|---|-----------------------------------------------|
|    | 4-azaindole     | = | 1H-pyrrolo[3,2-b]pyridine                     |
|    | 5-azaindole     | = | 1H-Pyrrolo[3,2-c]pyridine                     |
|    | 6-azaindole     | = | 1H-pyrrolo[2,3-c]pyridine                     |
|    | 7-azaindole     | = | 1H-Pyrrolo[2,3-b]pyridine                     |
| 5  | 4,6-diazaindole | = | 5H-Pyrrolo[3,2-d]pyrimidine                   |
|    | 5,6-diazaindole | = | 1H-Pyrrolo[2,3-d]pyridazine                   |
|    | 5,7-diazaindole | = | 7H-Pyrrolo[2,3-d]pyrimidine                   |
|    | PMB             | = | 4-Methoxybenzyl                               |
|    | DDQ             | = | 2, 3-Dichloro-5, 6-dicyano-1, 4-benzoquinone  |
| 10 | OTf             | = | Trifluoromethanesulfonyl                      |
|    | NMM             | = | 4-Methylmorpholine                            |
|    | PIP-COPh        | = | 1-Benzoylpiperazine                           |
|    | NaHMDS          | = | Sodium hexamethyldisilazide                   |
|    | EDAC            | = | 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide |
| 15 | TMS             | = | Trimethylsilyl                                |
|    | DCM             | = | Dichloromethane                               |
|    | DCE             | = | Dichloroethane                                |
|    | MeOH            | = | Methanol                                      |
|    | THF             | = | Tetrahydrofuran                               |
| 20 | EtOAc           | = | Ethyl Acetate                                 |
|    | LDA             | = | Lithium diisopropylamide                      |
|    | TMP-Li          | = | 2,2,6,6-tetramethylpiperidinyllithium         |
|    | DME             | = | Dimethoxyethane                               |
|    | DIBALH          | = | Diisobutylaluminum hydride                    |
| 25 | HOBT            | = | 1-hydroxybenzotriazole                        |
|    | CBZ             | = | Benzyloxycarbonyl                             |
|    | PCC             | = | Pyridinium chlorochromate                     |

### Chemistry

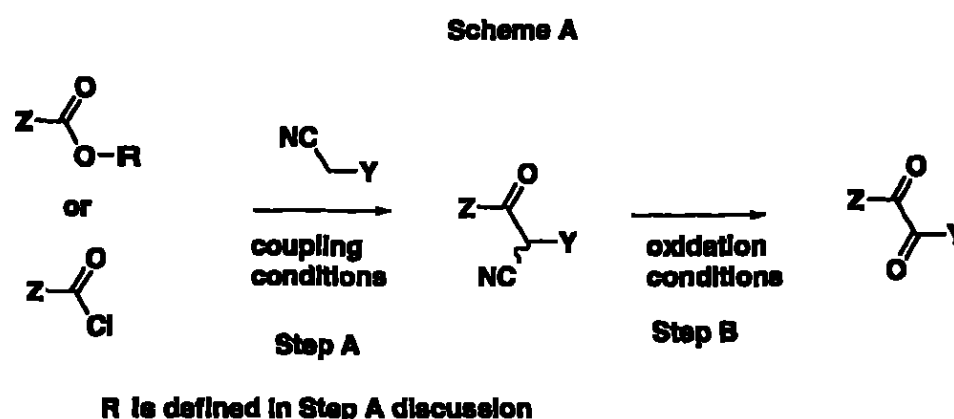
30        The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to



HIV infection. The compounds of Formula I include pharmaceutically acceptable salts thereof.

The synthesis procedures and anti-HIV-1 activities of substituted diazaindole oxoacetic and piperidine containing analogs are described below.

Scheme A depicts one of the preferred methods for preparing the compounds of the invention. In this method, as shown in Step A, a functionalized diazaindole which also has a carboxy ester appended to the three position is condensed with an acetonitrile anion functionalized with Y to provide the alpha cyano ketone examples of the invention. Oxidation of these compounds as shown in Step B, provides further compounds of the invention.



15

**Step A.** The carboxylic ester intermediates  $Z\text{-CO}_2\text{R}$  or more preferably the acid chlorides  $Z\text{-CO}_2\text{Cl}$  from Scheme A are condensed with a cyanomethyl intermediate  $\text{YCH}_2\text{CN}$  under basic conditions to form the  $\alpha$ -cyanoketo intermediate  $Z\text{C(O)CH(CN)Y}$ . The base KHMDS in THF at r.t. is employed most often, but other amide bases such as NaHMDS could be utilized. The typical solvent utilized is THF but DMF can be employed for less soluble molecules. Typically the reaction with an acid chloride  $Z\text{-CO}_2\text{Cl}$  is conducted with the reaction flask immersed in a dry ice acetone cooling bath ( $\sim -78^\circ\text{C}$ ) when THF is the solvent and an acetonitrile / acetone cooling bath ( $\sim -42^\circ\text{C}$ ) when DMF is the solvent but temperatures between  $-78^\circ$  and  $50^\circ\text{C}$  could be employed in appropriate cases. The reaction is stirred between 1 h and 1 day. Typically the reaction when judged to be complete by TLC or LC or

20

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LC/MS is maintained at the cold temperature and oxidant added directly to the reaction as described in Step B. Alternatively the reaction could be allowed to attain ambient temperature and either allowed to react further if necessary and then quenched or be immediately quenched with saturated aqueous sodium bicarbonate.

5 The mixture could then be extracted with EtOAc, concentrated and the  $\alpha$ -cyanoketo intermediate  $ZC(O)CH(CN)Y$  could be purified by preparative HPLC. When the same reaction is carried out with an ester  $Z-CO_2R$  as the reactant, the alkylation reaction is initiated and then is usually allowed to warm to ambient temperature for further reaction. Typically R is methyl or ethyl or less ideally another lower alkyl

10 group. Phenoxy, pentafluorophenoxy, or Weinreb esters ( $R = -NH_2OMe$ ) might also be employed. As mentioned above, in the event that the carboxylic ester intermediates  $Z-CO_2R$  are less reactive than desired under the standard condensation conditions, they may be activated by the initial conversion to an acid chloride  $Z-COCl$  (OR where  $R = H$  converted to  $Cl$ ). This is currently the preferred method for

15 diazaindole esters of this invention. The preparation of the acid chlorides from  $Z-CO_2R$  - is accomplished by initial hydrolysis of the ester to the analogous carboxylic acid  $Z-CO_2H$ . A typical procedure involves stirring the ester with  $LiOH$  in THF and water at  $100^\circ C$  for 6 h to 2 days, concentrating the crude mixture and recrystallizing the carboxylic acid from water. The carboxylic acid  $Z-CO_2H$  is then dissolved or

20 more typically suspended as a slurry in dichloromethane and stirred with oxalyl chloride and a catalytic amount of DMF from 4-24h but typically overnight. The solvents are removed in vacuo and the acid chloride used directly. Possible alternative solvents are benzene or toluene. A possible alternative method for conversion of the carboxylic acid to an acid chloride entails reacting thionyl chloride

25 in benzene at  $100^\circ C$  between 2 h and 6 h with the acid in the presence of catalytic DMF followed by concentration in vacuo to yield the acid chloride  $Z-CO_2Cl$ . As mentioned above, the acid chloride  $Z-CO_2Cl$  is the preferred reactant for conducting step A for the preparation of diazindole compounds of formula I. Alternatively, the acid may be converted to an acid anhydrides which may also find utility in the

30 alkylation reaction.

*Step B.* The preferred method for accomplishing step B, the conversion of the  $\alpha$ -cyanoketo intermediate  $ZC(O)CH(CN)Y$  to the diacarbonyl compounds of

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formula I or ketoamide intermediates to prepare compounds of formula I is to add 1-20 equivalents but most preferably 5 equivalents of a commercially available solution of 32% peracetic acid in dilute aq acetic acid to the reaction flask containing the completed reaction described in Step A. The reaction is typically stirred at the same temperature at which the alkylation reaction was conducted (for the Step A reactions with an acid chloride in THF  $\sim -78^\circ$  and for the step A reactions in DMF  $\sim -42^\circ$ ) for a period of 1h and then allowed to warm to ambient temperature if not already at that temperature. The reaction mixture is then either allowed to react further or immediately diluted with saturated aq. ammonium chloride and EtOAc.

For relatively insoluble acid products which precipitate, the resultant precipitate is isolated by filtration as the oxoacetyl product  $ZC(O)C(O)Y$ . For organic soluble acid products, the acid is extracted into the organic layer and the layers separated. The organic layer is concentrated in vacuo and the product purified via preparative HPLC. The  $\alpha$ -cyanoketo intermediate  $ZC(O)CH(CN)Y$ , if isolated, can be oxidized to the oxoacetyl product  $ZC(O)C(O)Y$  using a variety of oxidants including mCPBA, NaOCl (bleach), peracetic acid, or nickel peroxide. In a typical procedure a solution of peracetic acid in acetic acid is added to a solution of  $\alpha$ -cyanoketo intermediate  $ZC(O)CH(CN)Y$  in THF and the reaction is stirred at between r.t. and  $-70^\circ C$  for between 30 min and 2 h. The reaction mixture is then diluted with saturated aq. ammonium chloride and EtOAc and the resultant precipitate is isolated by filtration as the oxoacetyl product  $ZC(O)C(O)Y$ . Step A and Step B can be combined into a one pot reaction by adding the oxidant directly to the reaction pot after the completion of step A without isolating the  $\alpha$ -cyanoketo intermediate  $ZC(O)CH(CN)Y$ .

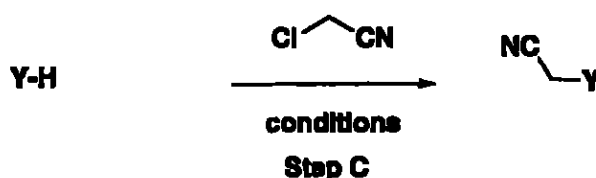
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Scheme B depicts a typical method for preparing the cyanomethyl piperazine or piperidine analogues utilized in scheme A. Two general literature references for some of the chemistry depicted in these initial schemes are Takahashi, K.; Shibasaki, K.; Ogura, K.; Iida, H.; *Chem Lett.* 1983, 859 or Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T.; *Org. Lett.* 2002, 4, 1103.

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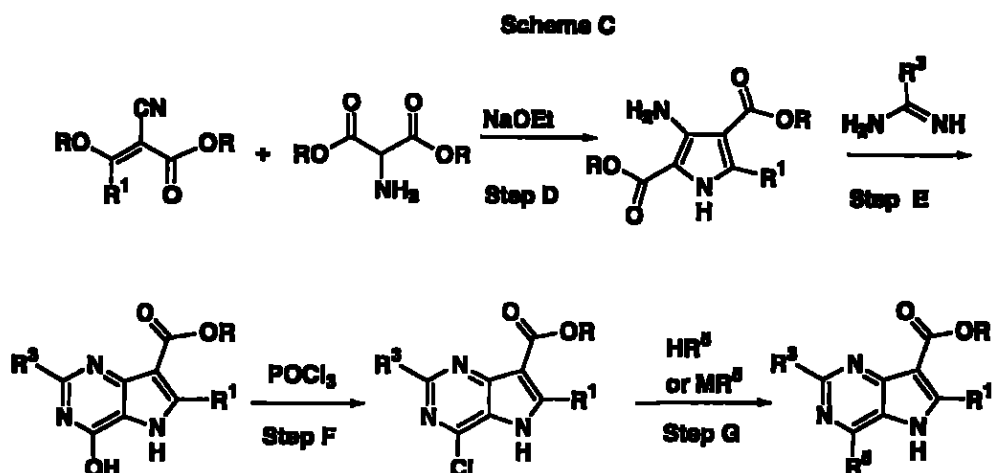
Scheme B



Step C. The secondary amine of a functionalized piperazine or piperidine can be alkylated with a haloacetonitrile under basic conditions to yield a cyanomethyl piperazine or piperidine analogue. In a typical procedure N-benzyl piperazine was added to a solution of chloroacetonitrile and TEA in THF and stirred at r.t. for between 2 and 5 days. A resulting precipitate is removed by filtration, the filtrate is concentrated in vacuo, and the residue purified via chromatography to yield the cyanomethyl intermediate YCH<sub>2</sub>CN. The alkylation with haloacetonitrile can also be carried out with an alternate base, such as 4-methylmorpholine or diisopropylethyl amine.

The diazaindole carboxylic ester condensation partners Z-C(O)OR utilized in Scheme A can be prepared as shown in the following schemes:

One preferred method for preparing 4,6 diazaindole is shown in Scheme C.



R is as defined in Step A

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**Step D.** The reaction of an (alkoxymethylene)cyanoacetate with an amino malonate under basic conditions is known to yield a 2,4-dicarboxylic ester-3-aminopyrrole. As shown in Scheme C, step D is carried out by reacting an amino malonate with an 2-alkoxy 1-cyano acrylate in the presence of a base such as sodium ethoxide. For a representative example see; Elliot, A. J.; Montgomery, J. A., and Walsh, D. A. *Tetrahedron Lett*, 1996, 37(25), 4339-4340. A typical procedure and conditions is is described in the experimental section.

**Step E.** The 3-Aminopyrrole 2-carboxylic ester resulting from step D can be cyclized to the desired 7-hydroxyl-4,6-diazaindole using a number of reagents including formamides, dialkyl acetal formamides, nitriles and formamidines. In a typical procedure 3-aminopyrrole-2,4-dicarboxylic acid diethyl ester and formidine acetate are heated at reflux in EtOH for 1 to 3 days. The reaction solution is filtered hot and the product usually crystallized upon cooling and is then rinsed with diethyl ether.

**Step F.** A 3-carboxylic ester 7-hydroxyl-4,6-diazaindole can then be converted to a 7-chloro analogue by treatment with a chlorinating reagent such as POCl<sub>3</sub> or SOCl<sub>2</sub>. In a typical reaction procedure 3-ethylester-7-hydroxyl-4,6-diazaindole and POCl<sub>3</sub> are combined and heated at 105 °C for between 3 and 5 h, cooled to r.t. and diluted with diethyl ether. The precipitate that forms is collected by filtration and was shown to be the 7-chloro-4,6-diazaindole. Alternatively, when greater reactivity is desired for further functionalization and for carrying out step G, the corresponding 7-bromo-4,6-diazaindole may be prepared by substituting POBr<sub>3</sub> for the chlorinating agents described above.

**Step G.** A 7-chloro-4,6-diazaindole can be displaced with a variety of nucleophiles to form the claimed R<sup>5</sup> substituents or intermediates from which the claimed R<sup>5</sup> substituents can be formed. Included in these are cyanide, alkoxides, amines, alcohols and various metallated species (cuprates, lithiates, zincates and Grignard reagents). In a typical procedure 3-ethylester-7-chloro-4,6-diazaindole and 3-methyl pyrazole in EtOH are heated at between 100 °C and 140 °C for 20 min to 1 h. Upon cooling the reaction is concentrated and purified by silica gel

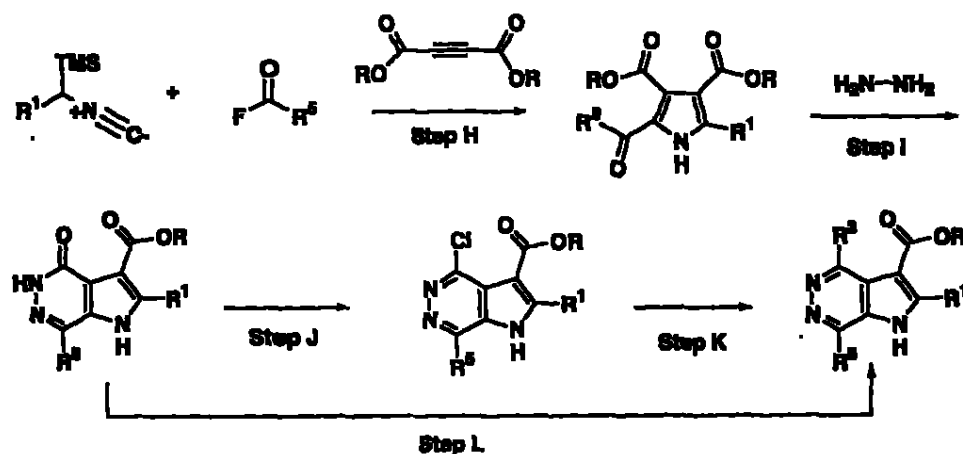
chromatography or by preparative HPLC. This step may also be carried out after the initial coupling and oxidation steps (steps A and B) have been preformed on the 3-ethylester-7-chloro-4,6-diazaindoles intermediate. A cyano moiety could be introduced and converted to acids, esters, amides, imidates, or heteraromatics.

- 5 Typical amide coupling methodology could be used to prepare amides from acids. It should also be noted that the halogen moiety may be carried through until compounds of the invention are realized and then the conditions described in Step G may frequently be used to prepare further compounds of the invention.

- 10 Alternatively, a 7-chloro or 7-bromo-4,6-diazaindoles could be coupled to a heteroaryl stannane or boronic ester via Stille or Suzuki methodology respectively. Other metal catalyzed methodology such as copper mediated displacements could also be used to prepare N linked heteraromatic or heteroalicyclic derivatives. In general, substituted diazaindoles containing a chloride, bromide, iodide, triflate, or
- 15 phosphonate should undergo coupling reactions with a boronate (Suzuki type reactions) or a stannane to provide substituted diazaindoles. Stannanes and boronates are prepared via standard literature procedures or as described in the experimental section of this application. The vinyl bromides, chlorides, triflates, or phosphonates may undergo metal mediated coupling to provide compounds of formula W-H. Stille
- 20 or Suzuki couplings are particularly useful. A detailed discussion of the references and best conditions for these kinds of metal mediated coupling is described later in this application where the discussion is combined with a description of how these types of reactions may also be used to functionalize diazaindoles. In additions, applications incorporated in their entirety elsewhere in this application contain
- 25 methods for preparing heteroaryls from functional groups appended to indoles and azaindoles. This methodology is also applicable to diazaindoles.

One potential method for preparing the 5,6-diazaindoles QCOOR is shown in Scheme D.

Scheme D



R is as defined in step J

- 5 **Step H.** A TMS-isocyanide would be reacted with an acid fluoride in the presence of a dialkyl acetylene dicarboxylate to form a substituted pyrrole. For representative examples see: Livinghouse, T.; Smith, R.; *J. Chem. Soc., Chem. Commun* 1983, 5, 210. In a typical procedure, trimethylsilylmethyl isocyanide (generated from the lithiation of methyl isocyanide, followed by silylation with
- 10 TMSCl) would be stirred with an aryl acid fluoride and dimethyl acetylenedicarboxylate in toluene at 80° C. After a standard workup a functionalized pyrrole where R<sup>1</sup> is hydrogen and R<sup>5</sup> is aryl would be realized.

- 15 **Step I.** A mixture of the keto-diester-pyrrole and hydrazine dihydrochloride in ethanol heated at reflux should result in the formation of the desired 4-hydroxyl-5,6-diazaindole. Alternatively, the keto-diester-pyrrole, hydrazine hydrate and a catalytic amount of p-toluenesulfonic acid could be heated to reflux in toluene or benzene in the presence of a Dean-Stark trap and upon dehydration, the desired 4-hydroxyl-5,6-diazaindole should form.

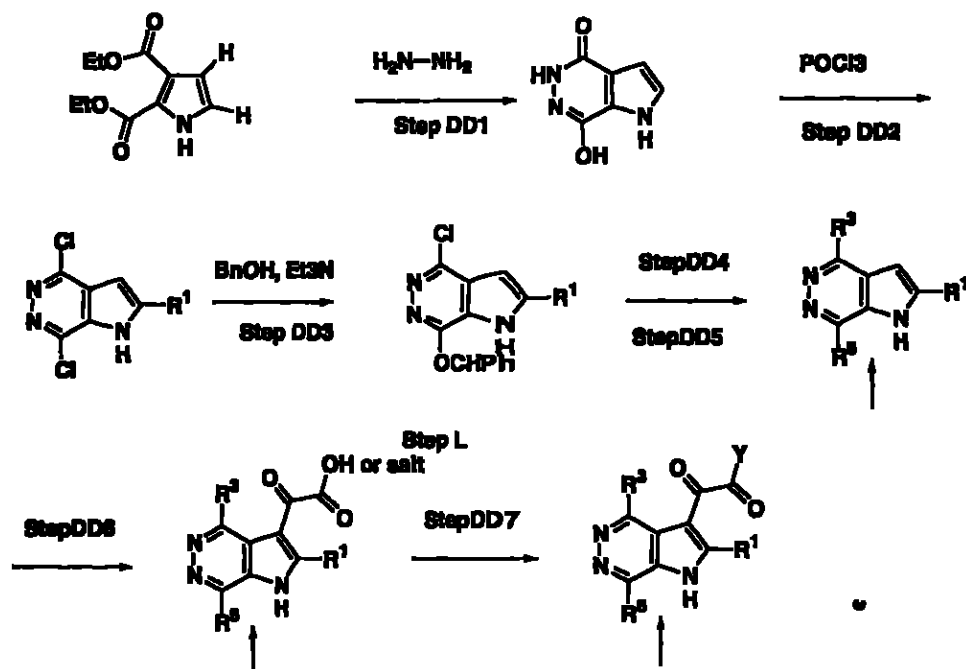
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**Step J, Step K and Step L.** A 4-hydroxyl-5,6-diazaindole intermediate could be converted to the intermediates in which R<sup>3</sup> is modified by direct functionalization of the hydroxyl group or by conversion of the hydroxyl group to a leaving group (halogen or triflate) followed by nucleophilic displacement or a metal

(Pd or Cu) mediated coupling. These step(s) might also be carried out after the initial coupling and oxidation steps (steps A and B) have been performed on the 4-hydroxyl-5,6-diazaindole intermediate. The conditions described for step G could also be utilized for this system.

5

Scheme DD



R is as defined in step J

- As shown in Scheme DD pyrrole 2,3 di-carboxylic ethyl ester prepared as in
- 10 either of the following two references: Roeder, Erhard; Wiedenfeld, Helmut; Bourauel, Thomas. *Synthesis of ethyl 2,3-bis(ethoxycarbonyl)-1H-pyrrole-1-proplionate*. Liebigs Annalen der Chemie (1987), (12), 1117-19. and Swan, George A.; Waggott, A. *Chemistry of melanins. VI. Syntheses of 3-carboxypyrrole-2-acetic acid, 3,5-dicarboxypyrrole-2-acetic acid, and related compounds*, Journal of the
- 15 Chemical Society [Section] C: Organic (1970), (2), 285-90. could be reacted with hydrazine in ethanol between RT and reflux to provide the cyclized product of step DD1. Reaction with phosphoryl chloride (2.2 to 5 equivalents) should provide the dichloride as shown in step DD2. In step DD3, selective reaction of the C-7 chloride could occur by using benzyl alcohol and triethylamine in a cosolvent such as THF.
- 20 In step DD4, the 4-chloro group might then be displaced with sodium or potassium



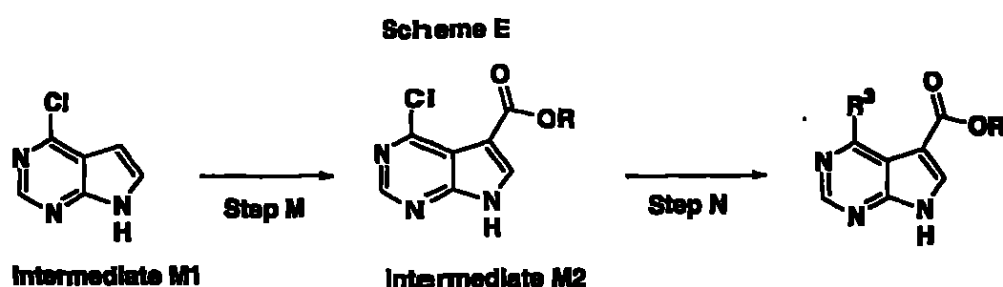
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methoxide in solvents such as methanol or toluene or a mixture. Stoichiometric copper I iodide could be added to speed slow reactions. In step DD5, selective hydrogenation of the benzyl group using 5 to 10% Pd/C in EtOH under a balloon pressure of hydrogen provides the 7-hydroxy compound. Alternatively the benzyl group may be cleaved selectively with TMSI in acetonitrile at temperatures from 0 to 65°C or using HBr in 1,2-dichloroethane at temps from -20 to 50°C. An alternate prep is to react the dichlorointermediate above with methoxide rather than benzyl alcohol and then to selectively cleave the C-7 ether using conditions described for the benzyl cleavage. Reacting the C-7 hydroxy group /amide tautomer with POCl<sub>3</sub> or POBr<sub>3</sub> would generate the chloride or bromide selectively which may be functionalized as described in step G of Scheme C for the 4,6-diazindoles. Step DD6 describes acylation of the functionalized intermediate and is done using the same procedures described in step O of Scheme F. Step DD7, amide coupling with piperazine or piperidine is carried out according to the general procedures described in Step P of Scheme F to provide compounds of the invention. It should be understood that the order of steps DD5-DD7 could be switched to determine which order provides best yields.

The 5,7-diazaindole could be prepared as shown in Scheme E. Intermediate M1 is a known compound whose synthesis has been described in the literature in the following references: Olsen, David B.; Lafemina, Robert L.; Eldrup, Anne B.; Bera, Sanjib. *Methods of inhibiting orthopoxvirus replication with nucleoside compounds*. PCT Int. Appl. (2003), 99 pp. WO 2003068244A1 Mekouar, Khalid; Deziel, Robert; Mounir, Samir; Iyer, Radhakrishnan P. *Preparation of 7-deaza L-nucleosides as antiviral agents against the hepatitis B virus*. PCT Int. Appl. (2003), WO 2003055896A2 Carroll, Steven S.; Lafemina, Robert L.; Hall, Dawn L.; Himmelberger, Amy L.; Kuo, Lawrence C.; Maccoss, Malcolm; Olsen, David B.; Rutkowski, Carrie A.; Tomassini, Joanne E.; An, Haoyun; Bhat, Balkrishen; Bhat, Neelima; Cook, Phillip Dan; Eldrup, Anne B.; Guinosso, Charles J.; Phavc, Marija; Prakash, Thazha P. *Preparation of nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase*. PCT Int. Appl. (2002), 235 pp. CODEN: PIXXD2 WO 2002057425A2 Carroll, Steven S.; Maccoss, Malcolm; Olsen, David B.; Bhat, Balkrishen; Bhat, Neelima; Cook, Phillip Dan; Eldrup, Anne B.; Prakash, Thazha P.;

Prhenc, Marija; Song, Quanlai. *Preparation of nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase*. PCT Int. Appl. (2002), WO 2002057287A2. 68



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**Step M.** Friedel-Crafts acylation of diazindole.

Intermediate M2 where R is ethyl is a known compound which could be prepared as described in the following three literature references:

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Ugarkar, Bheemarao G.; DaRe, Jay M.; Kopcho, Joseph J.; Browne, Clinton E., III; Schanzer, Juergen M.; Wiesner, James B.; Erion, Mark D. *Adenosine Kinase Inhibitors. 1. Synthesis, Enzyme Inhibition, and Anti-seizure Activity of 5-Iodotubercidin Analogues*. *Journal of Medicinal Chemistry* (2000), 43(15), 2883-2893.

15

Firestein, Gary Steven; Ugarkar, Bheemarao Ganapatrao; Miller, Leonard Paul; Gruber, Harry Edward; Bullough, David Andrew; Erion, Mark David; Castellino, Angelo John. *Preparation of adenosine kinase-inhibiting purine nucleoside analogs as antiinflammatory agents*. PCT Int. Appl. WO 9417803A1.

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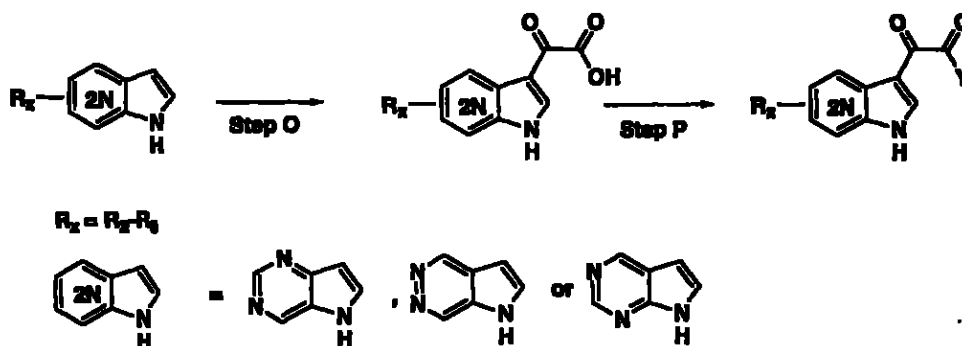
Browne, Clinton E.; Ugarkar, Bheemarao G.; Mullane, Kevin M.; Gruber, Harry E.; Bullough, David A.; Erion, Mark D.; Castellino, Angelo. *Adenosine kinase inhibitors*. *Eur. Pat. Appl.* EP 496617 A1.

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**Step N.** Nucleophilic or metal catalyzed substitution of the 4-chloro-5,7-diazindole will yield the R<sup>3</sup> substituents of claim 1.

The diazaindole core may be coupled to the functionalized piperidine or piperazine through an oxoacetate or through an acylation/amidation process as shown in Scheme F.

Scheme F



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**Step O.** Conversion of a specific 3H-diazaindole to the depicted ketoacid might be accomplished via several methods. *Method a for step O:* One successful method has been to use Friedel-Crafts acylation conditions mediated by an ionic liquid. In particular the ionic liquid 1-alkyl-3-alkylimidazolium chloroaluminate is generally useful in promoting the Friedel-Crafts type acylation and does work with some diazaindoles. 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 diazaindoles with methyl or ethyl chlorooxoacetate would be the 1-ethyl-3-methylimidazolium chloroaluminate. The reaction would typically be performed at ambient temperature and the diazaindoleglyoxyl ester would be expected to be isolated. The resulting ester could then be hydrolyzed using the hydrolysis methods for Step O described below.

More conveniently, it is probable that the glyoxyl ester could be hydrolyzed *in situ* at ambient temperature upon prolonged reaction time (typically overnight) to give the corresponding glyoxyl acid which would be ready for amide formation.

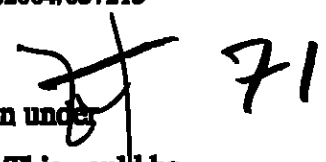
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A representative experimental procedure is as follows: 1-ethyl-3-methylimidazolium chloride (2 equiv.; purchased from TCI; weighted under a stream of nitrogen) would be stirred in an oven-dried round bottom flask at r.t. under a nitrogen atmosphere, and then aluminium chloride (6 equiv.; anhydrous powder packaged under argon in ampules purchased from Aldrich preferred would be added; after weighing under a stream of nitrogen). The mixture would be vigorously stirred to form a liquid, to which would then be added diazaindole (1 equiv.) followed by stirring until a homogenous mixture resulted. To the reaction mixture would then be added dropwise ethyl or methyl chlorooxoacetate (2 equiv.) and then stirring would be continued at r.t. for 2 to 24h, probably approximately 16 h. After stirring was completed, the mixture an ice-water bath and the reaction would be quenched by carefully adding excess water. The precipitates would be filtered, washed with water and dried under high vacuum to give the diazaindoleglyoxylic acid. For some examples, 3 or even equivalents of 1-ethyl-3-methylimidazolium chloride and chlorooxoacetate may be required. A more comprehensive reference with analogous examples with non diazaindoles but with conditions that could be utilized with diazaindoles is contained in: Yeung, Kap-Sun; Parkas, Michelle B.; Qiu, Zhilei; Yang, Zhong. *Friedel-Crafts acylation of indoles in acidic imidazolium chloroaluminate ionic liquid at room temperature*. *Tetrahedron Letters* (2002), 43(33), 5793-5795.4 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 00/15594.

*Step O method B.* The diazaindole could be treated with a Grignard reagent such as MeMgI (methyl magnesium iodide), methyl magnesium bromide or ethyl magnesium bromide and then a zinc halide, such as ZnCl<sub>2</sub> (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 diaza-indole glyoxyl ester. Oxalic acid esters such as methyl oxalate, ethyl oxalate or as above are used. Aprotic solvents such as CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, benzene, toluene, DCE, THF, dioxane or the like could potentially be used alone or in combination for this sequence.



*Step O method c:* A Lewis acid catalyzed Friedel-Crafts reaction under standard conditions with an alkyl chloroacetoacetate might be utilized. This could be followed by in situ hydrolysis of the ester by the method described below to form the diazindole ketocarboxylic acid (cite previous patent(s)). Thus the diazindole ketoester precursors to the depicted acid could be prepared by reaction of diazindoles with an excess of ClCOCOOME in the presence of AlCl<sub>3</sub> (aluminum chloride). Some further descriptions of the exact procedures to carry out this reaction but on indoles or azaindoles are contained in a) Zhang, Zhongxing; Yang, Zhong; Wong, Henry; Zhu, Juliang; Meanwell, Nicholas A.; Kadow, John F.; Wang, Tao. "An Effective Procedure for the Acylation of Azaindoles at C-3." *J. Org. Chem.* 2002, 67(17), 6226-6227; b) Tao Wang et. al. US Patent 6,476,034 B2 "Antiviral Azaindole derivatives" published Nov 5, 2002; c) W. Blair et al. PCT patent application WO 00/76521 A1 published Dec 21, 2000; d) O. Wallace et. al. PCT application WO 02/04440A1 published January 17, 2002. Some reactions of 5-cyano-6-chloro-7-azaindoles and lactam-lactim tautomerism in 5-cyano-6-hydroxy-7-azaindoles. *Khim. Geterotsikl. Soedin.*, 1987, 100-106). Typically an inert solvent such as CH<sub>2</sub>Cl<sub>2</sub> would be used but others such as THF, Et<sub>2</sub>O, 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. Lewis acid catalysts, such as tin tetrachloride, titanium IV chloride, and aluminum chloride could be employed with this transformation with aluminum chloride being most preferred.

*Hydrolysis methods for Step O.* Hydrolysis of a diazindole keto methyl ester would afford a potassium salt of the acid product shown as the product for Step O in Scheme F and this would then be ready for coupling with amines as shown in the next step. Acidification during workup, typically with aqueous HCl would provide the acid products from Step O as shown. 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  $\text{CH}_2\text{Cl}_2$  or THF in the presence of Triton B.

5 Temperatures of  $-78^\circ\text{C}$  to the boiling point of the solvent may be employed but  $-10^\circ\text{C}$  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.

10 *Step P.* The ketocarboxylic acid may be coupled with functionalized piperidines or piperazines using a number of standard amide bond or peptide bond forming coupling reagents. The acid intermediate  $\text{Z-C(O)(O)OH}$  from Scheme F could be coupled with either a substituted piperazine or piperidine, H-Y using standard amide bond or peptide bond forming coupling reagents. The combination of

15 EDAC and triethylamine in tetrahydrofuran or BOPCl and diisopropyl ethyl amine in chloroform could be utilized but DEPBT, or other coupling reagents such as PyBop could be utilized. Another useful coupling condition employs HATU (L.A. Carpino et. al. J.Chem.Soc. Chem Comm. 1994, 201-203; A. Virgilio et.al. J.Am. Chem. Soc. 1994, 116,11580-11581). A general procedure for using this reagent is Acid (1eq)

20 and H-Y or H-W-Boc or HCl salt (2eq) in DMF are stirred at rt for between 1 h and 2 days. HATU (2eq) is added in one portion and then DMAP(3eq). The reaction could be stirred at rt for 2 to 15h (reaction progress monitored by standard methods is TLC, LC/MS). The mixture is filtered through filter paper to collect the solid. The filtrate is concentrated and water is added. The mixture is filtered again and the solid is

25 washed with water. The solid is combined and washed with water. Many reagents for amide bond couplings are known by an organic chemist skilled in the art and nearly all of these are applicable for realizing coupled amide products.

DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one) and *N,N*-

30 diisopropylethylamine, commonly known as Hunig's base, represents another efficient method to form the amide bond (step P). DEPBT is either purchased from Adrich or prepared according to the procedure of Ref. 28, Li, H.; Jiang, X.; Ye, Y.-

o

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 amide bond construction reaction could be carried out using the preferred conditions described above, the HDC conditions described below, other coupling conditions described in this application, or alternatively by applying the conditions or coupling reagents for amide bond construction described in incorporated applications for construction of substituents R<sub>2</sub>-R<sub>5</sub> on indoles or azaindoles. Some specific nonlimiting examples are given in this application.

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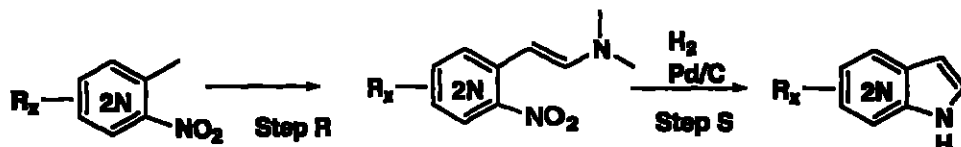
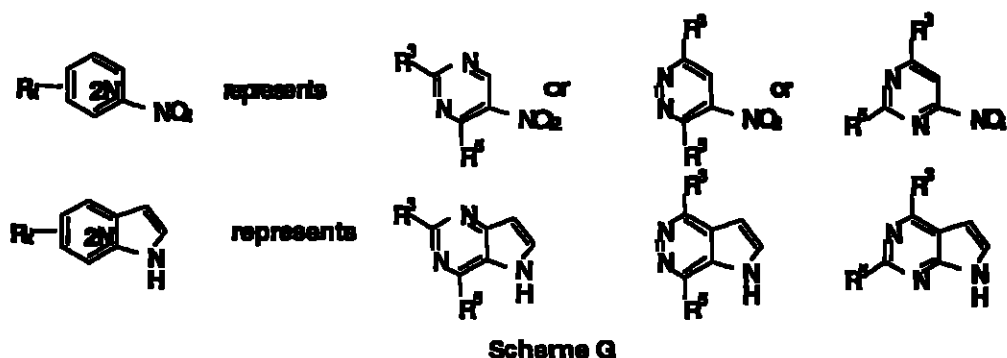
Alternatively, the acid could be converted to a methyl ester using excess diazomethane in THF/ether. The methyl ester in dry THF could be reacted with the lithium amide of intermediate H-Y. The lithium amide of H-Y, Li-Y is formed by reacting H-Y with lithium bistrimethylsilylamide in THF for 30 minutes in an ice water cooling bath. Sodium or potassium amides could be formed similarly and utilized if additional reactivity is desired. Other esters such as ethyl, phenyl, or pentafluorophenyl could be utilized and would be formed using standard methodology.

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In addition, the acid can be converted to the acid chloride using oxalyl chloride in a solvent such as benzene or thionyl chloride either neat or containing a catalytic amount of DMF. Temperatures between 0°C and reflux may be utilized depending on the substrate. Compounds of Formula I can be obtained from the resultant compounds of formula Z-C(O)(O)Cl by reaction with the appropriate H-Y in the presence of a tertiary amine (3-10 eq.) such as triethylamine or diisopropylethylamine in an anhydrous aprotic solvent such as dichloromethane, dichloroethane, diethyl ether, dioxane, THF, acetonitrile, DMF or the like at temperatures ranging from 0°C to reflux. Most preferred are dichloromethane, dichloroethane, or THF. The reaction can be monitored by LC/MS. The 3H-diazaindoles may also be prepared under Bartoli or Liebig-Batchko reaction conditions as shown in schemeG. Conditions for carrying out these reactions were contained in the incorporated patent applications.

30

Note: For the purposes of brevity, the following symbol is taken to represent the following systems:



$R_1 = H$

5

Step Q. Step Q in Scheme G depicts a potential synthesis of a diazaindole intermediate, via the well known Bartoli reaction in which vinyl magnesium bromide reacts with an aryl or heteroaryl nitro groups, to form a five-membered nitrogen containing ring as shown. Some references for the above transformation to form an indole ring include: Bartoli et al. a) *Tetrahedron Lett.* 1989, 30, 2129. b) *J. Chem. Soc. Perkin Trans. I* 1991, 2757. c) *J. Chem. Soc. Perkin Trans. II* 1991, 657. d) *SynLett* (1999), 1594. In the preferred procedure, which could be applied to diazaindole synthesis, 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  $-78^\circ$  under an inert atmosphere of either nitrogen or Argon. After addition is completed, the reaction temperature is allowed to warm to  $-20^\circ$  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

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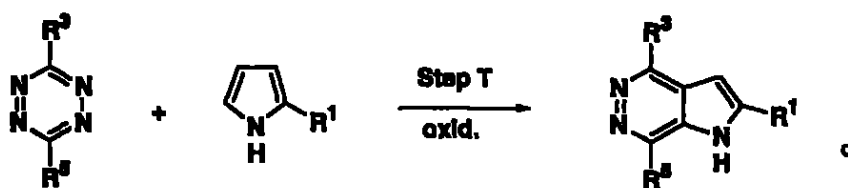
achieved using freshly prepared vinyl Magnesium bromide. In some cases, vinyl Magnesium chloride may be substituted for vinyl Magnesium bromide.

**Step R.** Reaction with dimethylformamide dimethyl acetal in an inert solvent or neat under conditions for forming Batcho-Leimgruber precursors would provide the cyclization precursor, 33, as shown. A typical condition would employ 20% DMF dimethyl acetal in DMF heated to 105-110 degrees C. 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.

**Step S.** Reduction of the nitro group using for example hydrogenation over Pt on /C catalyst in a solvent such as MeOH, EtOH, or EtOAc could provide the cyclized product. Generally only a slight positive pressure of hydrogen would be required (a stream) but higher pressures may be needed (1.5 atm). 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.

Another possible method for preparation of 5,6-diazaindoles is shown in scheme H.

Scheme H

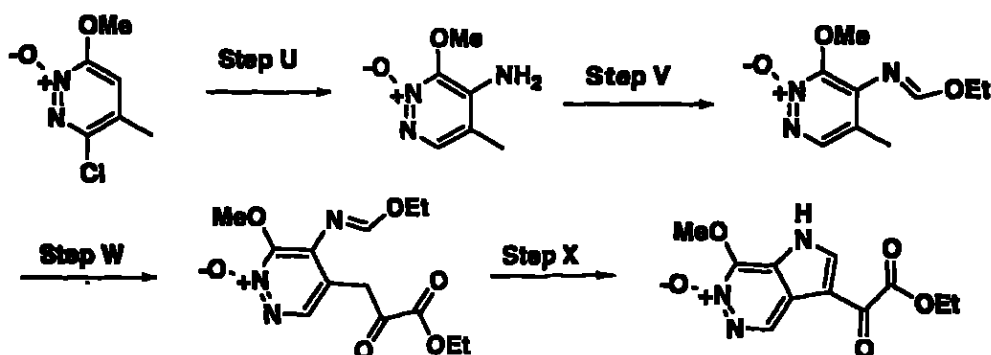


**Step T.** 1,2,3,4-Tetrazines have been shown to react with pyrrole and substituted pyrroles to form 5,6-diazaindole products. This reaction proceeds through a [4+2]-cycloaddition followed by a retro-[4+2]-cycloaddition to release nitrogen gas and a subsequent oxidation to establish aromaticity. For representative examples see: Seitz, Z.; Kaempchen, T.; *Arch. Pharm.* 1978, 311, 728. Takahashi,

M; Ishida, H.; Kohmoto, M. *Bull. Chem. Soc. Japan* 1976, 49, 1725. Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* 1987, 52, 4610. Gonzalez, J. C.; Lobo-Antunes, J.; Perez-Lourido, P.; Santana, L.; Uriate, E. *Synthesis* 2002, 4, 475-478.

- 5 Another possible method for preparing a 5,6-diazaindole with a C-3 oxoacetate is shown in Scheme I (Cook, P. D.; Castle, R. N. *J. Het. Chem.* 1973, 10, 551.

Scheme I



10

- Step U.** The starting pyridazine N-oxide would initially be nitrated and the resulting nitro group then would be reduced under standard conditions to an amine. The chloro would then be removed under hydrogenation conditions. Alternatively, the chloro could remain in the molecule and be carried through the subsequent steps. This should allow for the formation of a 4-chloro-5,6-diazaindole. The chloro could then be converted to a methoxy or an amino group by nucleophilic displacement or copper catalyzed assisted coupling. This would result in an intermediate that could be converted to molecules claimed within this application via previously described amide bond coupling.

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**Step V.** The amine could then be functionalized with ethyl orthoformate under acidic conditions to form an ethoxyimine. In a typical procedure the amine and triethyl orthoformate were dissolved into a solution of DMF and ethanol that had been adjusted to pH 1 with anhydrous hydrogen chloride. The reaction was then

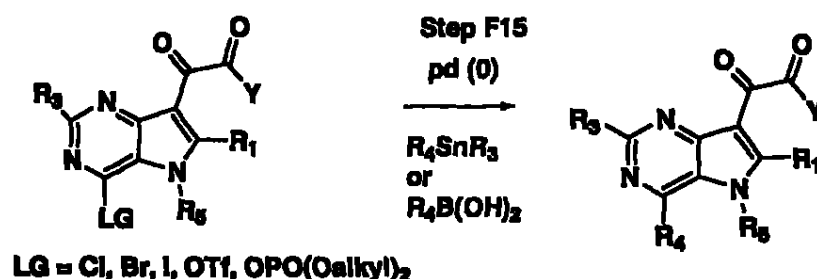
heated to 150-160 °C and ethanol was collected by distillation resulting in the formation of the desired ethoxyimine.

**Step W.** Deprotonation of the methyl group followed by acylation with diethyl oxalate would yield a ketoester intermediate that could be used to form a 3-oxoacetate-5,6-diazaindole (Step X) or could be used to make a 2-carboxylate-5,6-diazaindole by hydrolysis of the imine, followed by condensation of the amine onto the ketone five centers away.

**Step X.** The ketoester could then be cyclized onto the ethoxyimine under basic conditions to arrive at the 3-oxoacetate-5,6-diazaindole. To form the molecules of this claim, functionalized piperazine or piperidones could be coupled to the ester through standard amide bond forming reactions. This general scheme should also allow for the preparation of other 5,6-diazaindole intermediates with different R<sup>3</sup> and R<sup>4</sup> substituents by displacement or coupling to the chloro or displacement of the methoxy at some point in the sequence.

*Preparations of functionalized piperazines and piperidines are described later in the application.*

Scheme 15



**Step F15**

As shown above in Scheme 15, Step F15, substituted diazaindoles containing a chloride, bromide, iodide, triflate, or phosphonate could undergo coupling reactions with a boronate (Suzuki type reactions) or a stannane to provide substituted

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diazaindoles. Stannanes and boronates are prepared via standard literature procedures or as described in the experimental section of this application. The substituted diazaindoles may undergo metal mediated coupling to provide compounds of Formula I wherein  $R_4$  is aryl, heteroaryl, or heteroalicyclic for example. The bromo or chloro diazaindole intermediates, (or diazaindole 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 diazaindole 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 diazaindole 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 diazaindole intermediates are also feasible and have been utilized extensively for this invention. Preferred procedures for coupling of a chloro diazaindole 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 diazaindole 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°. 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. L.;  
 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.;  
 5 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.;  
 10 Hildebrand, D.; *Liebigs Ann. Chem.* 1993, 8, 837-839.

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

15

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.

20

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

Scheme T1a-01



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

Solvent = THF, ether, DME

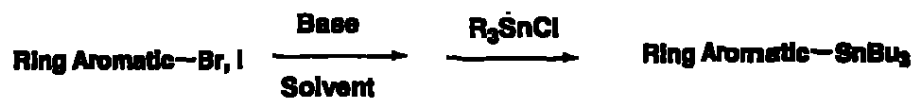
25

R = Me, Bu

75

## Scheme Tin-02

9 80



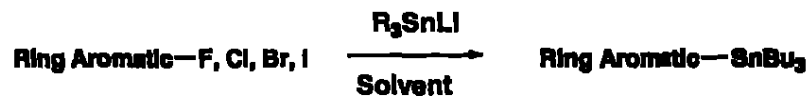
Base = n-BuLi, S-BuLi, t-BuLi

Solvent = THF, ether, DME

R = Me, Bu

5

## Scheme Tin-03

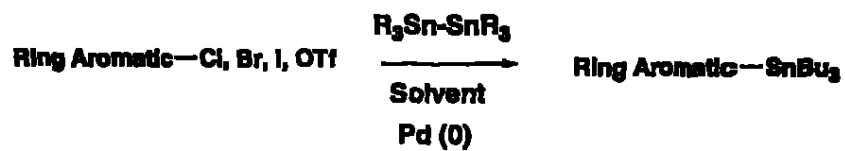


Solvent = THF, ether, DME

R = Me, Bu

## Scheme Tin-04

10



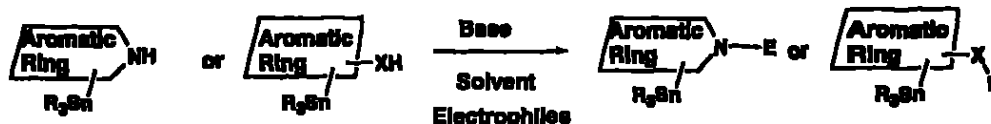
Solvent = Dioxane, Toluene

R = Me, Bu

15

20

## Scheme Tin-05



$E = \text{Electrophile} = R'-\text{halide}, R'-COCl, R'-OCOCi,$   
 $R'R''NCOCl, RSO_2Cl, R'NCO, R'NSO, R'NCNR''$

Solvent =  $CH_2Cl_2$ , THF, Ether, DMF

$R = Me, Bu$

Base =  $NaH, BuLi, LDA, K_2CO_3, Et_3N, DBU,$   
 DMAP, NaHMOS

- 5 Boronate reagents are prepared 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  $PdCl_2$
- 10 (dppf), KOAc, DMSO, at  $80^\circ C$  until reaction is complete when followed by TLC or HPLC analysis.

Related examples are provided in the following experimental section.

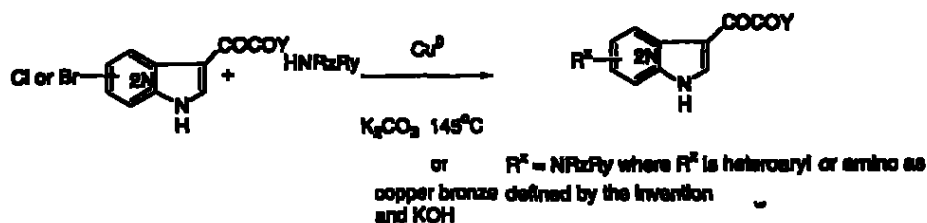
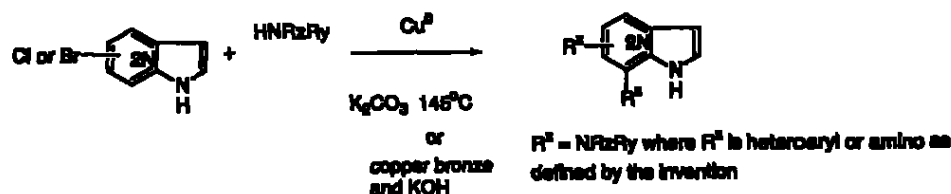
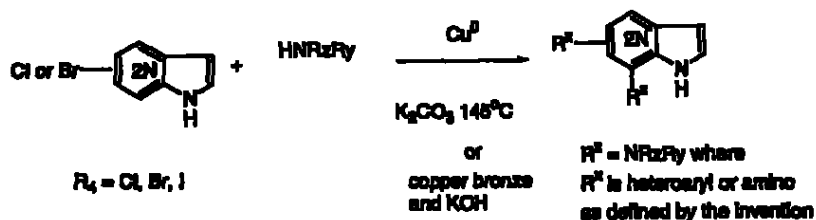
- 15 Methods for direct addition of aryl or heteroaryl organometallic reagents to alpha chloro nitrogen containing heterocycles or the N-oxides of nitrogen containing heterocycles are known and applicable to the diazaindoles. Some examples are Shiotani et. Al. *J. Heterocyclic Chem.* 1997, 34(3), 901-907;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

20

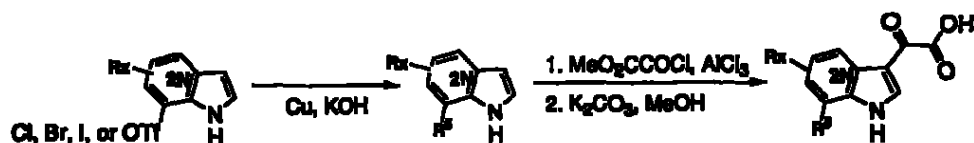
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71

## SCHEME 15aa

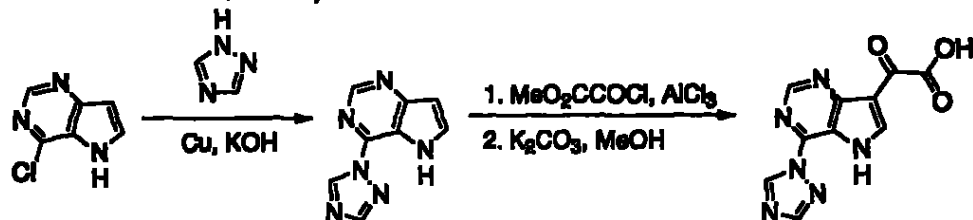


## SCHEME 15bb

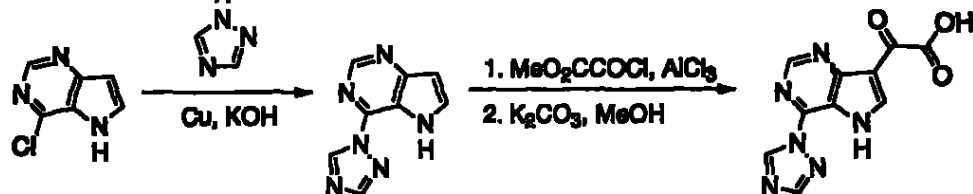


$(\text{R}^2\text{H}$  is a heteroaryl or amine with free N-H)

5



Proposed example



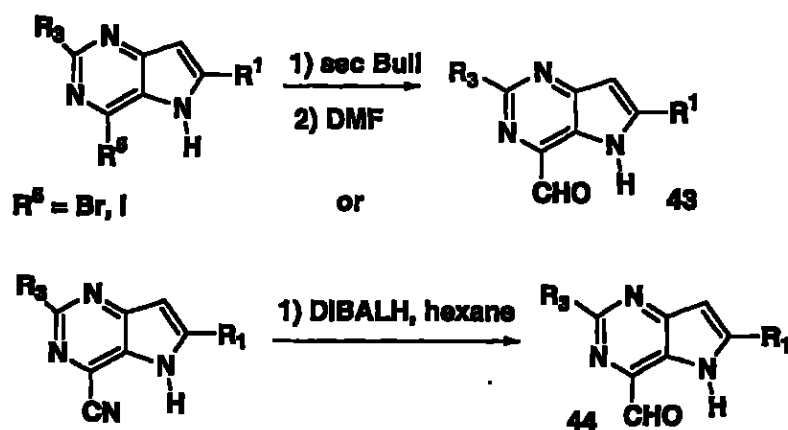
Direct displacements to install amine or N linked heteroaryl substituents could also be used to prepare compounds of Formula I. As shown in Schemes 15aa and 15bb, a mixture of halo-diazaindole intermediate, 1-2 equivalents of copper powder, 1-2 equivalents of potassium carbonate, and a 2-30 equivalents of the



corresponding heterocyclic reagent, with 10 equivalents preferred; was heated at 135-160°C for 4 to 9 hours. 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 could be carried out by heating 1 to 40 equivalents of the appropriate amine and an equivalent of the appropriate diazaindole chloride, bromide or iodide with copper bronze (from 0.1 to 10 equivalents (preferably about 2 equivalents) and from 1 to 10 equivalents of finely pulverized potassium hydroxide (preferably about 2 equivalents). Temperatures of 120° to 200° might be employed with 140-160° generally preferred. For volatile starting materials a sealed reactor may be employed. The reaction would most often be applicable when the halogen being displaced is at the 7-position of a diazaindole but the method could work when the halogen is at a different position (4-7 position possible). As shown above the reaction could be employed on diazaindoles 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

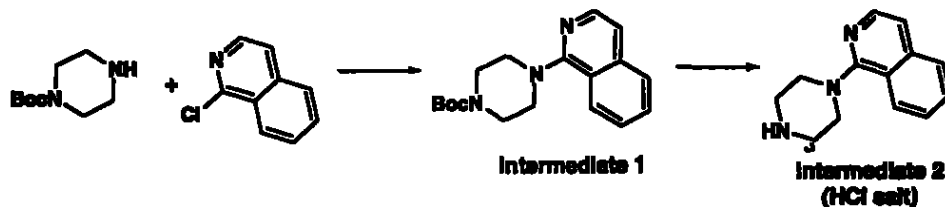
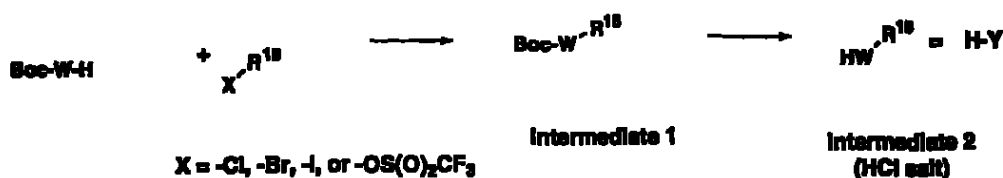


A possible preparation of a key aldehyde intermediate, 43, using a procedure adapted from the method of Gilmore et. Al. *Synlett* 1992, 79-80 is shown in Scheme

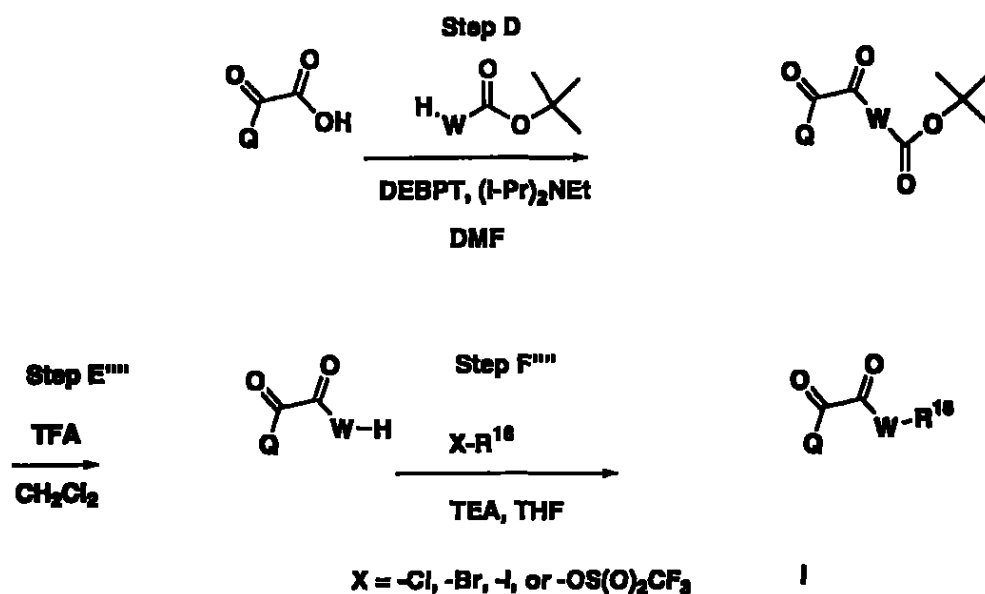
16 above. The aldehyde substituent is shown only at one position for the sake of clarity, and should not be considered as a limitation of the methodology. The bromide or iodide intermediate would be converted into an aldehyde intermediate, 43, by metal-halogen exchange and subsequent reaction with dimethylformamide in an appropriate aprotic solvent. Typical bases used could include, but would not be 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 would be initiated at -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 diazaindoles.

15 As shown in Scheme 52, the pieces HW-R<sup>18</sup> can be prepared by a number of different methods. One useful way is by reacting a mono protected piperazine with a heteroaryl chloride, bromide, iodide, or triflate. This reaction is typically carried out at elevated temperature (50 to 250 degrees celsius) in a solvent such as ethylene glycol, DME, dioxane, NMP, or DMF. A tertiary amine base such as triethyl amide or diisopropyl ethyl amine is typically employed and usually 2 to 4 equivalents are employed. At least 2 equivalents are used if a salt of HW R<sup>18</sup> is utilized. The piperazine is typically monoprotected with a BOC group since this material is commercially available. Removal of the Boc group is typically done using HCl (typically 1 to 6N) in dioxane to provide the HCl salt. TFA may also be used to generate the TFA salt. Alternatively, the conditions for coupling heterocycles using copper catalysis discussed earlier in Scheme 12 may be used to couple W to R<sup>18</sup> via displacement of X in X- R<sup>18</sup>. Alternatively Palladium catalysis in the presence of a bidentate catalyst via the procedures of Buchwald or the use of a ferrocenyl catalyst via the methods of Hartwig could be used to couple the piperazine to the heteroaryl (R<sup>18</sup>).

## Scheme 52



## Scheme 53



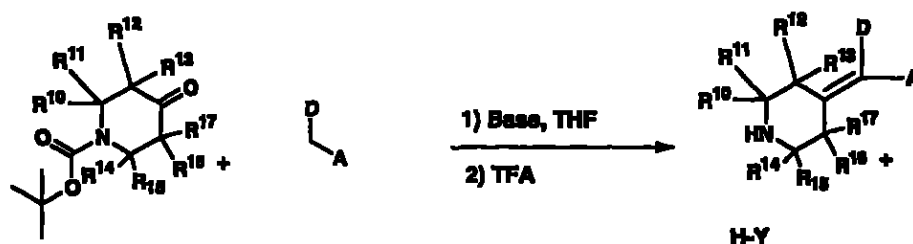
- 5        Scheme 53 describes how a protected piperazine can be coupled to Q-COOH via standard methodology. Conditions for removal of the amine protecting group which could be tBoc or other groups is protecting group specific. As shown in Scheme 53 where tBoc is the preferred protecting group used to exemplify the strategy, standard conditions for removal such as TFA in dichloromethane or
- 10       alternatively aqueous HCl can provide the free amine. The free amine is coupled to heteraromatic R<sup>18</sup> using the conditions described in Scheme 52 for step F'''.

**General Schemes:**

Scheme D1 describes a possible method for preparing the compounds described by H-W where Y is as defined in the description and claims of the invention. Typically, this methodology will work best when D is a group which lowers the PKA of the hydrogens on the adjacent methylene moiety. For example cyano, sulfonyl, amido and the like as specified in the claim. A preferably could be aryl or heteroaryl moieties as described in claim 1. A could also be other groups described in claim 1. Alkoxide bases of C1 to C4 alcohols can be utilized but other bases such as lithium, sodium, or potassium dialkyl amides or the corresponding bistrimethylsilyl amides could also be utilized.

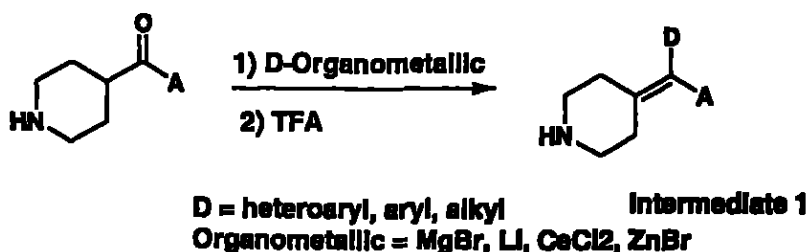
**Preparation of intermediates:**

15

**SCHEME D1**

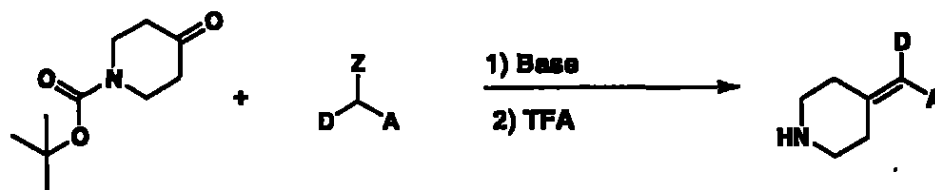
Note as shown in Scheme D1, the piperazine or piperidine moiety of Y may be substituted as defined by the invention. In the interest of clarity, unsubstituted piperidines and piperazines are used in the Schemes to keep them readable. It is understood substituents could be incorporated.

25

**SCHEME E1**

As shown in Scheme E1, addition of an organometallic reagent to a ketone can provide an intermediate tertiary alkoxide which undergoes protonation and acid catalyzed elimination to form the desired double bond. A number of organo metallic reagents could suffice as shown but an extra equivalent (at least two total) could be needed to compensate for deprotection of the amine nitrogen in many cases.

SCHEME F1



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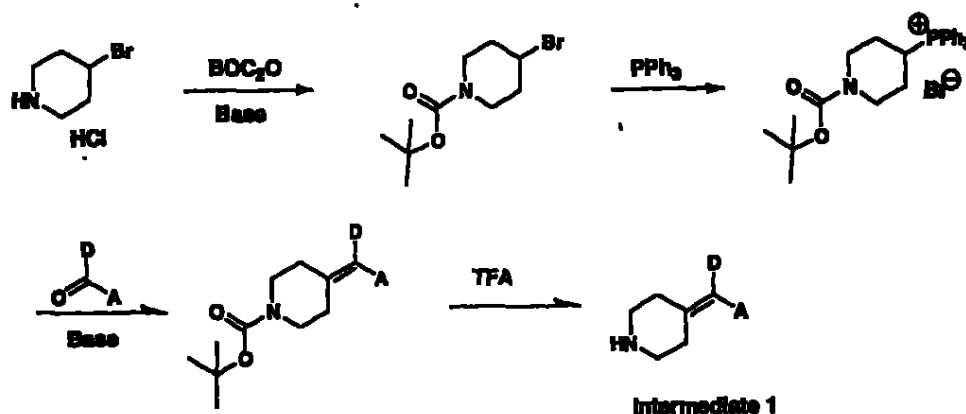
Standard olefination conditions such as Wittig, Horner Emmons, Petersen or Arsenic based could be used to convert the ketone to the desired products. Some general reviews of this methodology and directions for use are contained in the following references: Wadsworth, W.S., Jr., in "Organic Reactions", Dauben, W.G., Ed., Wiley, New York, 1977, 25, 73. McMurry, J.E. Acct. Chem. Res. 1983, 16, 405. Cushman, M., et al. Bioorg. Med. Chem. 2002, 10, 2807. When Z= triphenyl phosphine, butyl lithium or LDA could be used to generate the phosphorus ylide in THF and then the ylide reacted with the ketone to provide the desired product. The phosphinate or phosphine oxide based reagents could be used with similar bases or with sodium or potassium methoxide or ethoxide in the corresponding alcohol solvents.

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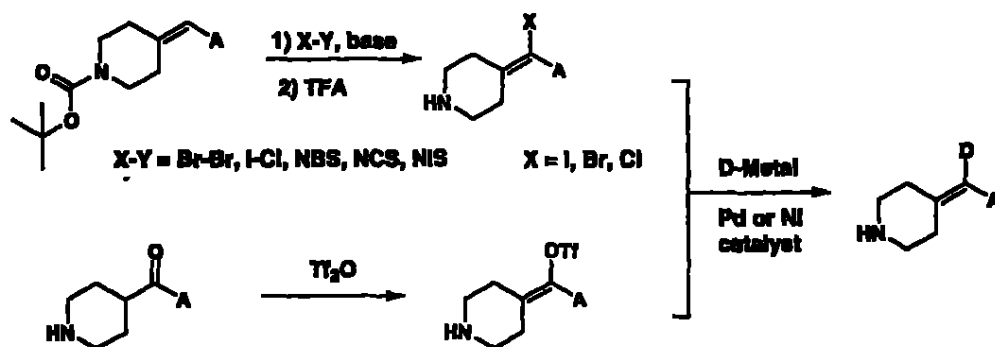
83

## SCHEME G1



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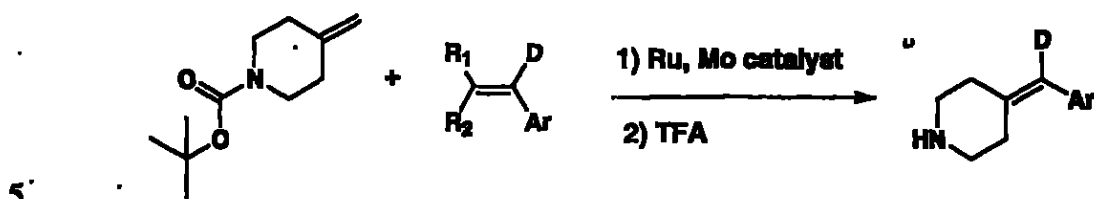
## SCHEME H1

Metal =  $\text{SnR}_3$ ,  $\text{B}(\text{OH})_2$ ,  $\text{AlR}_3$ ,  $\text{MgBr}$ , and allies

As shown above in Scheme H1, a chloride, bromide, iodide, triflate, or phosphonate undergo coupling reactions with a boronate (Suzuki type reactions). Stannanes and boronates are prepared via standard literature procedures or as described in the experimental section of this application. The vinyl bromides, chlorides, triflates, or phosphonates may undergo metal mediated coupling to provide compounds of formula W-H. Stille or Suzuki couplings are particularly useful. A detailed discussion of the references and best conditions for these kinds of metal mediated coupling is described later in this application where the discussion is combined with a description of how these types of reactions may also be used to functionalize diazaindoles.

When Ar is benzene, starting materials are commercially available

## SCHEME J1



Alternatively, the compounds Y-H could potentially be prepared via olefin metathesis using highly active Rhodium catalysts. The methylene starting material can be prepared via simple Wittig methylenation of the precursor ketone which is prepared via literature methods. The olefin metathesis is preferably carried out using 1% of the imadazoylidene ruthenium benzyldene catalyst described in the following reference. The reaction is carried out starting at low temperatures (-40°) or similar. Starting methylene material is mixed with excess olefin (5 to 100equivalents) and the reaction is warmed to -40°C. *Synthesis of Symmetrical Trisubstituted Olefins by Cross Metathesis*. Chatterjee, Arnab K.; Sanders, Daniel P.; Grubbs, Robert H. Organic Letters ACS ASAP.

Additional references are listed below which show additional conditions and substrates which could be used with this catalyst.

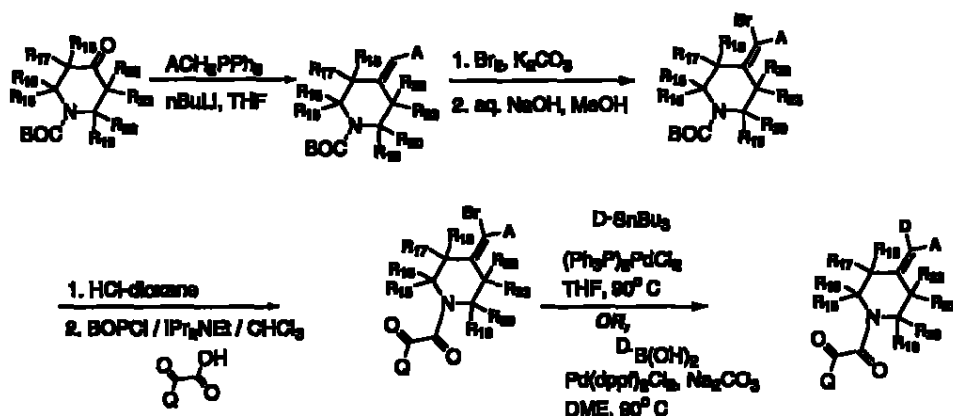
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*Functional group diversity by ruthenium-catalyzed olefin cross-metathesis*. Toste, F. Dean; Chatterjee, Arnab K.; Grubbs, Robert H.. The Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, USA. Pure and Applied Chemistry (2002), 74(1), 7-10. *A Versatile Precursor for the Synthesis of New Ruthenium Olefin Metathesis Catalysts*. Sanford, Melanie S.; Love, Jennifer A.; Grubbs, Robert H.. Arnold and Mabel Beckman Laboratories for Chemical Synthesis Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, USA. Organometallics (2001), 20(25), 5314-5318. *Olefin metathesis with 1,1-difluoroethylene*. Trnka, Tina M.; Day, Michael W.; Grubbs, Robert H.. Arnold and Mabel Beckman Lab. of Chemical Synthesis,

California Institute of Technology, Pasadena, CA, USA. Angewandte Chemie,  
International Edition (2001), 40(18), 3441-3444.

Scheme K1 shows a sequence in which a piperidone is converted to a  
5 monofunctionalized olefin via Wittig olefination. Bromination and  
dehydrobromination provides a versatile vinyl bromide intermediate. This  
intermediate is coupled to the QC(O)C(O)OH acid with BOPCl to provide a  
compound of formula I. This intermediate is then functionalized using palladium  
mediated couplings to either boronates or stannanes. Conditions for these couplings  
10 are described in this application.

SCHEME K1



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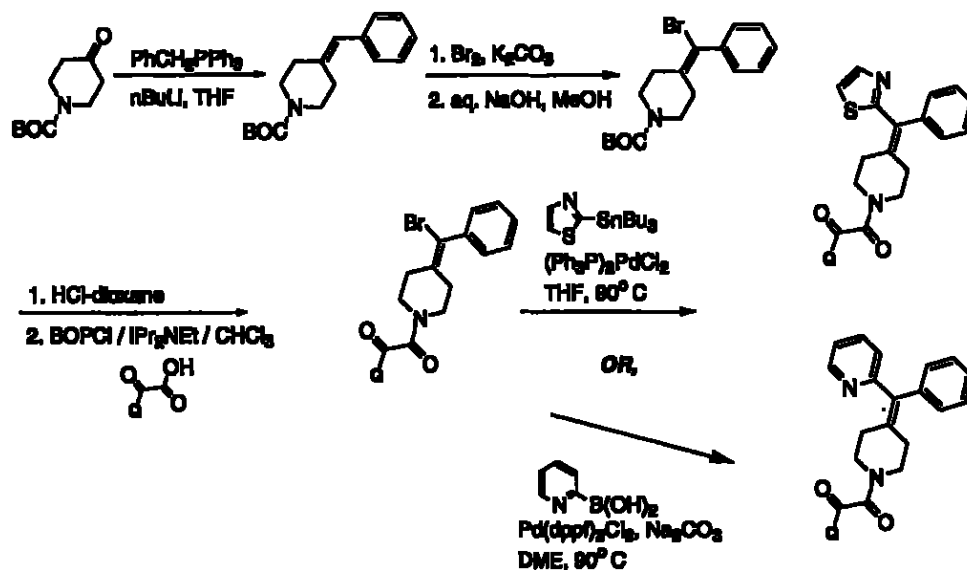
Scheme L1 shows specific examples of general Scheme K1 which are some  
of those described in the experimental section.

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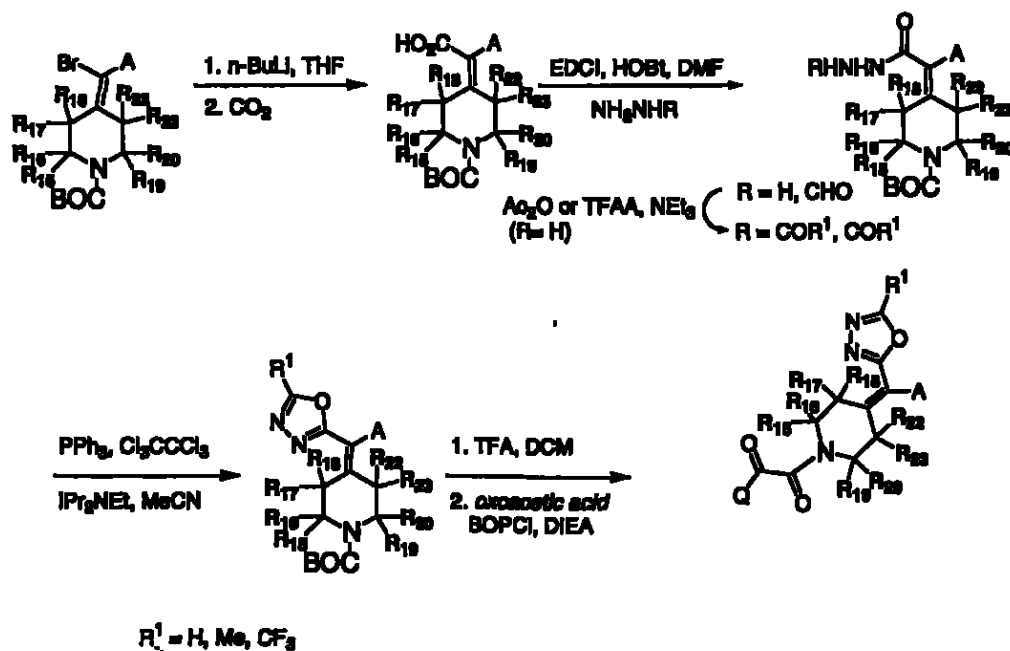
## SCHEME L1



Scheme M1 shows how a protected vinyl bromide can be converted to a carboxylic acid via lithium bromide exchange and reaction with carbon dioxide. As described in this application and the incorporated ones, carboxylic acids are excellent precursors to many heterocycles or amides. The rest of Scheme M1 shows conversion to functionalized oxadiazoles. Other chemistry described in this application depicts other methods for converting acids to groups of other compounds of the invention.

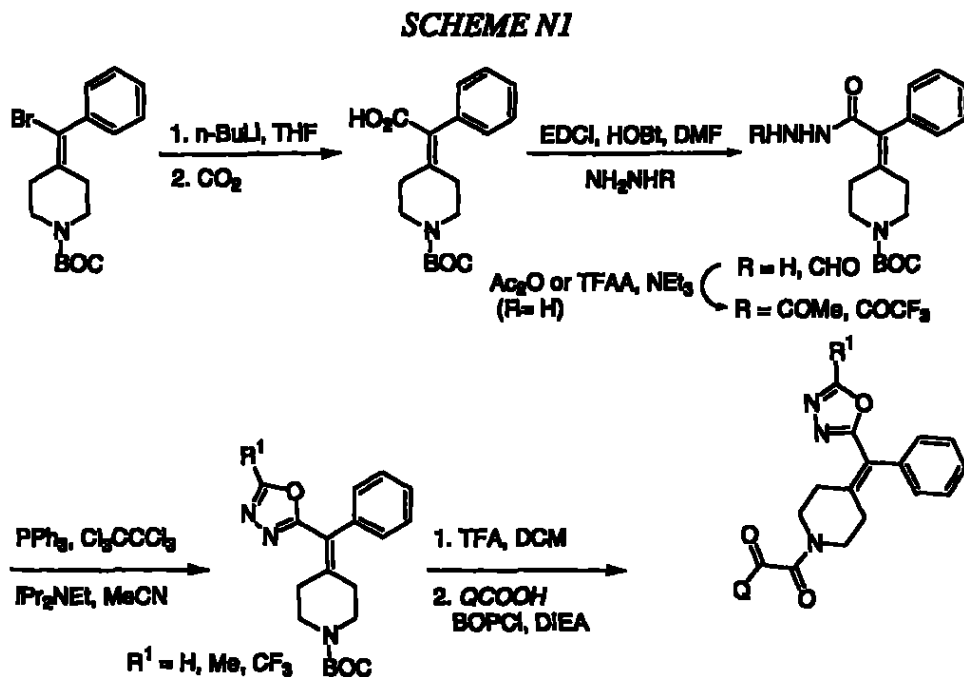
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## SCHEME M1



92

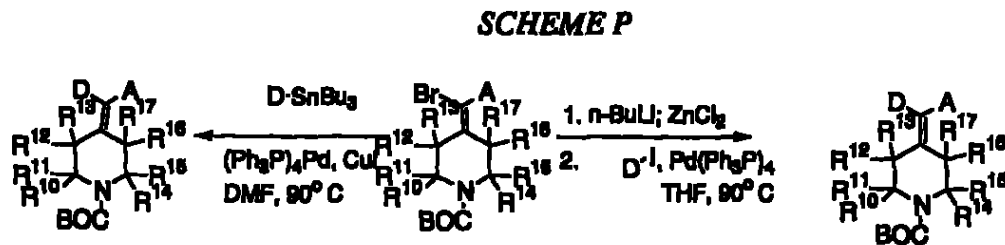
Scheme N1 depicts a more specific example of Scheme M1.



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Scheme P depicts methods for functionalizing the vinyl bromide to install groups D (or A). Either a modified Stille coupling or a zinc mediated coupling are depicted. Details of these transformations are discussed later in the section on metal couplings.

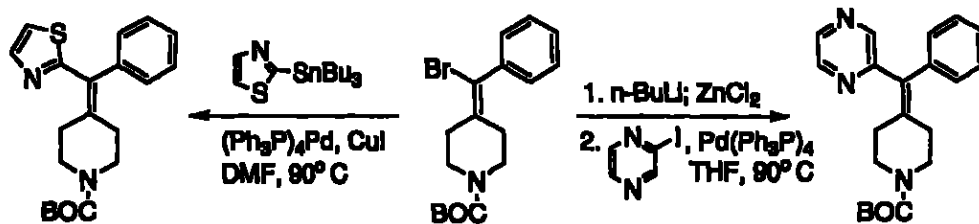
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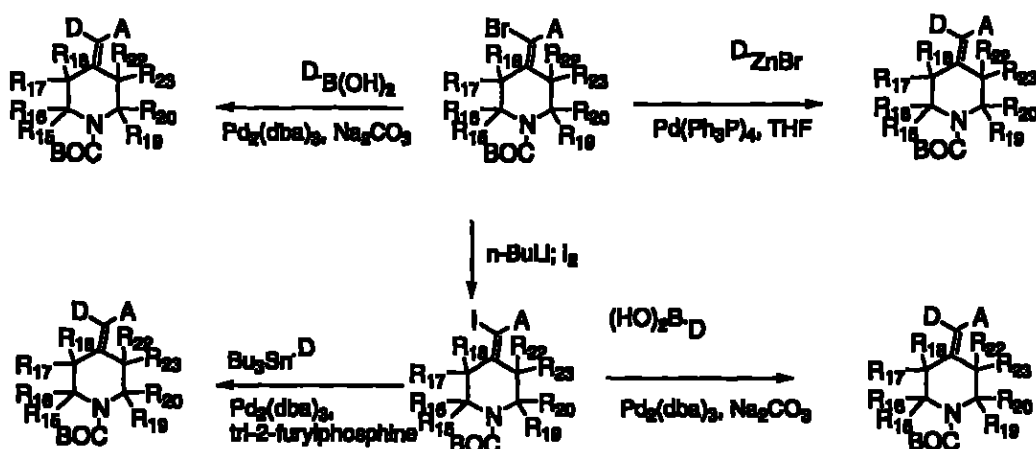
Scheme Q depicts some specific examples of Scheme P.

## SCHEME Q



- 5 Scheme R depicts methods for functionalizing the vinyl bromide to install groups D (or A). Either a modified Stille coupling, zinc mediated coupling, or a Suzuki boronic acid coupling are depicted. A method for converting the vinyl bromide to vinyl iodide is shown. If the vinyl bromide fails to undergo efficient reaction, the more reactive iodide can be prepared as a better partner. Details of these
- 10 transformations are discussed later in the section on metal couplings.

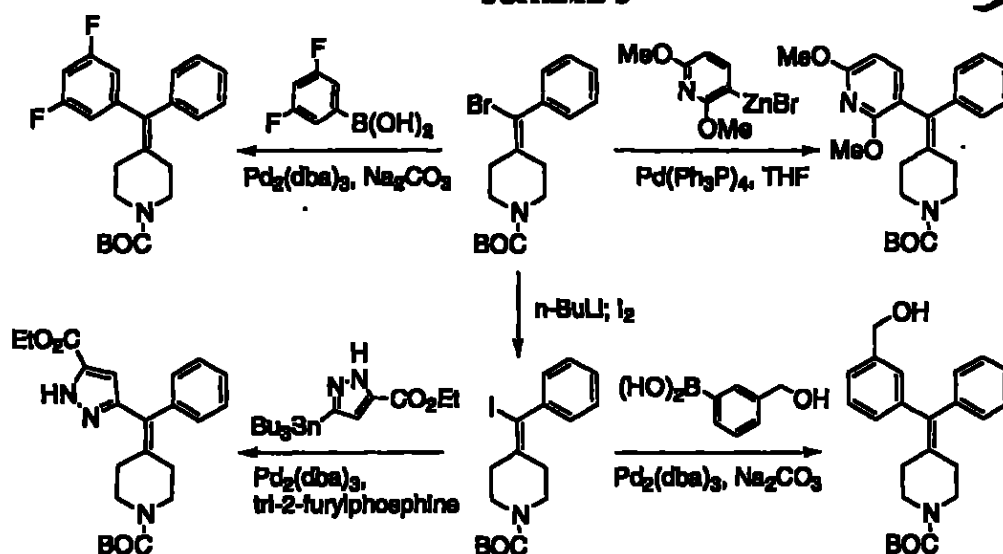
## SCHEME R



- 15 Scheme S provides specific examples of Scheme R.

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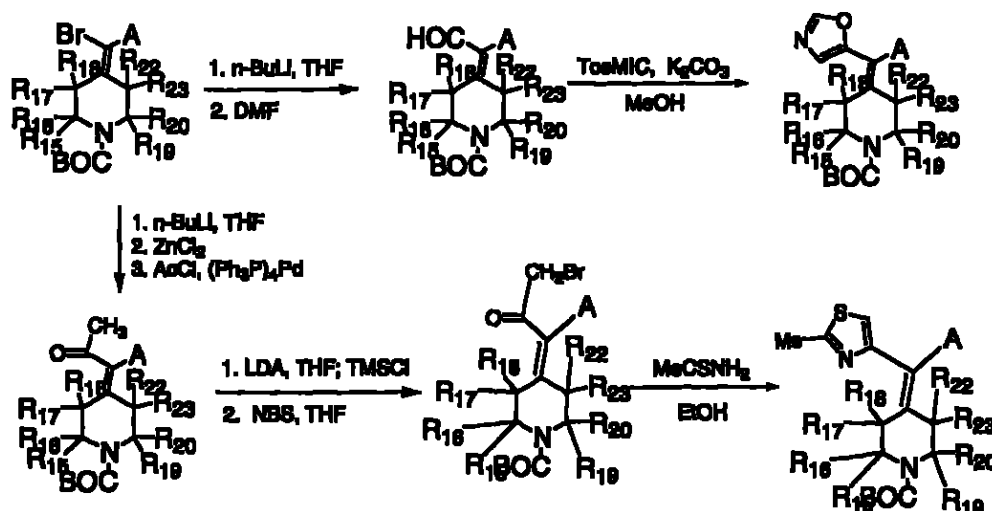
SCHEME S



Scheme T shows methods for converting the vinyl bromide into more functionalized groups D (or A). A key aldehyde intermediate is generated from the vinyl bromide and can be used to generate heteroaryls such as the oxazole via reaction with Tosmic.

SCHEME T

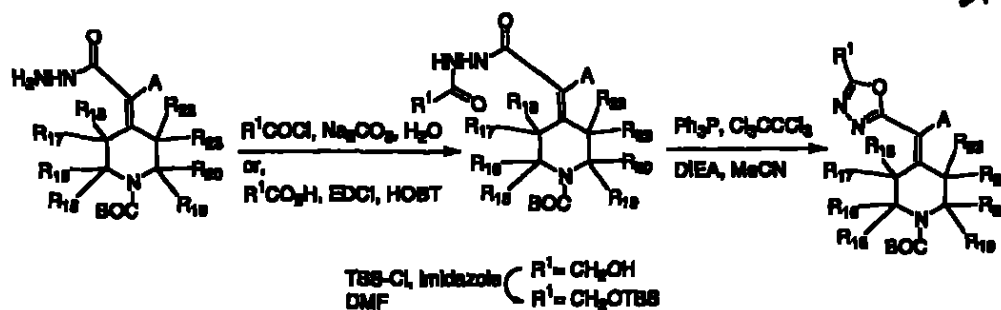
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Scheme U shows how a hydrazide (generated from the acid) can be used to prepare oxadiazoles with different substituents.

15

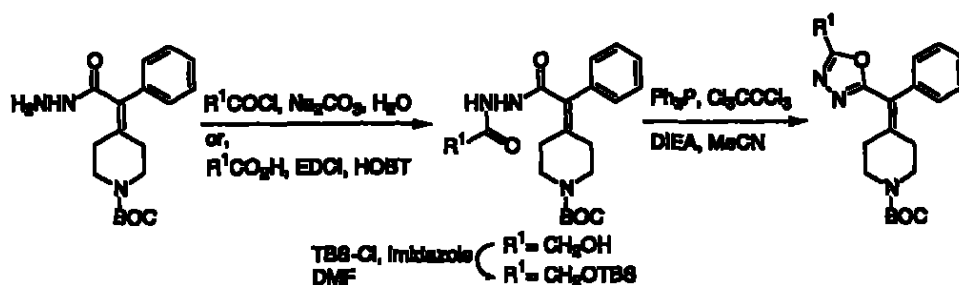
**SCHEME U**



**Scheme V** provides more specific examples of Scheme U.

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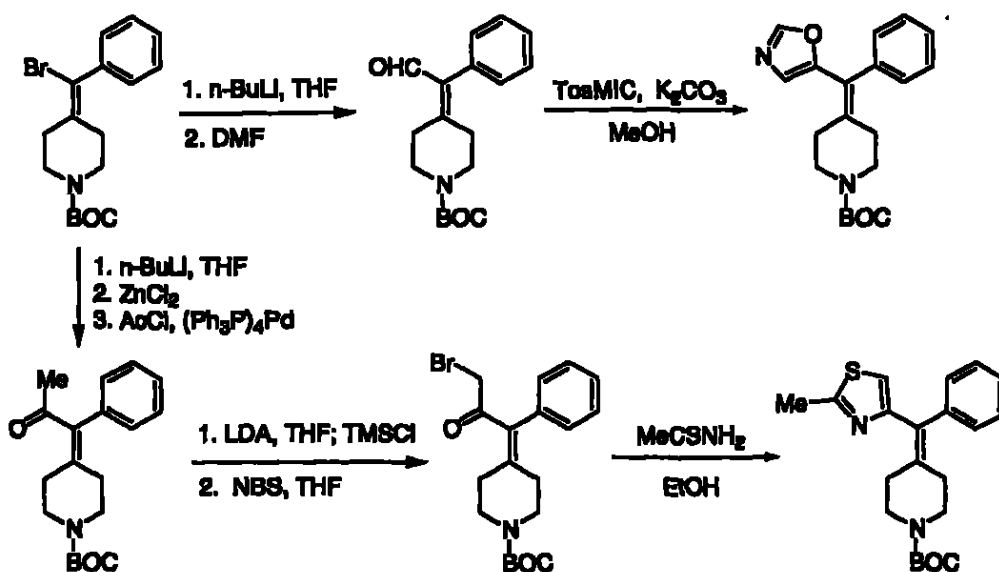
### SCHEME V



**Scheme W shows some other methods for installing D (or A).**

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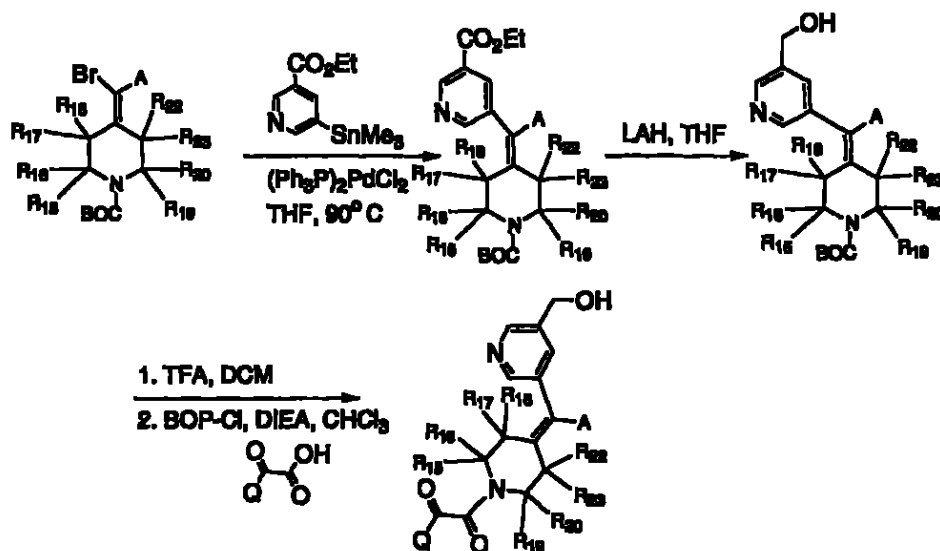
### SCHEME W



Scheme X shows a particular example where a functionalized heteroaryl or in this case aryl are coupled and then further functionalization can occur (in this case reduction of an ester to an alcohol).

5

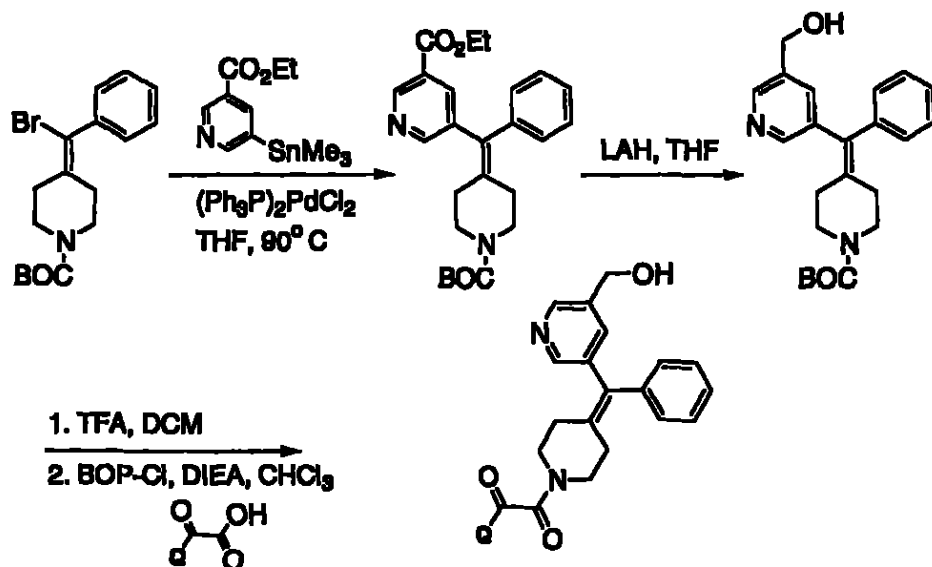
## SCHEME X



Scheme Y provides more specific examples of Scheme X.

10

## SCHEME Y

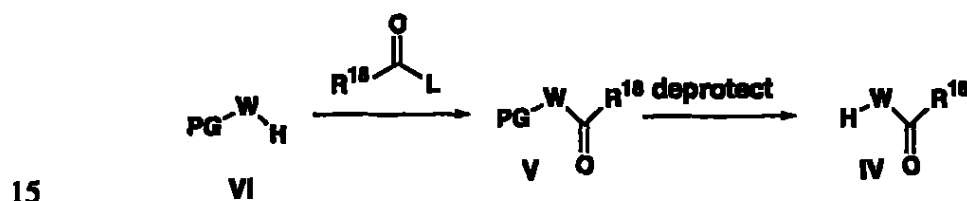


15

Procedures for coupling piperazine amides to oxoacetyl derivatives are described in the Blair, Wang, Wallace, or Wang references 93-95 and 106

OK 97

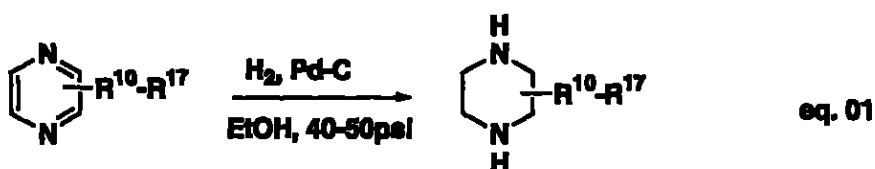
respectively. In addition, these applications describe preparations of heteroaryls and methods for functionalizing heteraromatic systems in the presence of oxoacetyl amides. The entire disclosures in U.S. Patent 6,469,006 granted October 22, 2002; U.S. Patent 6,476,034 granted November 5, 2002; U.S. Patent Application Serial Number 10/027,612 filed December 19, 2001, which is a continuation-in-part of U.S. Serial Number 09/888,686 filed June 25, 2001 (corresponding to PCT WO 02/04440, published January 17, 2002); and U.S. Patent Application Serial Number 10/214,982 filed August 7, 2002, which is a continuation-in-part of U.S. Serial Number 10/038,306 filed January 2, 2002 (corresponding to PCT WO 02/62423 published August 15, 2002) are incorporated by reference herein. The procedures used to couple diazaindole oxoacetic acids to piperazine amides in these references could potentially be used analogously to form the compounds of this invention except the H-Y are used in place of the piperazine benzamides.



Scheme 54a depict a general method suitable for the synthesis of many of the compounds of formula I. As shown in these schemes, a suitable protected piperazine derivative, PG-YH, of Formula VI, (wherein PG is an appropriate amine protecting group) is acylated with an appropriate acylating agent,  $\text{R}^{18}\text{C(O)L}$ , (wherein L is a suitable leaving group) to provide the protected acylated piperazine derivative of Formula V. Compound V is then deprotected using standard methods to provide the acylated piperazine derivative of Formula IV. For example, when PG represents *tertiary*-butoxycarbonyl the compound of Formula V can be deprotected to provide a compound of Formula IV by treatment with a strong acid, such as neat cold trifluoroacetic acid or aqueous hydrochloric acid, in an appropriate solvent such as dichloromethane. Alternatively, when PG represents benzyl the deprotection may be effected by hydrogenation.

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



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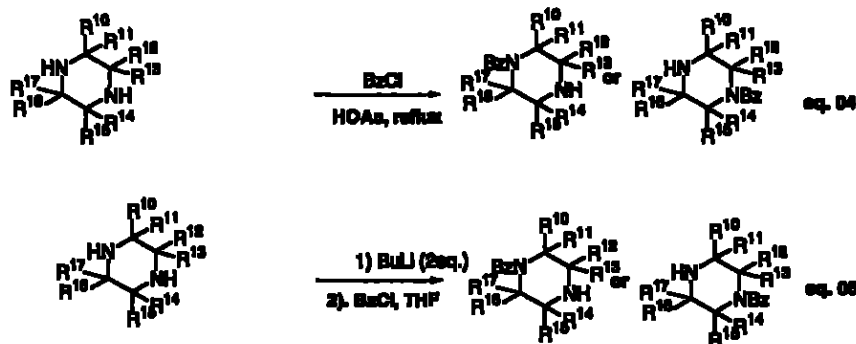
Mono-benzoylation of symmetric substituted piperazines could be achieved by using one of the following procedures (Scheme 57). (a) Treatment of a solution of piperazine in acetic acid with acetyl chloride afforded the desired mon-benzoylated piperazine (Desai et al. Ref. 27, Scheme 57, eq. 04). (b) Symmetric 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).

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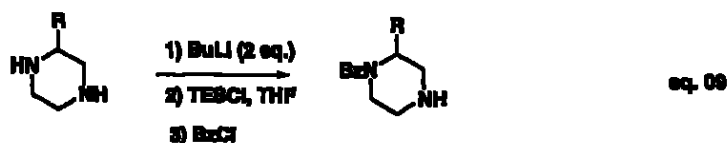
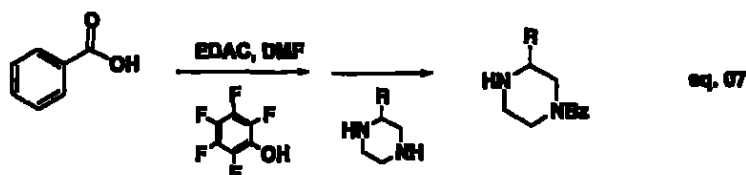
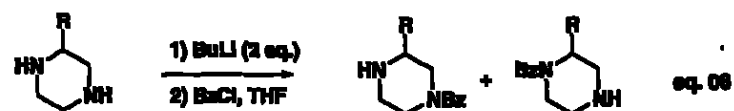
## SCHEME 57

~~10~~ 99

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).

## SCHEME 58

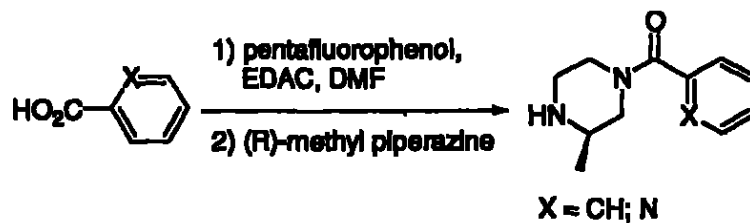
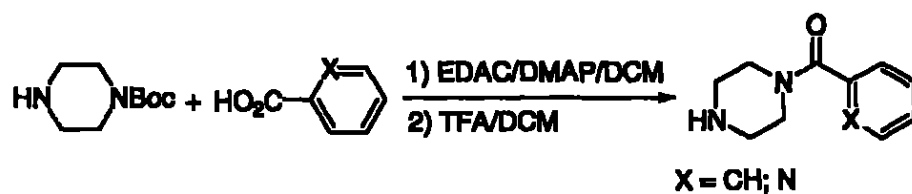
~~100~~ 100



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

5

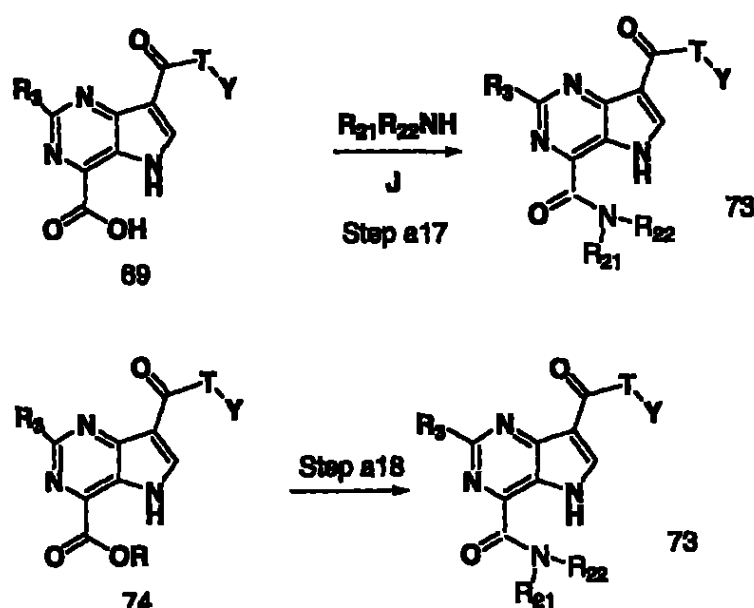
## SCHEME 64



10

## SCHEME 65

101



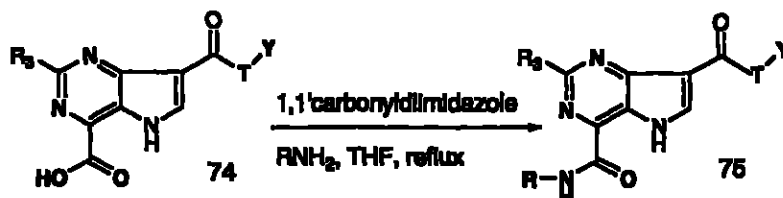
Steps a16, a17, and a18 encompasses reactions and conditions for 1<sup>o</sup>, 2<sup>o</sup> and 3<sup>o</sup> amide bond formation as shown in Schemes 65 which provide compounds such as those of Formula 73. Compounds of formula 73 represent intermediates for the preparation of Compounds I or compounds I depending on the identity of T and Y.

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 diazaindole 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 reaction 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. An example of more specific conditions which

5 are likely to be successful are depicted in Scheme 66.

SCHEME 66



10 The following four general methods provide a more detailed description of procedures potentially useful for the preparation of diazindoleindolecarboxamides and these methods could potentially be employed for the synthesis of intermediates 73 useful for the preparation of compounds I or for the preparation of compounds of Formula I themselves.

15

**Method 1:**

To a mixture of an acid intermediate, such as 74, (1 equiv., 0.48 mmol), an appropriate amine (4 equiv.) and DMAP (58 mg, 0.47 mmol) dissolved  $CH_2Cl_2$  (1

20 mL) should be added EDC (90 mg, 0.47 mmol). The resulting mixture should be shaken at rt for 12h, and then evaporated *in vacuo*. The residue could be dissolved in MeOH, and subjected to preparative reverse phase HPLC purification.

**Method 2:**

25

To a mixture of an appropriate amine (4 equiv.) and HOBt (16 mg, 0.12 mmol) in THF (0.5 mL) could be added an acid intermediate, such as 74, (25 mg, 0.06 mmol) and NMM (50  $\mu$ L, 0.45 mmol), followed by EDC (23 mg, 0.12 mmol).

103

The reaction mixture could be shaken at rt for 12 h. The volatiles could be evaporated *in vacuo*; and the residue dissolved in MeOH and subjected to preparative reverse phase HPLC purification.

5 **Method 3:**

To a mixture of an acid intermediate, such as 74, (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) could be added TEA (0.03 mL, 0.22 mmol). The resulting mixture could be shaken at rt for 12 h; and then diluted with MeOH (2 mL) and purified by preparative reverse phase HPLC.

15 **Method 4:**

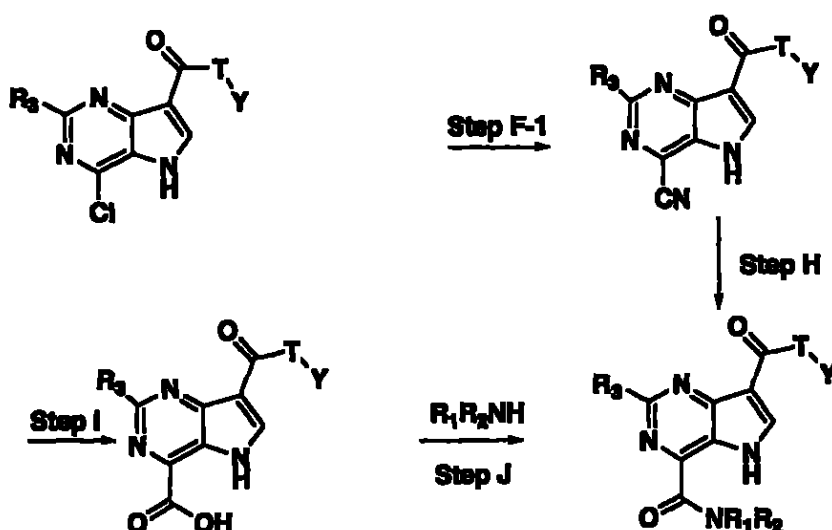
A mixture of an acid intermediate, such as 74, (0.047mmol) and 8.5 mg (0.052mmol) of 1,1-carbonyldiimidazole in anhydrous THF (2 mL) could be heated to reflux under nitrogen. After 2.5h, 0.052 mmol of amine could be added and heating continued. After an additional period of 3~20 h at reflux, the reaction mixture could be cooled and concentrated *in vacuo*. The residue could be purified by chromatography on silica gel to provide a compound of Formula I.

In addition, the carboxylic acid could 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<sub>2</sub>Cl<sub>2</sub>. The amides could 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<sub>2</sub>Cl<sub>2</sub> 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 could 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 could be converted to an ester preferably a methyl or ethyl ester and then reacted with an amine. The ester could 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 67



20

Scheme 67 shows possible synthetic transformations on a chloro diazazaindole. Step F-1 of Scheme 31 could 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 in which they use 1 eq of Chloride,

105

1.9 eq Cu(I)CN, in dry DMF and reflux for 48h. The concentration of chloride in DMF is preferably 0.094 mmol per mL of solvent. Reaction times of 1-48h may be appropriate depending on substrate and reaction temperatures between 80°C and reflux (156°C) may be employed. An alternate procedure for carrying out step F-1 as described in the experimental section for Example 12 occurs via reaction of the chloride intermediate with potassium cyanide (0.9 to 5 eqs, preferably 1.5 eqs) in a solvent such as DMF in the presence of catalytic sodium 4-toluene sulfinate at an elevated temperature such as 100° C for 3h. Reaction temperature may vary between 50 and 200°C depending on substrate and reaction time from 30 min to 48h. Reactions may be conducted in a sealed tube to minimize escape of volatiles if necessary.

Transformation step I, the hydrolysis of the nitrile to the acid may be carried out using acidic conditions such as MeOH and HCl at ambient temp followed by heating the intermediate imidate in the Methanol which provides the intermediate methyl ester which can then be hydrolyzed using potassium carbonate MeOH or LiOH or KOH in Methanol. This method is preferred to produce intact Compounds I. Alternatively, KOH/ in ethanol or methanol may be utilized to achieve this transformation in step I. Other methods for this transformations are well known in the literature or in the references incorporated in the experimental section.

Transformation step H can be used to directly produce unsubstituted carboxamides ( $R^1=R^2$  = hydrogen) via stirring in cold concentrated sulfuric acid or at ambient temperature for 0.5 to 15 days. Alternatively stirring with MeOH and HCl at room temperature followed by a hydrolytic workup (water and ethyl acetate or dichloromethane, may produce the same product.

Step J the amide coupling is carried out as described above in the discussions for Scheme 65 and 66.

~~108~~ 106**Chemistry****General:**

5 Additional preparations of starting materials and precursors particularly those for appending heteroaryls or carboxamides and for construction of substituted piperazines and alkenyl piperidines have been disclosed in a number different PCT and issued U.S. patents/applications (Reference 93-95, 106, 108, 109, 110, 111, 112, 113 and 114) and U.S. Appln. Serial Number 10/871,931 filed June 18, 2004, which  
10 are hereby incorporated by reference.

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  
15 electrospray mode.

**LC/MS Method (compound identification)**

|    |           |                                |
|----|-----------|--------------------------------|
| 20 | 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 |
| 25 | 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    |
| 30 | Column G: | XTERRA C18 S7 3.0x50 mm column |
|    | Column H: | YMC C18 S5 4.6x33 mm column    |



~~109~~ 107

- Column I: YMC ODS-A C18 S7 3.0x50 mm column
- Column J: XTERRA C-18 S5 4.6x50 mm column
- 5 Column K: YMC ODS-A C18 4.6x33 mm column
- Column L: Xtterra MS C18 5uM 4.6x30 mm column
- Column M: YMC ODS-A C18 S3 4.6x33 mm column
- 10 Column N: XTERRA MS C18 7u 3.0x50 mm column
- Column O: Phenomenex 10u 4.6x50 mm column
- 15 Column P: Waters Atlantis 4.6x50 mm C18 5um column
- Column Q: Phenomenex 5u 4.6x50 mm C18 column
- Column R: Phenomenex Lina C18 5um 3.0x50 mm column
- 20 Column S: Phenomenex C18 10u 3.0 x 50 mm column

*Standard LC Run Conditions A (used unless otherwise noted):*

- 25 Gradient: 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B
- Gradient time: 2 minutes
- Hold time: 1 minute
- 30 Flow rate: 5 mL/min

Detector Wavelength: 220 nm

5 Solvent A: 10% MeOH / 90% H<sub>2</sub>O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H<sub>2</sub>O / 90% MeOH / 0.1% Trifluoroacetic Acid

5 *Alternate LC Run Conditions B:*

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

10 Gradient time: 2 minutes

Hold time: 1 minute

Flow rate: 5 mL/min

15

Detector Wavelength: 220 nm

Solvent A: 5% CH<sub>3</sub>CN / 95% H<sub>2</sub>O / 10 mM Ammonium Acetate

20 Solvent B: 95% CH<sub>3</sub>CN / 55% H<sub>2</sub>O / 10 mM Ammonium Acetate

Compounds purified by preparative HPLC were diluted in MeOH and/or DMSO (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.

25

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

30 Purification Method: Initial gradient (10% B, 90% 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<sub>2</sub>O / 0.1% Trifluoroacetic Acid

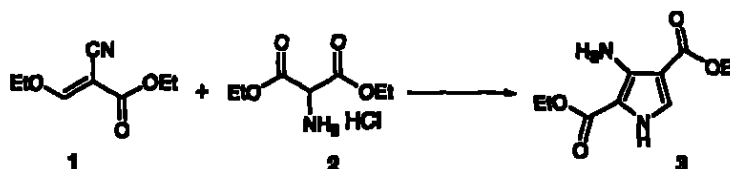
Solvent B: 10% H<sub>2</sub>O / 90% MeOH / 0.1% Trifluoroacetic Acid

Column: YMC C18 S5 20x100 mm column

5 Detector Wavelength: 220 nm

Starting materials, can be purchased from commercial sources or prepared using literature procedures.

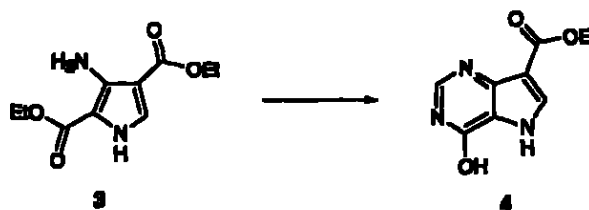
10



To a mixture of diethyl aminomalonate hydrochloride (8.0 g, 47.3 mmol) and ethyl (ethoxymethylene)cyanoacetate (10.0 g, 47.2 mmol) in ethanol (60 ml) at r.t. was added a 21 wt.% solution of sodium ethoxide in ethanol (62 ml, 165.4 mmol).

15 The reaction mixture was then stirred at reflux for 20 h. After cooling to r.t., the mixture was neutralized with AcOH (6.75 ml, 118 mmol), concentrated, diluted with H<sub>2</sub>O (250 mL) and extracted with CHCl<sub>3</sub> (3 x 250 mL). The combined organics were dried (MgSO<sub>4</sub>), filtered, concentrated and purified by flushing through a pad of silical gel (100g, EtOAc) to yield amino pyrrole 3 (10.2 g, 45.1 mmol, 95%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 11.55 (br s, 1H), 7.21 (d, J = 4.0, 1H), 5.57 (s, 2H), 4.21 (q, J = 7.5 Hz, 2H), 4.18 (q, J = 7.8 Hz, 2H), 1.27 (t, J = 7.5 Hz, 2H), 1.25 (t, J = 7.8 Hz, 2H); LC/MS: (ES+) m/z (M-OBt)<sup>+</sup> = 181; HPLC R<sub>t</sub> = 0.96, column N.

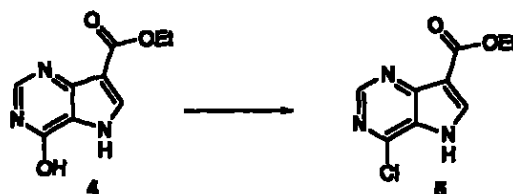
25 Preparation of 4-hydroxy-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid ethyl ester  
4



110  
A mixture of amino pyrrole 3 (10.0 g, 44.2 mmol) and formamidine acetate (13.8 g, 133 mmol) in ethanol (100 ml) was heated at 105°C for 20 h. The reaction mixture was filtered while still hot to collect solids that were rinsed with EtOH. The filtrate was allowed to cool to r.t., filtered to collect solids that were washed with EtOH. The combined solids were slurried with Et<sub>2</sub>O, filtered and dried under vacuum to yield 4,6-diazaindole 4 (6.60g 31.9 mmol, 72%) as a pale yellow solid which was used without further purification. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 7.91 (s, 1H), 7.89 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.17 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 208; HPLC R<sub>t</sub> = 0.55 min., column N.

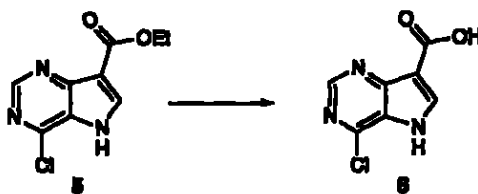
10

*Preparation of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid ethyl ester 5*



15 4,6-Diazaindole 4 (2.74 g, 13.2 mmol) was slurried in POCl<sub>3</sub> (37 mL, 400 mmol) and heated at 105°C for 3.5h. The reaction mixture was cooled, diluted with Et<sub>2</sub>O (150 mL) and the resulting precipitate was collected by filtration, rinsed with EtOAc and Et<sub>2</sub>O and dried under vacuum to yield 7-chloro-4,6-diazaindole 5 (2.48 g, 11.0 mmol, 83%) as a yellow powder which was used without further purification.  
20 LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 226; HPLC R<sub>t</sub> = 0.84 min., column N.

*Preparation of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid 6*

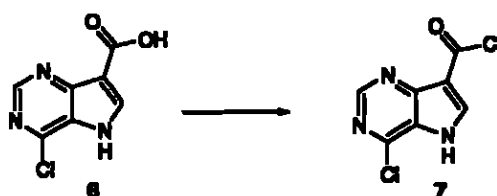


25

To a solution of 7-chloro-4,6-diazaindole 5 (4.0 g, 18 mmol) in THF (90 mL) was added a solution of LiOH·H<sub>2</sub>O (2.5g, 59 mmol) in H<sub>2</sub>O (60 mL). The reaction

17/11  
mixture was stirred at 100 °C for 1 d, concentrated and recrystallized from H<sub>2</sub>O (20 mL). The crystals were collected by filtration, washed with H<sub>2</sub>O and dried under high vacuum. The off-white solid was shown to be the lithium salt of the diazaindole carboxylic acid 6 (quantitative), which was used without further purification. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 8.28 (s, 1H), 8.14 (s, 1H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 198; HPLC R<sub>t</sub> = 0.47 min., column G.

*Preparation of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine-7-carbonyl chloride 7*



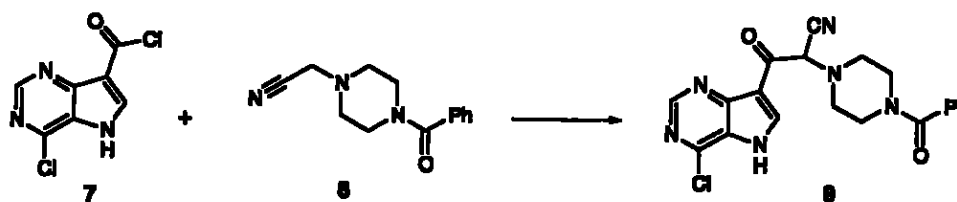
A solution of the lithium salt of the diazaindole carboxylic acid 6 (1.3 g, 6.6 mmol) in thionyl chloride (22 mL, 300 mmol) and benzene (30 mL) was heated at 105°C for 3 h. The reaction was cooled and concentrated under vacuum. The light yellow solid residue was shown to be acid chloride 7 and was used without further purification. The acid chloride 7 was identified by quenching a small amount with methanol to make the analogous methyl ester or with aniline to make the phenyl amide, each of which could be verified by LCMS. Methyl ester: LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 212; HPLC R<sub>t</sub> = 0.90 min., column G. Phenyl amide: LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 269; HPLC R<sub>t</sub> = 01.56 min., column G.

15

20

*Preparation of Example 1:*

2-(4-Benzoyl-piperazin-1-yl)-3-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-3-oxo-propionitrile (Compound 9)

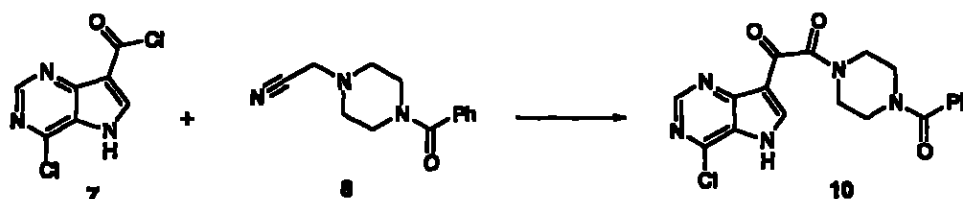


Example 1

To a solution of acid chloride 7 (0.5 mmol) and cyanomethylpiperazine 8 (150 mg, 0.66 mmol) in THF (4 mL) stirring at  $-35^{\circ}\text{C}$  was slowly added a solution of 0.5 M KHMDS in toluene (3.2 mL, 1.6 mmol). The reaction mixture was stirred at  $-35^{\circ}\text{C}$  for 1h, quenched with sat. aqueous  $\text{NaHCO}_3$  (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were concentrated and the residue purified by prep HPLC to yield the ketocyano intermediate 9 (39 mg, 0.96 mmol, 19%) as a yellow solid.  $^1\text{H}$  NMR: (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.80 (s, 0.5H), 8.80 (s, 0.5H), 8.65 (s, 0.5H), 8.64 (s, 0.5H), 7.50-7.36 (m, 5H), 4.82-4.77 (m, 1H) 3.80-3.25 (m, 4H) 3.02-2.55 (m, 4H); LC/MS: (ES+)  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  = 407; HPLC  $R_t$  = 0.94 min., column G, conditions B.

*Preparation of Example 2:*

1-(4-Benzoyl-piperazin-1-yl)-2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-ethane-1,2-dione (Compound 10)



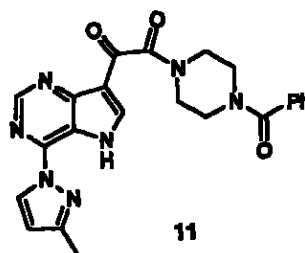
Example 2

To a solution of acid chloride 7 (6.6 mmol) and cyanomethylpiperazine 8 (1.96 g, 8.58 mmol) in THF (45 mL) stirring at  $-78^{\circ}\text{C}$  was slowly added a solution of 0.5 M KHMDS in toluene (42 mL, 21 mmol). The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 2h and then a solution of 32 wt.% peracetic acid in dilute AcOH (12 mL, 57 mmol) was added and the reaction was stirred at r.t. for 1h. The reaction mixture was quenched with sat. aqueous  $\text{NH}_4\text{Cl}$  (150 mL) and stirred with EtOAc (200 mL). The resultant precipitate was collected by filtration, rinsed with  $\text{H}_2\text{O}$  and EtOAc, dried under vacuum and shown to be dicarbonyl intermediate 10 (813 mg, 2.05 mmol, 24%) as an off-white solid.  $^1\text{H}$  NMR: (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.71 (s, 1H), 8.85 (s, 1H), 8.76 (s, 1H), 7.51-7.25 (m, 5H), 3.89-3.20 (m, 8H); LC/MS: (ES+)  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  = 398; HPLC  $R_t$  = 0.80 min., column G, conditions B.

2113

**Preparation of Example 3:**

1-(4-Benzoyl-piperazin-1-yl)-2-[4-(3-methyl-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-ethane-1,2-dione (Compound 11)

**Example 3**

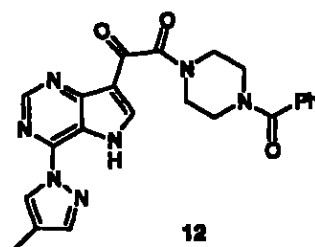
5

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-methylpyrazole (31 mg, 0.38 mmol) and ethanol (1 mL) were combined and heated to 140° C with microwaves for 45 min. The reaction was diluted with MeOH (2 mL), filtered and the filtrate was purified by preparative HPLC to yield 11 (36 mg, 0.08 mmol, 65%) as a light yellow solid. <sup>1</sup>H NMR: (300 MHz, CD<sub>3</sub>OD) δ 8.83 (s, 1H), 8.83 (d, J = 2.8 Hz, 1H), 8.52 (s, 1H), 7.50-7.41 (m, 5H), 6.50 (d, J = 2.8 Hz, 1H), 3.95-3.45 (m, 8H), 2.45 (s, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 444; HPLC R<sub>t</sub> = 0.97 min., column G, conditions B.

15

**Preparation of Example 4:**

1-(4-Benzoyl-piperazin-1-yl)-2-[4-(4-methyl-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-ethane-1,2-dione (Compound 12)

**Example 4**

20

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 4-methylpyrazole (31 mg, 0.38 mmol) and ethanol (1 mL) were combined and heated to 140° C with microwaves for 30 min. The reaction was diluted with MeOH (2 mL), filtered and the filtrate was purified by preparative HPLC to yield 12 (34 mg,

25

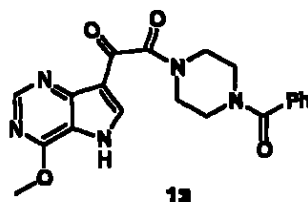
0.08 mmol, 61%) as a white solid.  $^1\text{H}$  NMR: (300 MHz,  $\text{CDCl}_3$ )  $\delta$  12.13 (br s), 9.17 (s, 1H), 8.74 (s, 1H), 8.40 (s, 1H), 7.85 (s, 1H), 7.46-7.36 (m, 5H), 3.85-3.55 (m, 8H), 2.20 (s, 3H); LC/MS: (ES+)  $m/z$  ( $M+H$ ) $^+$  = 444; HPLC  $R_t$  = 0.97 min., column G, conditions B.

5

*Preparation of Example 5:*

1-(4-Benzoyl-piperazin-1-yl)-2-(4-methoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-ethane-1,2-dione (Compound 13)

Example 5



10

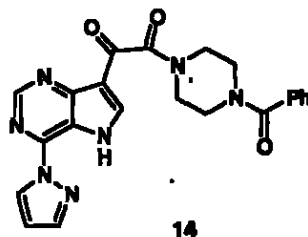
To a solution of dicarbonyl intermediate 10 (50 mg, 0.13 mmol) in MeOH (1 mL) was added KOMe (79 mg, 1.1 mmol). The reaction was heated at 90° C for 0.5 h, cooled, diluted with MeOH (2 mL) and H<sub>2</sub>O (1 mL) and purified by preparative HPLC to yield 13 (24 mg, 0.06 mmol, 48%) as a white solid.  $^1\text{H}$  NMR: (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.93 (s, 1H), 8.62 (s, 1H), 7.53-7.40 (m, 5H), 4.39 (s, 3H) 3.98-3.46 (m, 8H); LC/MS: (ES+)  $m/z$  ( $M+H$ ) $^+$  = 394; HPLC  $R_t$  = 0.79 min., column G, conditions B.

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20 *Preparation of Example 6:*

1-(4-Benzoyl-piperazin-1-yl)-2-(4-pyrazol-1-yl-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-ethane-1,2-dione (Compound 14)

Example 6



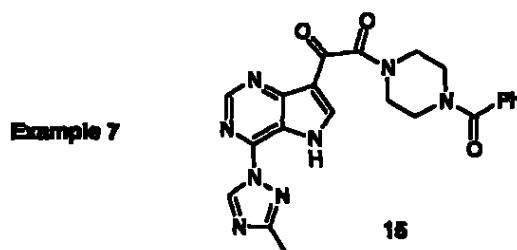
25



In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), pyrazole (26 mg, 0.38 mmol) and ethanol (1 mL) were combined and heated at 140° C with microwaves for 45 min. The reaction was diluted with MeOH (3 mL), filtered and the filtrate was purified by preparative HPLC to yield 14 (13 mg, 0.03 mmol, 24%) as a white solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.87 (s, 1H), 8.81 (s, 1H), 8.53 (s, 1H), 8.04 (s, 1H), 7.53-7.39 (m, 5H), 6.69 (s, 1H), 3.98-3.46 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 430; HPLC R<sub>t</sub> = 0.95 min., column G, conditions B.

*Preparation of Example 7:*

1-(4-Benzoyl-piperazin-1-yl)-2-[4-(3-methyl-[1,2,4]triazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-ethane-1,2-dione (Compound 15)



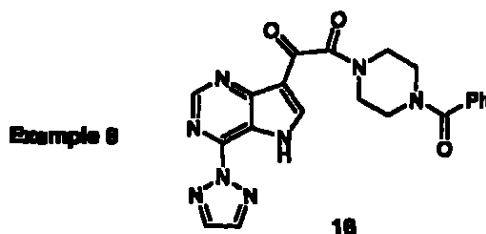
In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-methyl-1,2,4-triazole (22 mg, 0.38 mmol) and ethanol (1 mL) were combined and heated at 140° C with microwaves for 45 min. The reaction was diluted with MeOH/DMF (1:1, 3 mL), filtered and the filtrate was purified by preparative HPLC to yield 15 (9 mg, 0.02 mmol, 17%) as a white solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.74 (br s, 1H), 9.54 (s, 1H), 8.94 (s, 1H), 8.54 (s, 1H), 7.55-7.35 (m, 5H), 3.90-3.22 (m, 8H), 2.53 (s, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 445; HPLC R<sub>t</sub> = 0.88 min., column G, conditions B.

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**Preparation of Example 8:**

1-(4-(2H-1,2,3-Triazol-2-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-(4-benzoylpiperazin-1-yl)ethane-1,2-dione (Compound 16)



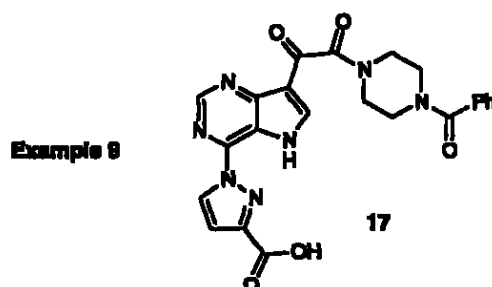
5

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-methyl-1,2,4-triazole (52 mg, 0.75 mmol) and copper powder (16 mg, 0.25 mmol) were combined and heated at 140° C with microwaves for 1 h. The reaction was diluted with MeOH (3 mL), filtered through celite and the filtrate was purified by preparative HPLC to yield 16 (3 mg, 0.007 mmol, 5%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.97 (s, 1H), 8.61 (s, 1H), 8.28 (s, 1H), 8.27 (s, 1H), 7.52-7.40 (m, 5H), 4.02-3.44 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 431; HPLC R<sub>t</sub> = 0.82 min., column G, conditions B.

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**Preparation of Example 9:**

1-{7-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}-1H-pyrazole-3-carboxylic acid (Compound 17)



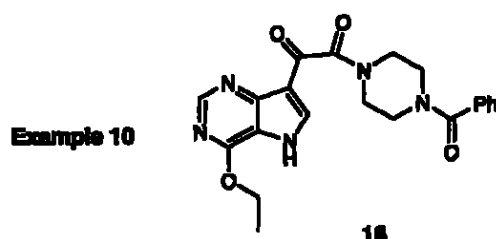
20

In a sealed tube dicarbonyl intermediate 10 (30 mg, 0.076 mmol) and 3-pyrazolecarboxylic acid (26 mg, 0.23 mmol), copper powder (10 mg, 0.16 mmol) and K<sub>2</sub>CO<sub>3</sub> (52 mg, 0.38 mmol) were combined and heated at 150° C with microwaves

for 2 h. The reaction was diluted with MeOH (3 mL), filtered through celite, concentrated, dissolved into DMSO and purified by preparative HPLC to yield 17 (5 mg, 0.01 mmol, 14%) as a white solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 13.32 (br s, 1H), 12.55 (br s, 1H), 8.98-8.96 (m, 2H), 8.71 (s, 1H), 7.51-7.38 (m, 5H), 7.13 (d, J = 2.4 Hz, 1 H), 3.90-3.20 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 474; HPLC R<sub>t</sub> = 0.76 min., column G, conditions B.

*Preparation of Example 10:*

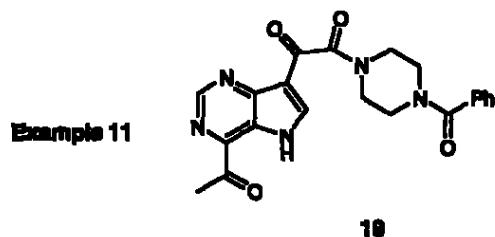
1-(4-Benzoylpiperazin-1-yl)-2-(4-ethoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 18)



In a sealed tube dicarbonyl intermediate 10 (30 mg, 0.076 mmol) and 3-pyrazolecarboxylic acid (26 mg, 0.23 mmol), copper powder (10 mg, 0.16 mmol) and K<sub>2</sub>CO<sub>3</sub> (52 mg, 0.38 mmol) in EtOH (1.0 mL) were combined and heated at 150° C with microwaves for 2 h. The reaction was diluted with MeOH (3 mL), filtered through celite, concentrated, dissolved into DMSO and purified by preparative HPLC to yield 18 (1 mg, 0.002 mmol, 3%) as a white solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.73 (s, 1H), 8.45 (s, 1H), 7.57-7.40 (m, 5H), 4.77 (q, J = 7.3 Hz, 2H), 4.04-3.42 (m, 8H), 1.53 (t, J = 7.3 Hz, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 408; HPLC R<sub>t</sub> = 0.85 min., column G, conditions B.

**Preparation of Example 11:**

1-(4-Acetyl-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-(4-benzoylpiperazin-1-yl)ethane-1,2-dione (Compound 19)

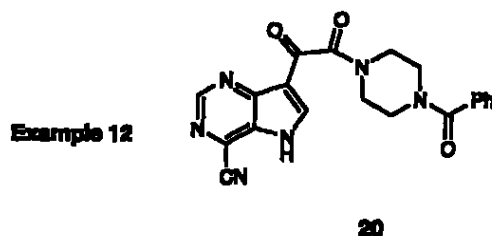


5

In a sealed tube dicarbonyl intermediate 10 (600 mg, 1.5 mmol), tributyl(1-ethoxyvinyl)stannane (1.5 mL 4.5 mmol), tetrakis(triphenylphosphine)palladium(0) (350 mg, 0.30 mmol) and 1,4-dioxane (15 mL) were combined and heated at 120° C with microwaves for 2h. The reaction mixture was divided and 25% v/v was concentrated diluted with MeOH/CH<sub>2</sub>Cl<sub>2</sub> (2:1, 1.5 mL) and 1N aqueous HCl (0.5 mL). The reaction was stirred overnight, neutralized with 1N aqueous NaOH (0.5 mL) and concentrated. The residue was dissolved into DMSO, filtered and purified by preparative HPLC to yield 19 (79 mg, 0.20 mmol, 53%) as a pink solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.19 (s, 1H), 8.62 (s, 1H), 7.52-7.40 (m, 5H), 3.92-3.41 (m, 8H), 2.80 (s, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 406; HPLC R<sub>t</sub> = 0.79 min., column N.

**Preparation of Example 12:**

7-(2-(4-Benzoylpiperazin-1-yl)-2-oxoacetyl)-5H-pyrrolo[3,2-d]pyrimidine-4-carbonitrile (Compound 20)



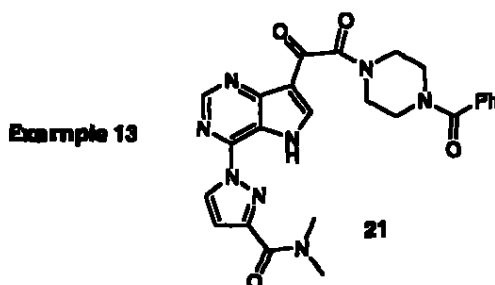
In a sealed tube dicarbonyl intermediate 10 (40 mg, 0.10 mmol), potassium cyanide (10 mg, 0.15 mmol), sodium 4-toluenesulfinate (20 mg, 0.11 mmol) and DMF (0.8 mL) were combined and heated at 100° C for 3h. The crude reaction mixture was partitioned between aqueous 5% Na<sub>2</sub>CO<sub>3</sub> (0.5 mL) and EtOAc (4 mL).

- 5 The organic layer was washed with aqueous 5% Na<sub>2</sub>CO<sub>3</sub> (0.7 mL), concentrated, dissolved into MeOH/DMSO (3:1, 2 mL) and purified by preparative HPLC to yield 20 (10 mg, 0.03 mmol, 26%) as a white solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 14.16 (br s, 1H), 9.20 (s, 1H), 8.96 (s, 1H), 7.52-7.36 (m, 5H), 3.90-3.28 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 389; HPLC R<sub>t</sub> = 0.92 min., column P, conditions B.

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*Preparation of Example 13:*

1-(7-(2-(4-Benzoylpiperazin-1-yl)-2-oxoacetyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl)-N,N-dimethyl-1H-pyrazole-3-carboxamide (Compound 21)



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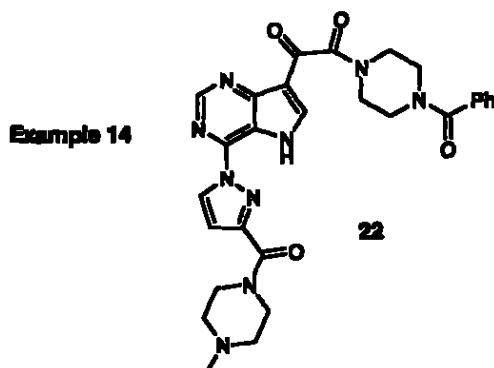
- In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), N,N-dimethyl-1H-pyrazole-3-carboxamide (53 mg, 0.38 mmol), copper(0) (10 mg) and 1,4-dioxane (0.8 mL) were combined and heated at 150° C with microwaves for 2h. The reaction mixture was concentrated, diluted with MeOH and DMSO, filtered and
- 20 purified by preparative HPLC to yield 21 (2.3 mg, 0.005 mmol, 4%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.94-8.87 (m, 2H), 8.59 (s, 1H), 7.56-7.36 (m, 5H), 6.94 (d, J = 2.8 Hz, 1H), 4.07-3.43 (m, 8H), 3.29 (s, 3H), 3.19 (s, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 501; HPLC R<sub>t</sub> = 1.16 min., column N.

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**Preparation of Example 14:**

1-(4-Benzoylpiperazin-1-yl)-2-(4-(3-(1-methylpiperazine-4-carbonyl)-1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 22)



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Carboxylic acid 17 (34 mg, 0.73 mmol), N-methylpiperazine (15 mg, 0.15 mmol), N,N-diisopropylethylamine (0.13 mL, 94 mg, 0.73 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (41 mg, 0.16 mmol) were dissolved into CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and stirred for 20h. The reaction mixture was concentrated, diluted with MeOH (1.7 mL) filtered and purified by preparative HPLC to yield 22 (41 mg, 0.73 mmol, 99%) as a white solid <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.93 (d, *J* = 2.8 Hz, 1H), 8.90 (s, 1H), 8.60 (s, 1H), 7.54-7.37 (m, 5H), 6.98 (d, *J* = 2.8 Hz, 1H), 4.06-3.12 (m, 16H), 2.97 (s, 3H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 556; HPLC R<sub>t</sub> = 1.03 min., column P., conditions B.

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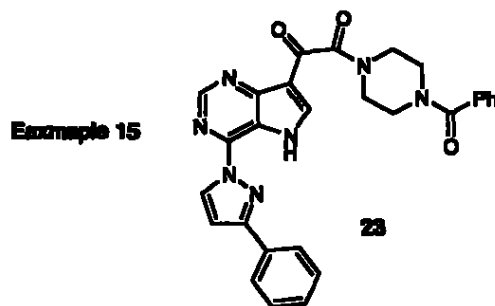
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**Preparation of Example 15:**

1-(4-Benzoylpiperazin-1-yl)-2-(4-(3-phenyl-1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 23)



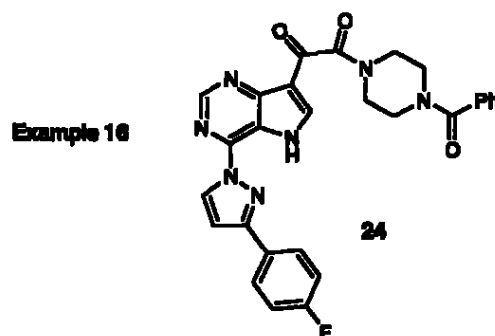
5

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-phenyl-1H-pyrazole (80 mg, 0.56 mmol) and 1,4-dioxane (2.5 mL) were combined and heated at 170° C with microwaves for 20 min. The reaction was concentrated and triturated with MeOH (3 mL). The resulting solids were washed with MeOH and with Et<sub>2</sub>O to yield 23 (33 mg, 0.07 mmol, 50%) as a tan solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.42 (br s, 1H), 8.95 (d, *J* = 2.8 Hz, 1H), 8.92 (s, 1H), 8.57 (br d, *J* = 3.1 Hz, 1H), 8.27 (d, *J* = 7.3 Hz, 2H), 7.55 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.51-7.38 (m, 5H), 7.30 (d, *J* = 2.8 Hz, 1H), 3.92-3.21 (m, 8H); LC/MS: (ES+) *m/z* (*M*+H)<sup>+</sup> = 505; HPLC *R*<sub>t</sub> = 1.40 min., column Q, conditions B.

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**Preparation of Example 16:**

1-(4-Benzoylpiperazin-1-yl)-2-(4-(3-(4-fluorophenyl)-1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 24)



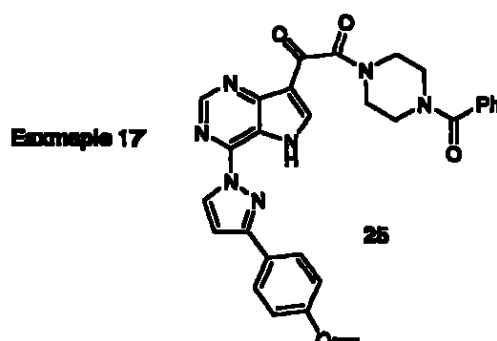
20

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-(4-fluorophenyl)-1H-pyrazole (150 mg, 0.93 mmol) and 1,4-dioxane (2 mL) were combined and heated at 160° C with microwaves for 20 min. The reaction was concentrated, diluted with MeOH (3 mL), neutralized with saturated aqueous NaHCO<sub>3</sub> and 24 (15 mg, 0.03 mmol, 22%) was collected by filtration as a tan solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.48 (br s, 1H), 8.96 (d, *J* = 2.8 Hz, 1H), 8.91 (s, 1H), 8.58 (br s, 1H), 8.34 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.50-7.39 (m, 5H), 7.88 (t, *J* = 8.7 Hz, 2H), 7.80 (d, *J* = 2.8 Hz, 1H), 3.91-3.23 (m, 8H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 524; HPLC *R*<sub>t</sub> = 1.42 min., column Q, conditions B.

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*Preparation of Example 17:*

1-(4-Benzoylpiperazin-1-yl)-2-(4-(3-(4-methoxyphenyl)-1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 25)



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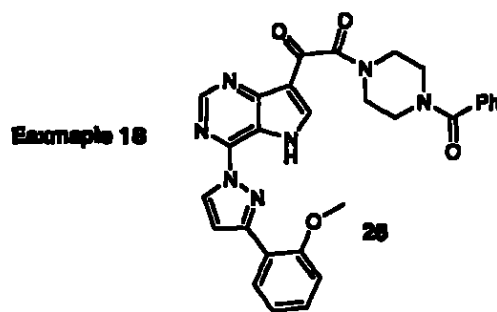
In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-(4-methoxyphenyl)-1H-pyrazole (105 mg, 0.60 mmol) and 1,4-dioxane (2.5 mL) were combined and heated at 170° C with microwaves for 20 min. The reaction was concentrated and triturated with MeOH (3 mL). The resulting solids were washed with MeOH and with Et<sub>2</sub>O to yield 25 (43 mg, 0.08 mmol, 61%) as a tan solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.41 (br s, 1H), 8.91 (d, *J* = 2.8 Hz, 1H), 8.89 (s, 1H), 8.55 (br d, *J* = 3.4 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 2H), 7.51-7.39 (m, 5H), 7.23 (d, *J* = 2.8 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 3.92-3.21 (m, 8H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 535; HPLC *R*<sub>t</sub> = 1.40 min., column Q, conditions B.

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**Preparation of Example 18:**

**1-(4-Benzoylpiperazin-1-yl)-2-(4-(3-(2-methoxyphenyl)-1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 26)**



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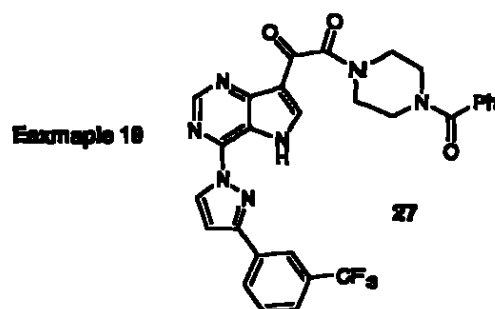
In a sealed tube dicarbonyl intermediate 10 (51 mg, 0.13 mmol), 3-(2-methoxyphenyl)-1H-pyrazole (109 mg, 0.60 mmol) and 1,4-dioxane (2 mL) were combined and heated at 170° C with microwaves for 20 min. The reaction was concentrated and triturated with MeOH (3 mL). The resulting solids were washed with MeOH and with Et<sub>2</sub>O to yield 26 (32 mg, 0.06 mmol, 47%) as a tan solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.34 (br s, 1H), 8.91 (s, 1H), 8.90 (d, *J* = 2.8 Hz, 1H), 8.55 (br d, *J* = 3.4 Hz, 1H), 8.37 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.50-7.39 (m, 5H), 7.47 (ddd, *J* = 8.2, 7.0, 1.5 Hz, 1H), 7.21 (d, *J* = 2.8 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.14 (dd, *J* = 7.8, 7.0 Hz, 1H), 3.94 (s, 3H), 3.91-3.23 (m, 8H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 535; HPLC R<sub>t</sub> = 1.42 min., column Q, conditions B.

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124**Preparation of Example 19:**

1-(4-Benzoylpiperazin-1-yl)-2-(4-(3-(3-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 27)



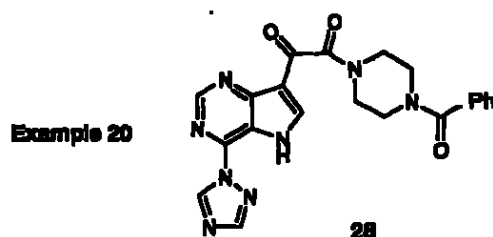
5

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-(3-(trifluoromethyl)phenyl)-1H-pyrazole (150 mg, 0.70 mmol) and 1,4-dioxane (2 mL) were combined and heated at 160° C with microwaves for 20 min. The reaction was concentrated, dissolved into MeOH (3 mL) and purified by preparative HPLC to yield 27 (34 mg, 0.06 mmol, 46%) as a white solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.63 (br s, 1H), 9.00 (d, *J* = 2.8 Hz, 1H), 8.94 (s, 1H), 8.64 (s, 1H), 8.62 (d, *J* = 7.9 Hz, 1H), 8.54 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.79 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.52-7.36 (m, 5H), 7.47 (d, *J* = 2.8 Hz, 1H), 3.90-3.25 (m, 8H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 574; HPLC R<sub>t</sub> = 1.77 min., column Q, conditions B.

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**Preparation of Example 20:**

1-(4-(1H-1,2,4-Triazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-(4-benzoylpiperazin-1-yl)ethane-1,2-dione (Compound 28)

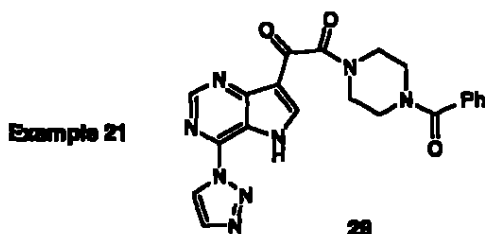


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In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 1,2,4-triazole (26 mg, 0.44 mmol), copper(0) (8 mg, 0.13 mmol), K<sub>2</sub>CO<sub>3</sub> (23 mg, 0.17 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 140° C with microwaves for 6h. The reaction mixture was diluted with MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 2 mL), filtered, concentrated, dissolved into MeOH/DMSO (5:4, 1.8 mL) and purified by preparative HPLC. The resulting yellow solid was triturated with MeOH to yield 28 (15 mg, 0.03 mmol, 28%) as a light yellow solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.95 (s, 1H), 9.71 (s, 1H), 8.98 (s, 1H), 8.61 (s, 1H), 8.56 (br s, 1H), 7.52-7.36 (m, 5H), 3.92-3.23 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 431; HPLC R<sub>t</sub> = 0.98 min., column C.

*Preparation of Example 21:*

1-(4-(1H-1,2,3-Triazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-(4-benzoylpiperazin-1-yl)ethane-1,2-dione (Compound 29)



In a sealed tube dicarbonyl intermediate 10 (60 mg, 0.15 mmol) and 1,2,3-triazole (95 mg, 1.4 mmol) in 1,4-dioxane (3 mL) were combined and heated at 170° C with microwaves for 20 min. The reaction was concentrated and the residue was triturated with MeOH to yield 29 (10 mg, 0.023 mmol, 16%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.08 (s, 1H), 9.04 (s, 1H), 8.66 (s, 1H), 8.07 (s, 1H), 7.57-7.41 (m, 5H), 4.08-3.43 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 431; HPLC R<sub>t</sub> = 0.95 min., column O, conditions B.

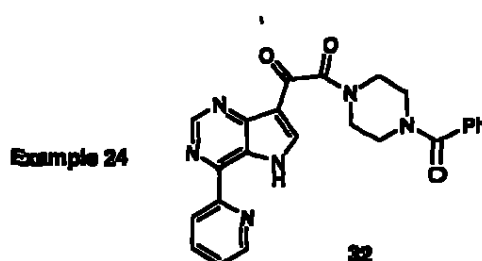
127

palladium(0) (30 mg, 0.03 mmol) and 1,4-dioxane (1 mL) were combined and heated at 110° C with microwaves for 2h, and then heated at 120° C for 2h. The reaction was repeated as described above and the reaction solution was heated at 110° C with microwaves for 5h. The two reactions were combined, diluted with MeOH/DMSO, filtered and purified by preparative HPLC. The resulting yellow solid was triturated with MeOH to yield 31 (4 mg, 0.008 mmol, 3%) as a white solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.11 (s, 1H), 8.66 (s, 1H), 7.56-7.42 (m, 5H), 7.27 (s, 1H), 4.06-3.45 (m, 8H), 2.47 (s, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 445; HPLC R<sub>t</sub> = 1.23 min., column L.

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*Preparation of Example 24:*

1-(4-Benzoylpiperazin-1-yl)-2-(4-(pyridin-2-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 32)



15

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 2-(tributylstannyl)pyridine (140 mg, 0.38 mmol), tetrakis(triphenylphosphine)-palladium(0) (30 mg, 0.03 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 110° C with microwaves for 1h. The reaction mixture was concentrated, diluted with MeOH, filtered and purified by preparative HPLC to yield 32 (8 mg, 0.02 mmol, 14%) as a yellow waxy solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.15-9.10 (m, 1H), 8.89 (m s, 1H), 8.70 (d, J = 7.9 Hz, 1H), 8.62 (s, 1H), 8.09-8.05 (m, 1H), 7.61-7.55 (m, 1H), 7.54-7.37 (m, 5H), 4.05-3.42 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 441; HPLC R<sub>t</sub> = 1.54 min., column P.

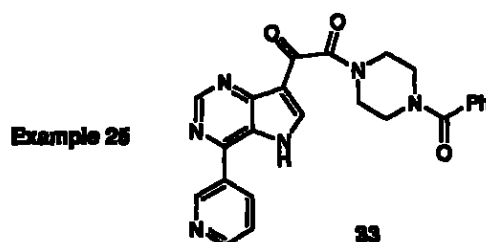
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**Preparation of Example 25:**

1-(4-Benzoylpiperazin-1-yl)-2-(4-(pyridin-3-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 33)



5

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 3-(tributylstannyl)pyridine (160 mg, 0.43 mmol), tetrakis(triphenylphosphine)-palladium(0) (40 mg, 0.03 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 130° C for 4h. The reaction mixture was concentrated to dryness and partitioned between EtOAc (5mL) and saturated aqueous NaHCO<sub>3</sub> with cesium fluoride. The biphasic suspension was filtered, separated and the aqueous layer was concentrated to dryness. The residue was diluted with MeOH (2 mL) and DMSO (0.5 mL), filtered and purified by preparative HPLC to yield 33 (7 mg, 0.02 mmol, 12%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.41 (s, 1H), 9.20 (s, 1H), 8.96 (d, *J* = 5.5 Hz, 1H), 8.91 (d, *J* = 7.6 Hz, 1H), 8.73 (s, 1H), 8.05 (dd, *J* = 7.6, 5.5 Hz, 1H), 7.56-7.42 (m, 5H), 4.10-3.43 (m, 8H); LC/MS: (ES+) *m/z* (*M*+H)<sup>+</sup> = 441; HPLC *R*<sub>t</sub> = 0.92 min., column S.

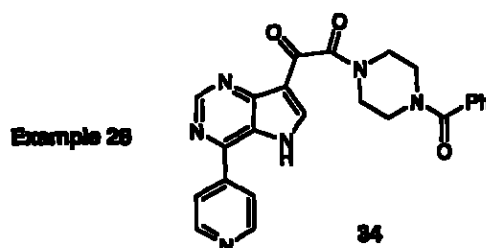
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**Preparation of Example 26:**

1-(4-Benzoylpiperazin-1-yl)-2-(4-(pyridin-4-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 34)



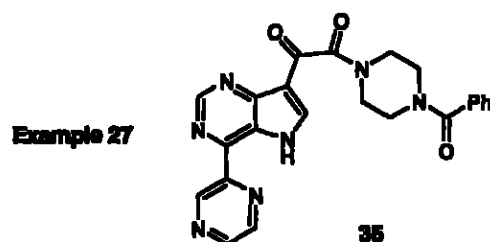
5

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 4-(tributylstannyl)pyridine (140 mg, 0.38 mmol), tetrakis(triphenylphosphine)-palladium(0) (30 mg, 0.03 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 110° C with microwaves for 2h, and then at 120° C for 2h. The reaction mixture was concentrated, diluted with MeOH/DMSO, filtered and purified by preparative HPLC to yield 34 (22 mg, 0.08 mmol, 38%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.24 (s, 1H), 9.04 (d, *J* = 5.8 Hz, 2H), 8.75 (s, 1H), 8.52 (d, *J* = 5.8 Hz, 2H), 7.57-7.40 (m, 5H), 4.12-3.44 (m, 8H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 441; HPLC *R*<sub>t</sub> = 0.78 min., column L.

15

**Preparation of Example 27:**

1-(4-Benzoylpiperazin-1-yl)-2-(4-(pyrazin-2-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 35)



20

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 2-(tributylstannyl)pyrazine (160 mg, 0.43 mmol), tetrakis(triphenylphosphine)-

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palladium(0) (30 mg, 0.03 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 120° C with microwaves for 2h, and then at 130° C for 2h. The reaction mixture was concentrated to dryness, diluted with MeOH (2.5 mL) and DMSO (0.5 mL), filtered and purified by preparative HPLC. The resulting yellow solid was

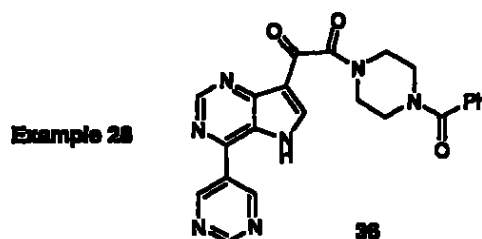
5 triturated with MeOH to yield 35 (8 mg, 0.02 mmol, 15%) as a light yellow solid.

<sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.93 (br s, 1H), 9.75 (d, J = 1.2 Hz, 1H), 9.21 (s, 1H), 8.93 (dd, J = 2.4, 1.2 Hz, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.64 (br s, 1H), 7.53-7.35 (m, 5H), 3.96-3.21 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 442; HPLC R<sub>t</sub> = 1.15 min., column S.

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*Preparation of Example 28:*

1-(4-Benzoylpiperazin-1-yl)-2-(4-(pyrimidin-5-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 36)



15

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 5-(tributylstannyl)pyrimidine (160 mg, 0.43 mmol), tetrakis(triphenylphosphine)-palladium(0) (30 mg, 0.03 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 130° C with microwaves for 2h. The reaction mixture was concentrated, diluted with MeOH/DMSO, filtered and purified by preparative HPLC. The resulting orange solid was triturated with acetone to yield 36 (36.3 mg, 0.08 mmol, 63%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 13.48 (br s, 1H), 9.42 (s, 1H), 9.41 (s, 2H), 9.18 (s 1H), 7.52-7.39 (m, 5H), 3.91-3.24 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 442; HPLC R<sub>t</sub> = 0.90 min., column S.

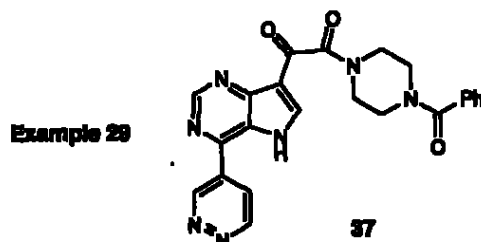
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X33

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**Preparation of Example 29:**

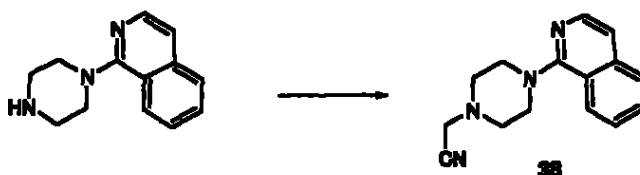
1-(4-Benzoylpiperazin-1-yl)-2-(4-(pyridazin-4-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 37)



5

In a sealed tube dicarbonyl intermediate 10 (50 mg, 0.13 mmol), 4-(tributylstannyl)pyridazine (160 mg, 0.43 mmol), tetrakis(triphenylphosphine)-palladium(0) (30 mg, 0.03 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 130° C with microwaves for 2h. The reaction mixture was concentrated, diluted with MeOH, filtered and purified by preparative HPLC. The resulting black oil was repurified by preparative HPLC and the resulting yellow solid was triturated with acetone to yield 37 (18.7 mg, 0.04 mmol, 33%) as an off-white solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 13.48 (br s, 1H), 9.82 (br s, 1H), 9.54 (dd, J = 5.2, 1.1 Hz, 1H), 9.22 (s 1H), 8.85 (br s, 1H), 8.29 (dd, J = 5.2, 2.0 Hz, 1H), 7.54-7.37 (m, 5H), 3.91-3.25 (m, 8H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 442; HPLC R<sub>t</sub> = 0.89 min., column S.

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**Preparation of 2-(4-(isoquinolin-1-yl)piperazin-1-yl)acetonitrile 38**

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To a solution of 1-(piperazin-1-yl)isoquinoline (459 mg, 2.15 mmol) in THF (15 mL) was added NEt<sub>3</sub> (3.6 mL, 27 mmol) and chloroacetonitrile (1.8 mL, 28 mmol) and the reaction was stirred 3h. The reaction mixture was filtered,

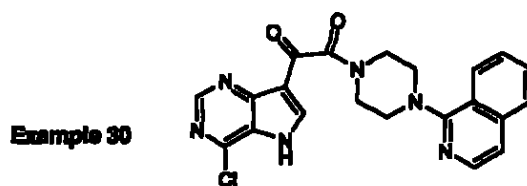


concentrated and the residue purified by silica gel chromatography (Biotage 25-short, 25% EtOAc/hexanes to 100% EtOAc/hex) to yield **38** (188 mg, 0.75 mmol, 35%) as a white solid. LC/MS: (ES+)  $m/z$  (M+H)<sup>+</sup> = 253; HPLC  $R_t$  = 1.23 min., column Q, conditions B.

5

*Preparation of Example 30:*

1-(4-Chloro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-(4-(isoquinolin-1-yl)piperazin-1-yl)ethane-1,2-dione (Compound **39**)



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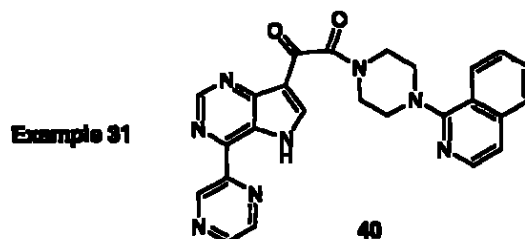
To a slurry of acid chloride intermediate **7** (115 mg, 0.53 mmol) and 2-(4-(isoquinolin-1-yl)piperazin-1-yl)acetonitrile **38** (188 mg, 0.75 mmol) in THF (5 mL), at -78° C, was added 0.5 M KHMDS in toluene (3.4 mL, 1.7 mmol). The reaction was stirred 2h. and the presence of the desired cyanoketone intermediate was verified

15 by LCMS. A solution of 32% peracetic acid in dilute aqueous acetic acid (0.5 mL, 2.4 mmol) was added and the reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with EtOAc (10 mL) and saturated aqueous NH<sub>4</sub>Cl (10 mL) and filtered. The layers were separated and the aqueous layer extracted with EtOAc (25 mL). The combined organic layers were  
20 concentrated and purified by preparative HPLC to yield **39** (102 mg, 0.24 mmol, 45%) as a bright yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.84 (s, 1H), 8.70 (s, 1H), 8.38 (d,  $J$  = 7.9 Hz, 1H), 8.06 (d,  $J$  = 7.2 Hz, 1H), 7.99 (dd,  $J$  = 7.9, 7.6 Hz, 1H), 7.89 (d,  $J$  = 6.7 Hz, 1H), 7.83 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.62 (d,  $J$  = 6.7 Hz, 1H), 4.20-3.79 (m, 8H); LC/MS: (ES+)  $m/z$  (M+H)<sup>+</sup> = 421; HPLC  $R_t$  = 0.83 min., column  
25 S.

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*Preparation of Example 31:*

1-(4-(Isoquinolin-1-yl)piperazin-1-yl)-2-(4-(pyrazin-2-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 40)



5

In a sealed tube dicarbonyl intermediate 39 (40 mg, 0.10 mmol), 2-(tributylstannyl)pyrazine (105 mg, 0.28 mmol), tetrakis(triphenylphosphine)-palladium(0) (30 mg, 0.03 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 130° C with microwaves for 2h. The reaction mixture was diluted with MeOH (1 mL) and DMSO (1 mL), filtered through celite and purified by preparative HPLC to yield 40 (12 mg, 0.03 mmol, 27%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.85 (s, 1H), 9.21 (s, 1H), 8.93 (br s, 1H), 8.83 (d, *J* = 2.4 Hz, 1H), 8.72 (s, 1H), 8.42 (d, *J* = 8.9 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 8.05 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.87 (dd, *J* = 8.9, 8.0 Hz, 1H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.66 (d, *J* = 6.7 Hz, 1H), 4.24-4.20 (m, 2H), 4.14-4.04 (m, 2H), 3.99-3.91 (m, 4H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 465; HPLC *R*<sub>t</sub> = 0.92 min., column S.

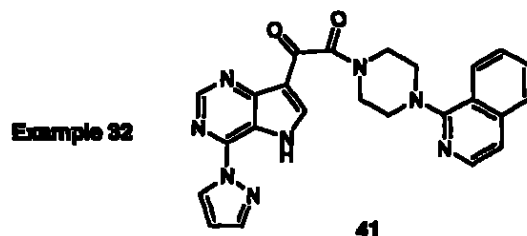
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*Preparation of Example 32:*

1-(4-(1H-Pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-(4-(isoquinolin-1-yl)piperazin-1-yl)ethane-1,2-dione (Compound 41)

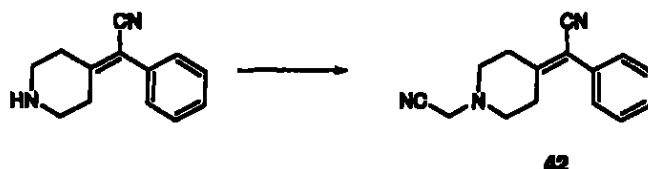
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In a sealed tube dicarbonyl intermediate 39 (41 mg, 0.10 mmol), pyrazole (26 mg, 0.38 mmol), copper(0) (10 mg) and 1,4-dioxane (0.8 mL) were combined and heated at 140° C with microwaves for 50 min. The reaction mixture was diluted with MeOH (1 mL) and DMSO (1 mL), filtered through celite and purified by preparative HPLC to yield 41 (11 mg, 0.02 mmol, 23%) as a light yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.90 (br s, 1H), 8.85 (d, *J* = 2.5 Hz, 1H), 8.61 (s, 1H), 8.42 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 8.08 (s, 1H), 8.04 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.89-7.85 (m, 1H), 7.85 (d, *J* = 6.7 Hz, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 6.72 (dd, *J* = 2.5, 1.6 Hz, 1H), 4.22-4.18 (m, 2H), 4.12-4.07 (m, 2H), 3.97-3.89 (m, 4H); LC/MS: (ES+) *m/z* (*M*+H)<sup>+</sup> = 453; HPLC *R*<sub>t</sub> = 0.97 min., column S.

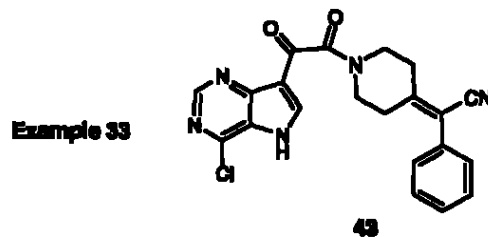
*Preparation of 2-(1-(cyanomethyl)piperidin-4-ylidene)-2-phenylacetonitrile 42*



To a solution of 2-phenyl-2-(piperidin-4-ylidene)acetonitrile (6.8 g, 34 mmol) in THF (150 mL) was added NEt<sub>3</sub> (40 mL, 300 mmol) and chloroacetonitrile (20 mL, 315 mmol) and the reaction was stirred 16h. The precipitates was filtered away and the filtrate concentrated to dryness. The residues was purified by silica gel chromatography (Biotage 40-short, 20% EtOAc/Hex to 50% EtOAc/Hex) to yield 42 (1.7 g, 7.2 mmol, 21%) as a yellow waxy solid. <sup>1</sup>H NMR: (500 MHz, CDCl<sub>3</sub>) δ 7.44-7.34 (m, 3H), 7.30-7.27 (m, 2H), 3.65 (s, 2H), 2.96 (t, *J* = 5.3 Hz, 2H), 2.90 (t, *J* = 5.3 Hz, 2H), 2.70 (t, *J* = 5.6 Hz, 2H), 2.62 (t, *J* = 5.6 Hz, 2H); LC/MS: (ES+) *m/z* (*M*+H)<sup>+</sup> = 238; HPLC *R*<sub>t</sub> = 1.33 min., column O, conditions B.

~~13~~ 139**Preparation of Example 33:**

2-(1-(2-(4-Chloro-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-oxoacetyl)piperidin-4-ylidene)-2-phenylacetonitrile (Compound 43)



5

To a slurry of acid chloride intermediate 7 (100 mg, 0.46 mmol) and phenylcyanoalkene intermediate 42 (143 mg, 0.60 mmol) in THF (4 mL) at -78° C was added a solution of 0.5 M KHMDS in toluene (3.0 mL, 1.5 mmol). The reaction was stirred 2h and the presence of the desired cyanoketone intermediate was verified by LCMS. A solution of 32% peracetic acid in dilute aqueous acetic acid (0.44 mL, 2.1 mmol) was added to the reaction mixture and then allowed to warm to ambient temperature overnight. The reaction mixture was diluted with EtOAc (15 mL) and saturated aqueous NH<sub>4</sub>Cl (10 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated, the residue was purified by preparative HPLC and the resulting yellow solid was triturated with MeOH to yield 43 (18.6 mg, 0.04 mmol, 10%) as a white solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 13.73 (s, 1H), 8.85 (s, 0.5H), 8.84 (s, 0.5H), 8.79 (s, 0.5H), 8.76 (s, 0.5H), 7.54-7.30 (m, 5H), 3.86 (t, J = 5.8 Hz, 1H), 3.70 (t, J = 5.8 Hz, 1H), 3.56 (t, J = 5.8 Hz, 1H), 3.38 (t, J = 5.8 Hz, 1H), 2.93 (t, J = 5.8 Hz, 1H), 2.65 (t, J = 5.8 Hz, 1H), 2.63 (dd, J = 5.8 Hz, 1H), 2.36 (t, J = 5.8 Hz, 1H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 406; HPLC R<sub>t</sub> = 1.28 min., column S.

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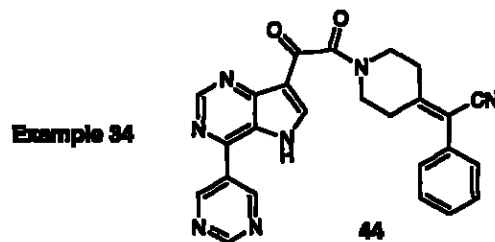
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*Preparation of Example 34:*

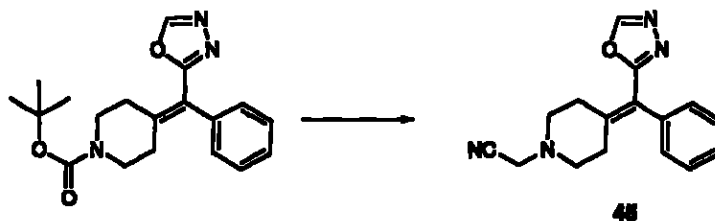
2-(1-(2-Oxo-2-(4-(pyrimidin-5-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)acetyl)piperidin-4-ylidene)-2-phenylacetonitrile (Compound 44)



5

In a sealed tube dicarbonyl intermediate 33 (30 mg, 0.074 mmol), 5-(tributylstannyl)pyrimidine (82 mg, 0.22 mmol), tetrakis(triphenylphosphine)-palladium(0) (20 mg, 0.02 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 130° C with microwaves for 2h. The reaction mixture was diluted with MeOH/DMSO, filtered and purified by preparative HPLC to yield 44 (8 mg, 0.02 mmol, 30%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.47 (s, 1H), 9.45 (s, 1H), 9.40 (s, 0.5H), 9.39 (s, 0.5H), 9.19 (s, 0.5H), 9.18 (s, 0.5H), 8.72 (s, 0.5H), 8.69 (s, 0.5H), 7.53-7.31 (m, 5H), 4.02 (dd, *J* = 6.1, 5.8 Hz, 1H), 3.84 (dd, *J* = 6.1, 5.8 Hz, 1H), 3.75 (dd, *J* = 5.8, 5.8 Hz, 1H), 3.57 (dd, *J* = 6.1, 5.8 Hz, 1H), 3.07 (dd, *J* = 6.1, 5.8 Hz, 1H), 2.86 (dd, *J* = 5.8, 5.8 Hz, 1H), 2.74 (dd, *J* = 6.1, 5.8 Hz, 1H), 2.54 (dd, *J* = 6.1, 5.8 Hz, 1H); LC/MS: (ES+) *m/z* (*M*+H)<sup>+</sup> = 450; HPLC *R*<sub>t</sub> = 1.48 min., column O.

Preparation of 2-(4-((1,3,4-oxadiazol-2-yl)(phenyl)methylene)piperidin-1-yl)acetonitrile 45

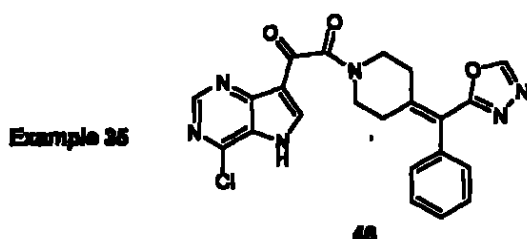


tert-Butyl 4-((1,3,4-oxadiazol-2-yl)(phenyl)methylene)piperidine-1-carboxylate (100 mg, 0.29 mmol) was diluted with 4 M HCl in 1,4-dioxane (1.2 mL,

4.8 mmol) and stirred 1h. The reaction was concentrated and the residue diluted with THF (1.5 mL), triethylamine (0.5 mL, 3.8 mmol) and chloroacetonitrile (0.25 mL, 3.9 mmol). The reaction was stirred 3 d, concentrated, diluted with MeOH, filtered and purified by preparative HPLC to yield 45 (43 mg, 0.15 mmol, 53%) as a white solid. <sup>1</sup>H NMR: (500 MHz, CDCl<sub>3</sub>) δ 8.27 (s, 1H), 7.41-7.31 (m, 3H), 7.20-7.16 (m, 2H), 3.55 (s, 2H), 3.02 (t, *J* = 5.8 Hz, 2H), 2.75 (t, *J* = 5.8 Hz, 2H), 2.61 (t, *J* = 5.8 Hz, 2H), 2.39 (t, *J* = 5.8 Hz, 2H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 281; HPLC R<sub>t</sub> = 0.97 min., column G, conditions B.

10 *Preparation of Example 35:*

1-(4-((1,3,4-Oxadiazol-2-yl)(phenyl)methylene)piperidin-1-yl)-2-(4-(1H-1,2,4-triazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 46)

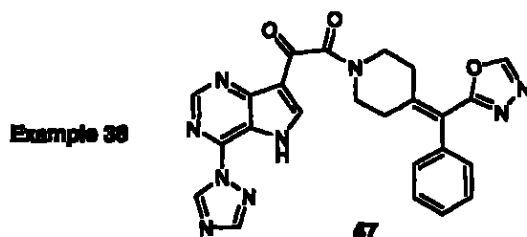


15 To a slurry of acid chloride intermediate 7 (600 mg, 2.8 mmol) and 2-(4-((1,3,4-oxadiazol-2-yl)(phenyl)methylene)piperidin-1-yl)acetonitrile 45 (800 mg, 2.9 mmol) in THF (5 mL), at -78° C was added a solution of 0.5 M KHMDS in toluene (17.2 mL, 8.6 mmol). The reaction was stirred 2h. A solution of 32% peracetic acid in dilute aqueous acetic acid (2.8 mL, 13 mmol) was added and the reaction mixture was allowed to warm to ambient temperature over 1h. The reaction mixture was diluted with EtOAc (30 mL) and brine (25 mL) and filtered. The layers were separated and the organic layer concentrated. The residue was triturated with Et<sub>2</sub>O to yield 46 (340 mg, 0.76 mmol, 27%) as an orange/yellow solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 13.73 (s, 1H), 9.17 (s, 0.5H), 9.10 (s, 0.5H), 8.83 (s, 0.5H), 8.82 (s, 0.5H), 8.76 (s, 0.5H), 8.74 (s, 0.5H), 7.49-7.15 (m, 5H), 3.80 (t, *J* = 5.8 Hz, 1H), 3.71 (t, *J* = 5.8 Hz, 1H), 3.49 (t, *J* = 5.8 Hz, 1H), 3.40 (t, *J* = 5.8 Hz, 1H), 3.02 (t, *J* = 5.8 Hz, 1H), 2.75 (t, *J* = 5.8 Hz, 1H), 2.52 (t, *J* = 5.8 Hz, 1H), 2.25 (t, *J* = 5.8 Hz,

1H); LC/MS: (ES+)  $m/z$  (M+H)<sup>+</sup> = 449; HPLC  $R_t$  = 1.10 min., column P, conditions B.

*Preparation of Example 36:*

- 5 1-(4-((1,3,4-Oxadiazol-2-yl)(phenyl)methylene)piperidin-1-yl)-2-(4-(1H-1,2,4-triazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 47)

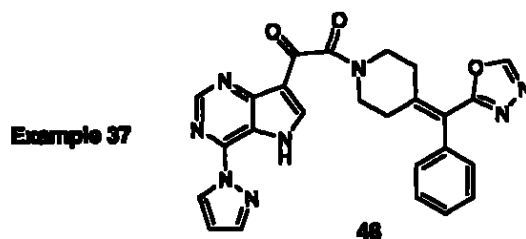


- In a sealed tube dicarbonyl intermediate 46 (30 mg, 0.07 mmol), 1,2,4-triazole (28 mg, 0.41 mmol), copper(0) (8 mg, 0.13 mmol),  $K_2CO_3$  (20 mg, 0.14 mmol) and 1,4-dioxane (1 mL) were combined and heated at 140° C with microwaves for 2h. The reaction mixture was diluted with MeOH/DMSO (2:3, 1 mL) and purified by preparative HPLC to yield 47 (4 mg, 0.008 mmol, 12%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz,  $CD_3OD$ )  $\delta$  9.62 (s, 0.5H), 9.62 (s, 0.5H), 8.87 (s, 0.5H), 8.79 (s, 0.5H), 8.60 (s, 0.5H), 8.58 (s, 0.5H), 8.44 (s, 0.5H), 8.43 (s, 0.5H), 7.48-7.14 (m, 6H), 3.95 (dd,  $J$  = 6.1, 5.8 Hz, 1H), 3.83 (dd,  $J$  = 6.1, 5.8 Hz, 1H), 3.68 (dd,  $J$  = 6.1, 5.5 Hz, 1H), 3.58 (dd,  $J$  = 5.8, 5.8 Hz, 1H), 3.10 (dd,  $J$  = 6.1, 5.8 Hz, 1H), 2.90 (dd,  $J$  = 6.1, 5.5 Hz, 1H), 2.61 (dd,  $J$  = 6.1, 5.8 Hz, 1H), 2.42 (dd,  $J$  = 6.1, 5.5 Hz, 1H); LC/MS: (ES+)  $m/z$  (M+H)<sup>+</sup> = 482; HPLC  $R_t$  = 1.13 min., column P, conditions B.

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**Preparation of Example 37:**

1-(4-((1,3,4-Oxadiazol-2-yl)(phenyl)methylene)piperidin-1-yl)-2-(4-(1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 48)



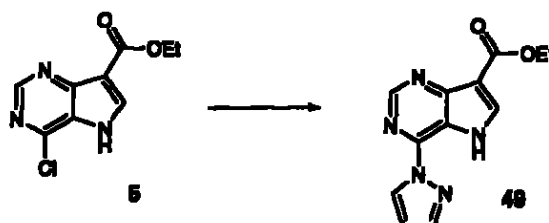
5

In a sealed tube dicarbonyl intermediate 46 (30 mg, 0.07 mmol), pyrazole (34 mg, 0.5 mmol) and 1,4-dioxane (0.7 mL) were combined and heated at 140° C with microwaves for 50 min. The reaction mixture was diluted with MeOH/DMSO (1:1, 1.2 mL) and purified by preparative HPLC to yield 48 (10 mg, 0.02 mmol, 32%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.86 (s, 1H), 8.85 (s, 0.5H), 8.82 (d, *J* = 2.8 Hz, 0.5H), 8.81 (d, *J* = 2.8 Hz, 0.5H), 8.79 (s, 0.5H), 8.53 (s, 0.5H), 8.51 (s, 0.5H), 8.04 (d, *J* = 1.5 Hz, 0.5H), 8.03 (d, *J* = 1.5 Hz, 0.5H), 7.46-7.16 (m, 5H), 6.71-6.67 (m, 1H), 3.94 (dd, *J* = 6.1, 5.8 Hz, 1H), 3.81 (dd, *J* = 6.1, 5.8 Hz, 1H), 3.69 (dd, *J* = 6.1, 5.8 Hz, 1H), 3.57 (dd, *J* = 5.8, 5.8 Hz, 1H), 3.08 (dd, *J* = 5.8, 5.8 Hz, 1H), 2.91 (dd, *J* = 6.1, 5.8 Hz, 1H), 2.59 (dd, *J* = 6.1, 5.8 Hz, 1H), 2.43 (dd, *J* = 6.1, 5.8 Hz, 1H); LC/MS: (ES+) *m/z* (*M*+H)<sup>+</sup> = 481; HPLC *R<sub>t</sub>* = 1.27 min., column P, conditions B.

20

**Preparation of ethyl 4-(1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate**

49

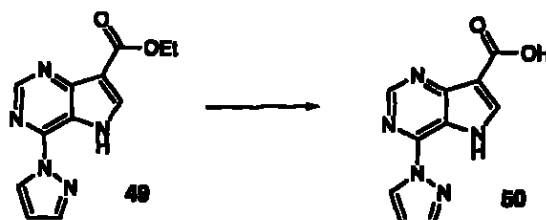


In a sealed tube 4-chloro-5H-pyrrolo[3,2-d]pyrimidine-7-carboxyl chloride 5 (2.0 g, 8.9 mmol), pyrazole (1.8 g, 26.5 mmol) and 1,4 dioxane (10 mL) were heated



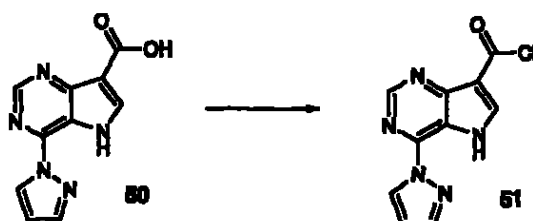
at 138° C for 2h. Upon cooling to ambient temperature a precipitate formed which was collected and washed with saturated aqueous NaHCO<sub>3</sub> and diethyl ether to yield 49 (340 mg, 1.3 mmol) as a white solid. The filtrate was treated with saturated aqueous NaHCO<sub>3</sub> (20 ml) and the resulting precipitate was washed with saturated aqueous NaHCO<sub>3</sub> and diethyl ether to yield additional 49 (2.0 g, 7.8 mmol, 99% total yield). <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.99 (br s, 1H), 8.78 (br s, 1H), 8.29 (s, 1H), 8.06 (br s, 1H), 6.72 (br s, 1H), 4.30 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 258; HPLC R<sub>t</sub> = 1.20 min., column L.

10 **Preparation of 4-(1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid 50**



To a solution of 4-(1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate 49 (2.0 g, 7.8 mmol) in THF (45 mL) was added a solution of LiOH•H<sub>2</sub>O (1.3 g, 31 mmol) in H<sub>2</sub>O (30 mL) and the reaction was stirred at 100° C for 16h. Additional LiOH•H<sub>2</sub>O (2.0 g, 48 mmol) was added, heating continued for 2h, MeOH was added (10 mL) and heating continued at 100° C for 1d. The reaction mixture was cooled, filtered, concentrated to ~20% volume and neutralized with ice and conc HCl. The white precipitate that formed was collected by filtration and washed with brine, H<sub>2</sub>O, EtOAc, and Et<sub>2</sub>O to yield 50 (quantitative), which was used without further purification. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.07 (br s, 1H), 8.89 (br s, 1H), 8.75 (s, 1H), 8.14 (s, 1H), 8.09 (br s, 1H), 6.76-6.73 (m, 1H); LC/MS: (ES+) m/z (M+H)<sup>+</sup> = 230; HPLC R<sub>t</sub> = 0.75 min., column S.

*Preparation of 4-(1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carboxyl chloride 51*



Oxalyl chloride (4.5 mL, 51 mmol) was added to a solution of diazaindole carboxylic acid 50 (1.08 g, 4.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) and the reaction mixture was stirred 14h. Catalytic DMF (3 drops) was added to the reaction mixture and after 3h the reaction was quenched with MeOH. The crude reaction mixture was concentrated to dryness to yield 51 (1.21 g, 4.9 mmol, 96%) as a tan solid with was used without further purification.  $^1\text{H}$  NMR: (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  12.45 (br s, 1H), 8.87 (s, 1H), 8.87 (d,  $J = 2.6$  Hz, 1H), 8.32 (d,  $J = 3.3$  Hz, 1H), 8.14 (d,  $J = 1.5$  Hz, 1H), 6.77 (dd,  $J = 2.6, 1.5$  Hz, 1H); Methyl ester (obtained by stirring 51 in MeOH): LC/MS: (ES+)  $m/z$  ( $M+H$ ) $^+$  = 244; HPLC  $R_t$  = 0.95 min., column O, conditions B.

*Preparation of 2-(1-(cyanomethyl)piperidin-4-ylidene)-2-(pyridin-2-yl)acetonitrile 52*



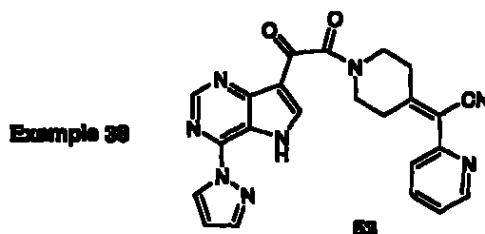
To a solution of 2-(piperidin-4-ylidene)-2-(pyridin-2-yl)acetonitrile (560 mg, 2.8 mmol) in THF (20 mL) was added  $\text{NBT}_3$  (5 mL, 38 mmol) and chloroacetonitrile (3 mL, 47 mmol) and the reaction was stirred 16h. The resulting precipitates were filtered away and the filtrate concentrated to dryness. The residues was purified by silica gel chromatography (Biotage 40-short, 50% EtOAc/hexanes to 100%

EtOAc/hexanes) to yield 52 (470 mg, 2.0 mmol, 71%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CDCl<sub>3</sub>) δ 8.64 (br d, *J* = 4.9 Hz, 1H), 7.77 (ddd, *J* = 7.9, 7.6, 1.9 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 7.6, 4.9 Hz, 1H), 3.58 (s, 2H), 2.94 (t, *J* = 5.8 Hz, 2H), 2.91 (t, *J* = 5.8 Hz, 2H), 2.83 (t, *J* = 5.8 Hz, 2H), 2.67 (t, *J* = 5.8 Hz, 2H);  
 5 LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 239; HPLC *R*<sub>t</sub> = 0.99 min., column O, conditions B.

*Preparation of Example 38:*

2-(1-(2-(4-(1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-oxoacetyl)piperidin-4-ylidene)-2-(pyridin-2-yl)acetonitrile (Compound 53)

10



To a slurry of acid chloride pyrazole intermediate 51 (100 mg, 0.40 mmol) and 3-pyridinylcyanoalkene intermediate 52 (100 mg, 0.42 mmol) in THF (4 mL) at -78° C was added a solution of 0.5 M KHMDS in toluene (3.0 mL, 1.5 mmol). The  
 15 reaction mixture was stirred at -78° C for 3h and the presence of the desired cyanoketone intermediate was verified by LCMS. A solution of 32% peracetic acid in dilute aqueous acetic acid (0.44 mL, 2.1 mmol) was added to the reaction mixture and then allowed to warm to ambient temperature overnight. The reaction mixture  
 20 was diluted with H<sub>2</sub>O (5 mL) and saturated aqueous NH<sub>4</sub>Cl (5 mL) and extracted with EtOAc (3 x 20mL). The layers were separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated, the residue was purified by preparative HPLC to yield 53 (7.3 mg, 0.02 mmol, 4%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.95 (s, 0.5H), 8.93 (s, 0.5H), 8.88 (d, *J* = 2.8 Hz, 0.5H), 8.86 (d, *J* = 3.1 Hz, 0.5H), 8.71 (br d, *J* = 4.9 Hz, 0.5H), 8.64-8.61  
 25 (m, 1H), 8.60 (s, 0.5H), 8.11 (br s, 0.5H), 8.10 (br s, 0.5H), 8.03 (ddd, *J* = 7.9, 7.6, 1.5 Hz, 0.5H), 7.97 (ddd, *J* = 7.9, 7.6, 1.5 Hz, 0.5H), 7.65 (d, *J* = 7.9 Hz, 0.5H), 7.60 (d, *J* = 7.9 Hz, 0.5H), 7.52 (dd, *J* = 7.9, 4.9 Hz, 0.5H), 7.46 (dd, *J* = 7.9, 4.9 Hz,

~~143~~ 143

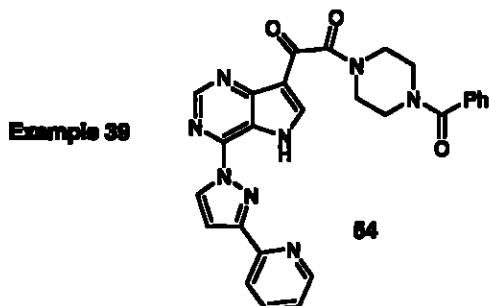
0.5H), 6.76-6.72 (m, 1H), 4.03 (dd,  $J = 6.1, 6.1$  Hz, 1H), 3.86 (dd,  $J = 6.1, 5.8$  Hz, 1H), 3.81 (dd,  $J = 6.1, 5.5$  Hz, 1H), 3.64 (dd,  $J = 5.8, 5.8$  Hz, 1H), 3.10 (dd,  $J = 6.1, 5.8$  Hz, 1H), 2.94 (dd,  $J = 6.1, 5.5$  Hz, 1H), 2.90 (dd,  $J = 6.1, 5.8$  Hz, 1H), 2.75 (dd,  $J = 5.8, 5.8$  Hz, 1H); LC/MS: (ES+)  $m/z$  (M+H)<sup>+</sup> = 439; HPLC  $R_t$  = 1.37 min., column

5 O.

*Preparation of Example 39:*

1-(4-Benzoylpiperazin-1-yl)-2-(4-(3-(pyridin-2-yl)-1H-pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)ethane-1,2-dione (Compound 54)

10

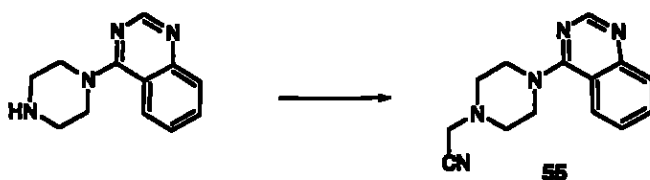


In a sealed tube dicarbonyl intermediate 10 (52 mg, 0.13 mmol), 2-(1H-pyrazol-3-yl)pyridine (104 mg, 0.71 mmol) and 1,4-dioxane (2.0 mL) were combined and heated at 150° C with microwaves for 1h. The reaction mixture was

15 concentrated, diluted with MeOH, filtered and purified by preparative HPLC to yield 54 (31 mg, 0.06 mmol, 47%) as an off-white solid. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.60 (br s, 1H), 8.97 (d,  $J = 1.8$  Hz, 1H), 8.94 (s, 1H), 8.73-8.66 (m, 2H), 8.61 (br s, 1H), 8.02 (t,  $J = 7.0$  Hz, 1H), 7.54-7.38 (m, 6H), 7.31 (d,  $J = 1.8$  Hz, 1H), 3.92-3.13 (m, 8H); LC/MS: (ES+)  $m/z$  (M+H)<sup>+</sup> = 507; HPLC  $R_t$  = 1.19 min., column N.

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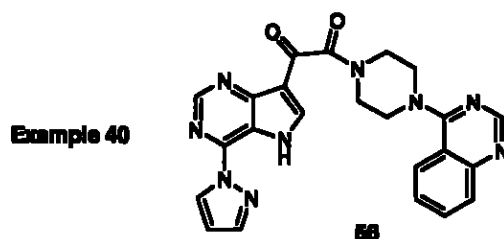
25

~~146~~ 144**Preparation of 2-(4-(quinazolin-4-yl)piperazin-1-yl)acetonitrile 55**

To a solution of 4-(piperazin-1-yl)quinazoline (1.8 g, 8.3 mmol) in THF (50 mL) was added  $\text{NEt}_3$  (20 mL, 150 mmol) and chloroacetonitrile (12 mL, 190 mmol) and the reaction was stirred 16h. The reaction mixture was quenched with 50% saturated aqueous  $\text{NaHCO}_3$  and extracted with EtOAc (3 x 200 mL). The combined organics were purified by silica gel chromatography (50% EtOAc/hexanes to 80% EtOAc/hexanes) to yield 55 (1.6 g, 6.1 mmol, 73%) as a viscous yellow oil.  $^1\text{H}$  NMR: (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.74 (s, 1H), 8.06 (d,  $J = 8.6$  Hz, 1H), 7.90 (d,  $J = 8.5$  Hz, 1H), 7.82-7.55 (m, 1H), 7.54-7.50 (m, 1H), 3.94-3.88 (m, 4H), 3.63 (s, 2H), 2.86-2.81 (m, 4H); LC/MS: (ES+)  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  = 254; HPLC  $R_t$  = 0.71 min., column O.

**Preparation of Example 40:**

15 1-(4-(1H-Pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-(4-(quinazolin-4-yl)piperazin-1-yl)ethane-1,2-dione (Compound 56)



To a slurry of acid chloride pyrazole intermediate 51 (100 mg, 0.40 mmol) and 2-(4-(quinazolin-4-yl)piperazin-1-yl)acetonitrile 55 (98 mg, 0.39 mmol) in THF (4 mL), at  $-78^\circ\text{C}$  was added a solution of 0.5 M  $\text{KHMDs}$  in toluene (3.0 mL, 1.5 mmol). The reaction mixture was stirred 3h and the presence of the desired cyanoketone intermediate was verified by LCMS. The reaction was treated with a

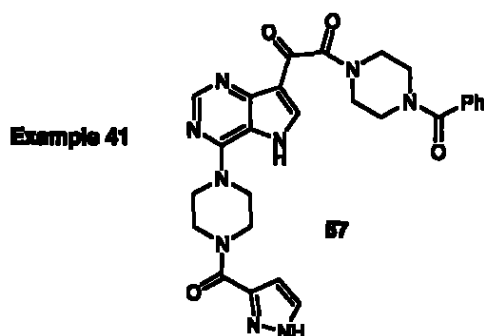
145

solution of 32% peracetic acid in dilute aqueous acetic acid (0.40 mL, 1.9 mmol) and then allowed to warm to ambient temperature overnight. The reaction mixture was diluted with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and extracted with  $\text{EtOAc}$  (3 x 20 mL). The combined organic layers were concentrated, the residue was purified by  
5 preparative HPLC to yield **56** (33 mg, 0.07 mmol, 18%) as a yellow solid.  $^1\text{H}$  NMR: (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.86 (s, 1H), 8.5 (d,  $J = 2.7$  Hz, 1H), 8.75 (s, 1H), 8.61 (s, 1H), 8.30 (d,  $J = 8.2$  Hz, 1H), 8.09-8.05 (m, 2H), 7.84 (d,  $J = 8.5$  Hz, 1H), 7.79 (dd,  $J = 8.2, 7.6$  Hz, 1H), 6.72 (br s, 1H), 4.62-4.56 (m, 2H), 4.43-4.38 (m, 2H), 4.12-4.07 (m, 2H), 3.91-3.86 (m, 2H); LC/MS: (ES+)  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  = 439; HPLC  $R_t$  = 1.06  
10 min., column O.

*Preparation of Example 41:*

1-(4-(4-(1H-Pyrazole-3-carbonyl)piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-  
2-(4-benzoylpiperazin-1-yl)ethane-1,2-dione (Compound **57**)

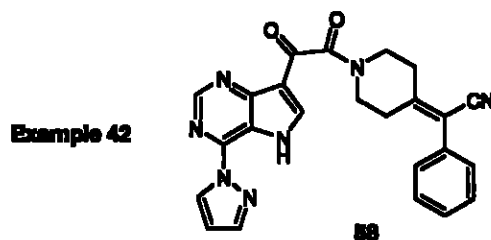
15



In a sealed tube dicarbonyl intermediate **10** (50 mg, 0.13 mmol), (4-methylpiperazin-1-yl)(1H-pyrazol-3-yl)methanone (75 mg, 0.39 mmol) and copper  
20 powder (10 mg, 0.16 mmol) were combined and heated at 150° C with microwaves for 2h. The reaction was purified by preparative HPLC to yield **57** (65 mg, 0.12 mmol, 92%) as a white solid.  $^1\text{H}$  NMR: (500 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  10.31 (br s, 2H), 8.82 (s, 1H), 8.85 (s, 1H), 7.80 (s, 1H), 7.50-7.40 (m, 5H), 6.74 (s, 1H), 4.50-4.37 (m, 6H), 4.09-3.96 (m, 2H), 3.86-3.60 (m, 8H); LC/MS: (ES+)  $m/z$  ( $\text{M}+\text{H}$ ) $^+$  = 542;  
25 HPLC  $R_t$  = 0.85 min., column G, conditions B.

~~141~~ 146**Preparation of Example 42:**

2-(1-(2-(4-(1H-Pyrazol-1-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-oxoacetyl)piperidin-4-ylidene)-2-phenylacetonitrile (Compound 58)

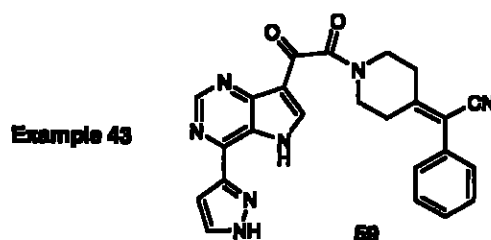


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In a sealed tube dicarbonyl intermediate 33 (31 mg, 0.077 mmol), pyrazole (20 mg, 0.29 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 140° C with microwaves for 50 min. The reaction mixture was diluted with MeOH/DMSO (2:1, 1.5 mL), filtered and purified by preparative HPLC to yield 58 (10 mg, 0.024 mmol, 31%) as an orange solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.90 (s, 0.5H), 8.88 (s, 0.5H), 8.86 (d, *J* = 2.8 Hz, 0.5H), 8.84 (d, *J* = 2.8 Hz, 0.5H), 8.57 (s, 0.5H), 8.54 (s, 0.5H), 8.08 (br s, 0.5H), 8.06 (br s, 0.5H), 7.53-7.31 (m, 5H), 6.74-6.70 (m, 1H), 4.00 (t, *J* = 5.8 Hz, 1H), 3.82 (t, *J* = 5.8 Hz, 1H), 3.75 (t, *J* = 5.8 Hz, 1H), 3.56 (t, *J* = 5.8 Hz, 1H), 3.05 (t, *J* = 5.8 Hz, 1H), 2.87 (t, *J* = 5.8 Hz, 1H), 2.72 (t, *J* = 5.8 Hz, 1H), 2.55 (t, *J* = 5.8 Hz, 1H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 438; HPLC R<sub>t</sub> = 1.73 min., column O.

**Preparation of Example 43:**

2-(1-(2-(4-(1H-pyrazol-3-yl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-2-oxoacetyl)piperidin-4-ylidene)-2-phenylacetonitrile (Compound 59)



147

In a sealed tube dicarbonyl intermediate 33 (33 mg, 0.081 mmol), 3-(tributylstannyl)-1H-pyrazole (73 mg, 0.20 mmol), tetrakis(triphenylphosphine)-palladium(0) (20 mg, 0.02 mmol) and 1,4-dioxane (0.8 mL) were combined and heated at 130° C with microwaves for 2h. The reaction mixture was diluted with MeOH/DMSO (2:1, 1.5 mL), filtered and purified by preparative HPLC to yield 59 (3.4 mg, 0.008 mmol, 10%) as a yellow solid. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>COCD<sub>3</sub>) δ 11.84 (br s, 1H), 9.06 (s, 0.5H), 9.05 (s, 0.5H), 8.58 (s, 0.5H), 8.55 (s, 0.5H), 8.01 (d, *J* = 2.7 Hz, 0.5H), 8.01 (d, *J* = 2.7 Hz, 0.5H), 7.55-7.32 (m, 5H), 7.24 (d, *J* = 2.7 Hz, 0.5H), 7.23 (d, *J* = 2.7 Hz, 0.5H), 4.01 (t, *J* = 5.8 Hz, 1H), 3.84 (t, *J* = 5.8 Hz, 1H), 3.74 (t, *J* = 5.8 Hz, 1H), 3.56 (t, *J* = 5.8 Hz, 1H), 3.07 (t, *J* = 5.8 Hz, 1H), 2.84 (t, *J* = 5.8 Hz, 1H), 2.78 (t, *J* = 5.8 Hz, 1H), 2.54 (t, *J* = 5.8 Hz, 1H); LC/MS: (ES+) *m/z* (M+H)<sup>+</sup> = 438; HPLC R<sub>f</sub> = 1.29 min., column L.

### Biology

15

- "μM" means micromolar;
- "mL" means milliliter;
- "μl" means microliter;
- "mg" means milligram;

20

The materials and experimental procedures used to obtain the results reported in Tables 1-3 are described below.

### Cells:

25

- *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

30



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).

10

### *Experiment*

1. Compound was added to HeLa CD4 CCR5 cells plated in 96 well plates at a cell density of  $1 \times 10^4$  cells per well in 100  $\mu$ l Dulbecco's Modified Eagle Medium containing 10 % fetal Bovine serum at a concentration of  $<20 \mu$ M.
2. 100  $\mu$ l 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  $\mu$ l per well and a final compound concentration of  $<10 \mu$ M.
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  $\mu$ l of Dulbecco's Modified Eagle Medium (without phenol red) and 50  $\mu$ l 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.

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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.
- 5
6. An EC<sub>50</sub> provides a method for comparing the antiviral potency of the compounds of this invention. The effective concentration for fifty percent inhibition (EC<sub>50</sub>) 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<sub>50</sub> data for the compounds is shown in Tables 2-4. Table 1 is the key for the data in Tables 2-4.

Cytotoxicity 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<sub>50</sub>s

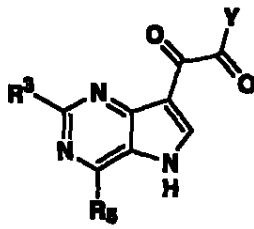
|                                                   |                                                               |                                                                                      |                                  |
|---------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------|
| Compounds<br>* with<br>EC <sub>50</sub> s<br>>5µM | Compound<br>s with<br>EC <sub>50</sub> s >1<br>µM but<br><5µM | Compounds<br>with EC50<br>>50nM but<br>not yet tested<br>at higher<br>concentrations | Compounds<br>with<br>EC50 < 1 µM |
| Group C                                           | Group B                                                       | Group A'                                                                             | Group A                          |

*Handwritten:* 150

\*Some of these compounds may have been tested at a concentration lower than their EC<sub>30</sub> but showed some ability to cause inhibition and thus should be evaluated at a higher concentration to determine the exact EC<sub>30</sub>.

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Table 2

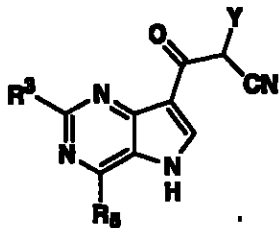


Examples

| Example Number | Compound Number | R3 | R5 | Y | EC <sub>30</sub> Group from Table 1 |
|----------------|-----------------|----|----|---|-------------------------------------|
| Example 2      | 10              | H  | Cl |   | A                                   |
| Example 3      | 11              | H  |    |   | A                                   |
| Example 4      | 12              | H  |    |   | A                                   |
| Example 5      | 13              | H  |    |   | A                                   |
| Example 6      | 14              | H  |    |   | A                                   |
| Example 7      | 15              | H  |    |   | A                                   |
| Example 8      | 16              | H  |    |   | A                                   |
| Example 9      | 17              | H  |    |   | A                                   |
|                |                 |    |    |   |                                     |

Table 3

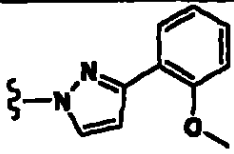
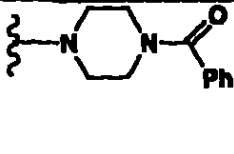
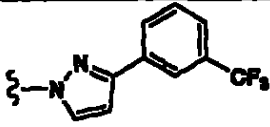
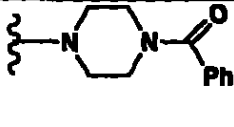
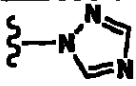
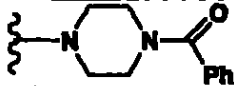
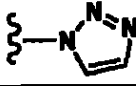
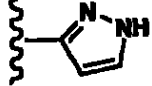
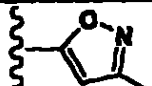
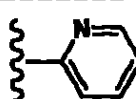
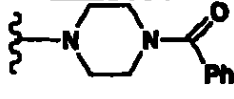
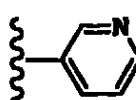
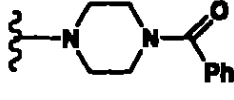
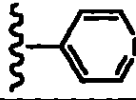
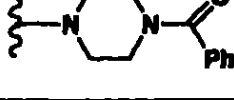
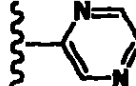
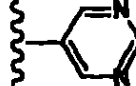
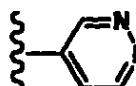
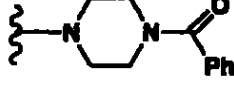
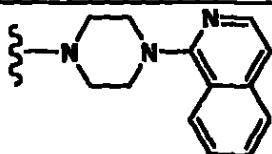
43 151



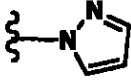
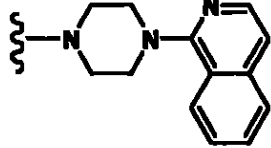
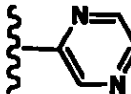
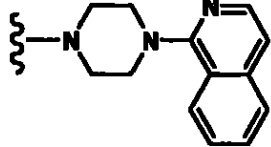
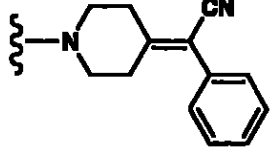
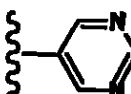
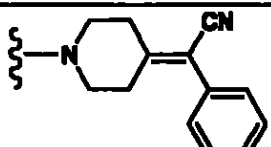
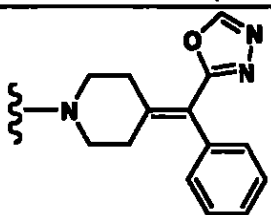
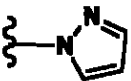
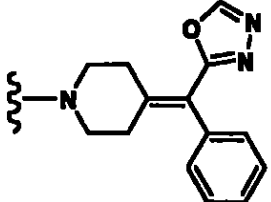
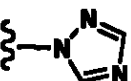
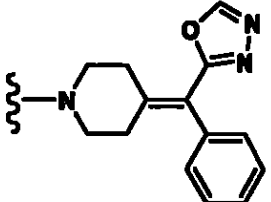
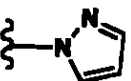
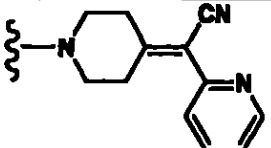
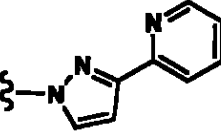
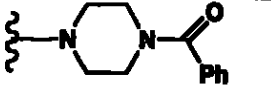
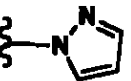
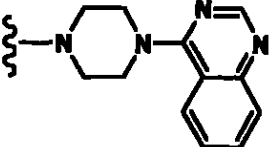
Examples

| Example No. | Cmpd. No. | R3 | R5 | Y | EC <sub>50</sub> Group from Table 1 |
|-------------|-----------|----|----|---|-------------------------------------|
| Example 1   | 9         | H  | Cl |   | A                                   |
| Example 10  | 18        | H  |    |   | A                                   |
| Example 11  | 19        | H  |    |   | A                                   |
| Example 12  | 20        | H  |    |   | A                                   |
| Example 13  | 21        | H  |    |   | A                                   |
| Example 14  | 22        | H  |    |   | A                                   |
| Example 15  | 23        | H  |    |   | A                                   |
| Example 16  | 24        | H  |    |   | A                                   |
| Example 17  | 25        | H  |    |   | A                                   |

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|            |    |   |                                                                                     |                                                                                      |   |
|------------|----|---|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---|
| Example 18 | 26 | H |    |    | A |
| Example 19 | 27 | H |    |    | A |
| Example 20 | 28 | H |    |    | A |
| Example 21 | 29 | H |    |    | A |
| Example 22 | 30 | H |    |    | A |
| Example 22 | 30 | H |    |    | A |
| Example 24 | 32 | H |   |   | A |
| Example 25 | 33 | H |  |  | A |
| Example 26 | 34 | H |  |  | A |
| Example 27 | 35 | H |  |  | A |
| Example 28 | 36 | H |  |  | A |
| Example 29 | 37 | H |  |  | A |
| Example 30 | 39 | H | Cl                                                                                  |  | A |

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|            |    |   |                                                                                     |                                                                                      |   |
|------------|----|---|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---|
| Example 31 | 40 | H |    |    | A |
| Example 32 | 41 | H |    |    | A |
| Example 33 | 43 | H | Cl                                                                                  |    | A |
| Example 34 | 44 | H |    |    | A |
| Example 35 | 46 | H | Cl                                                                                  |   | A |
| Example 36 | 47 | H |  |  | A |
| Example 37 | 48 | H |  |  | A |
| Example 38 | 53 | H |  |  | A |
| Example 39 | 54 | H |  |  | A |
| Example 40 | 56 | H |  |  | A |

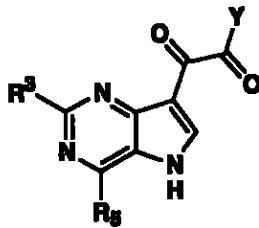
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|            |    |   |  |  |   |
|------------|----|---|--|--|---|
| Example 41 | 57 | H |  |  | A |
| Example 42 | 58 | H |  |  | A |
| Example 43 | 59 | H |  |  | A |

Table 4 shows other compounds of the invention which could be prepared by the methodology described herein and which are expected to have antiviral activity.

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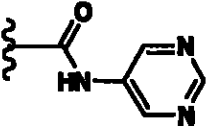
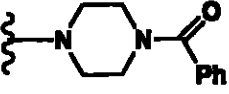
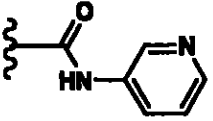
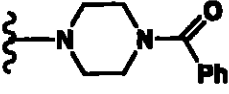
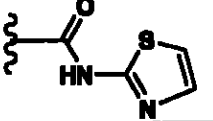
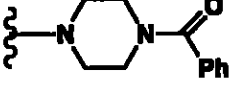
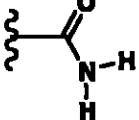
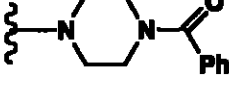
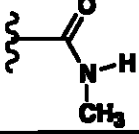
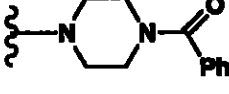
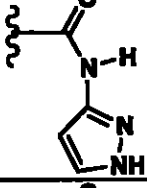
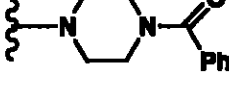
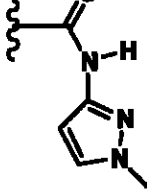
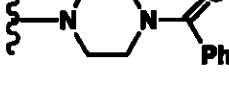
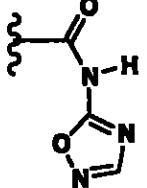
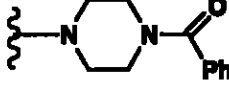
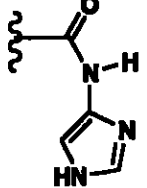
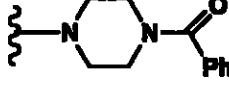
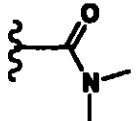
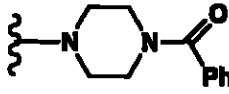
Table 4



|             |            |    |    |   |                                     |
|-------------|------------|----|----|---|-------------------------------------|
| Example No. | Compd. No. | R3 | R5 | Y | EC <sub>50</sub> Group from Table 1 |
| Example #   | #          | H  |    |   |                                     |
|             |            | H  |    |   |                                     |

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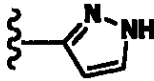
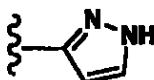
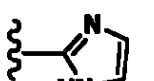
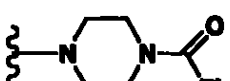
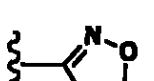
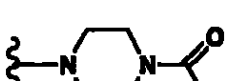
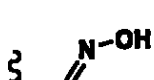
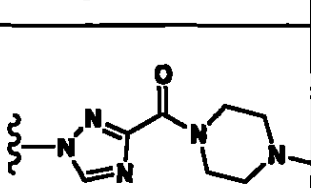
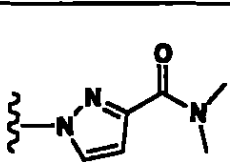
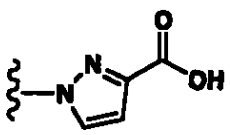
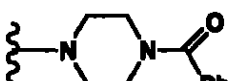
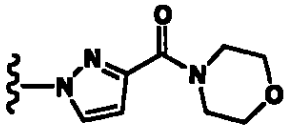
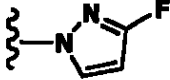
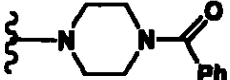
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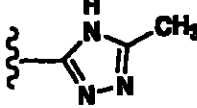
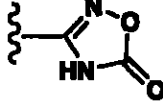
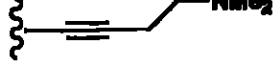
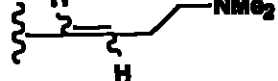
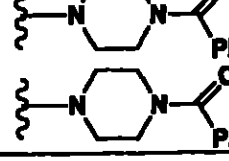
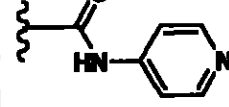
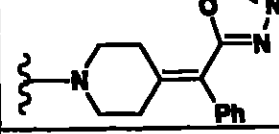
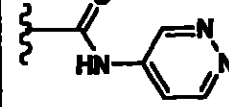
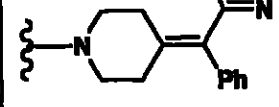
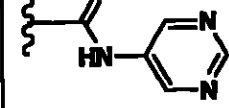
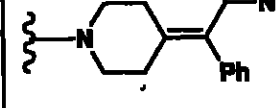
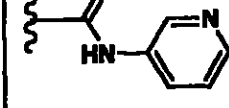
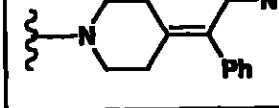
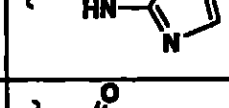
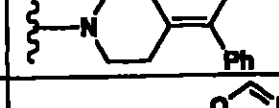
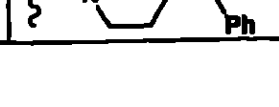
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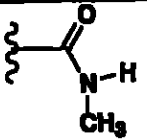
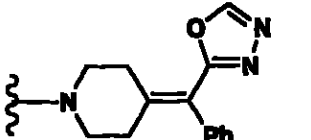
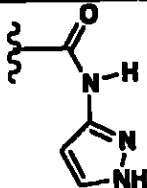
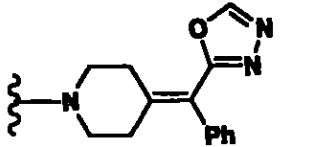
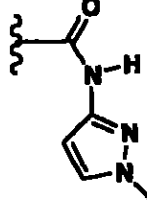
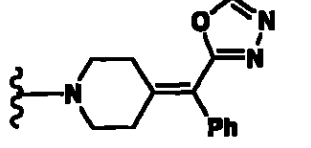
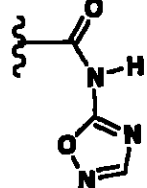
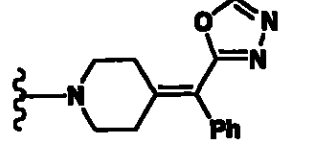
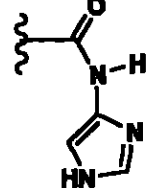
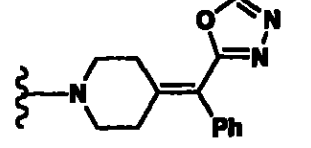
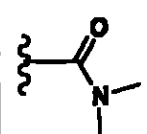
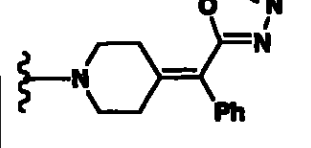
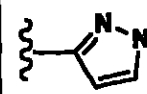
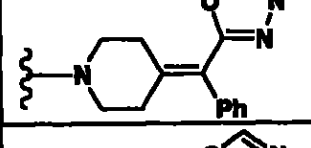
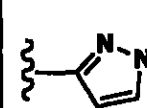
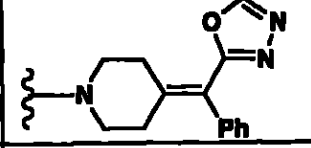
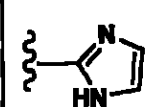
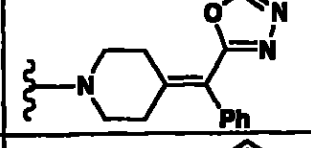
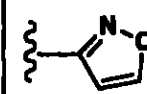
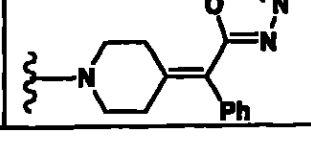
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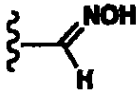
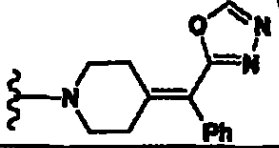
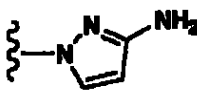
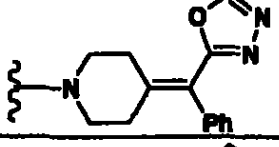
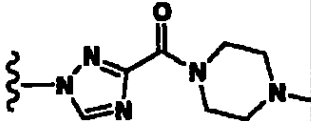
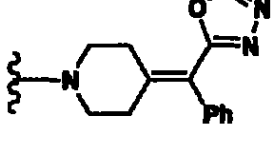
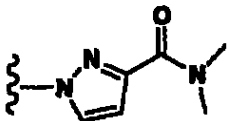
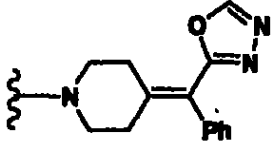
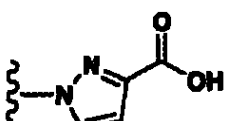
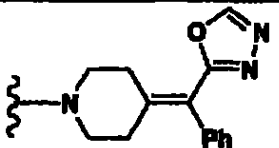
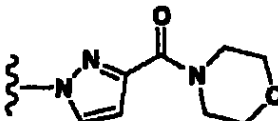
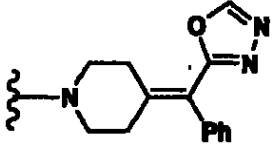
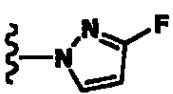
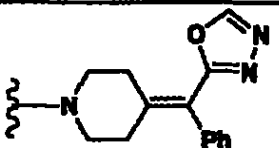
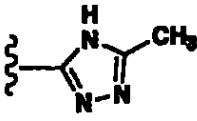
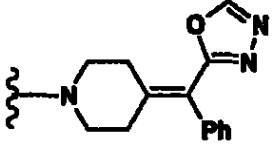
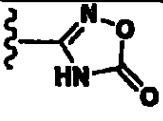
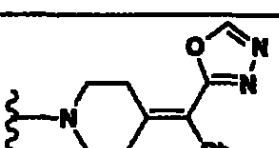
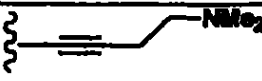
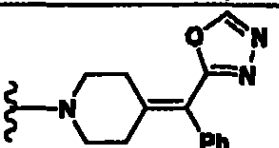
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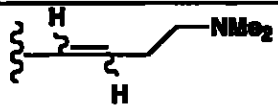
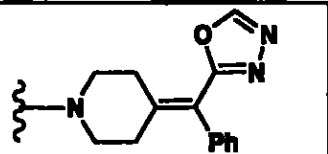
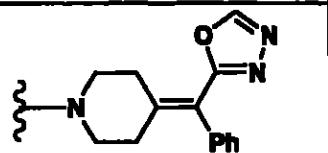
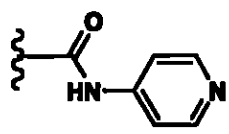
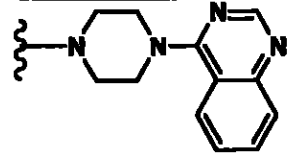
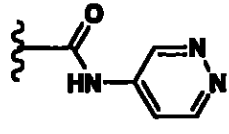
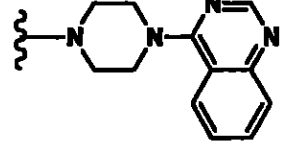
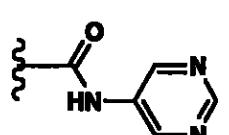
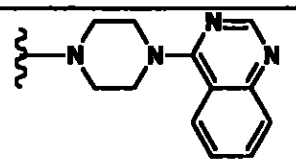
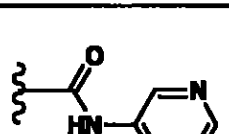
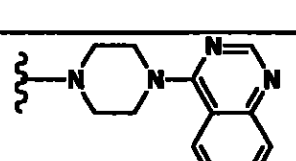
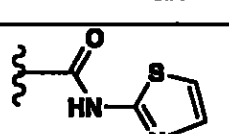
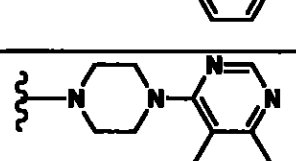
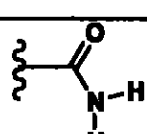
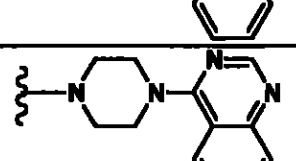
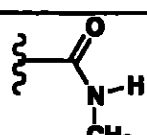
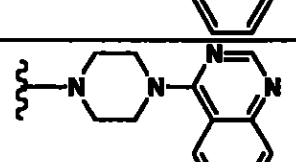
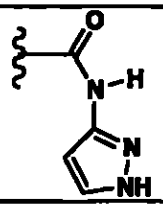
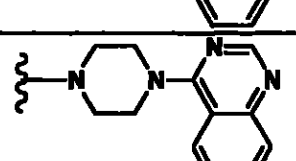
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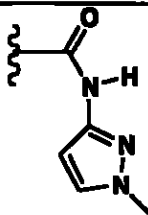
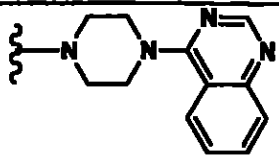
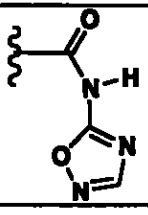
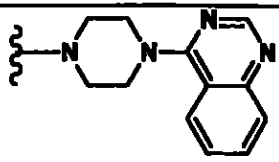
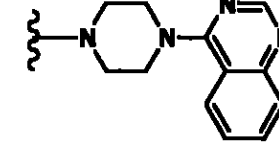
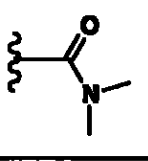
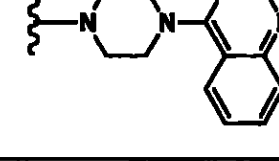
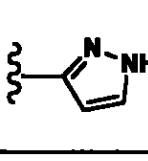
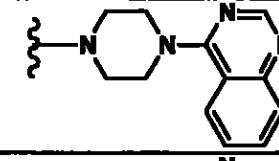
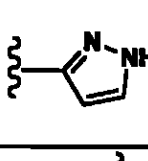
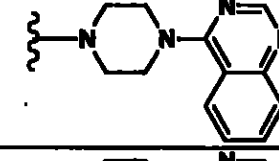
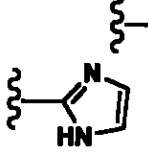
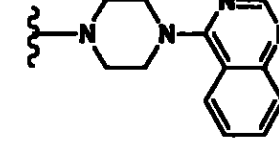
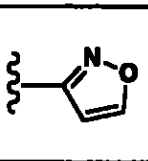
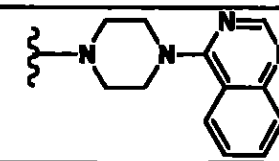
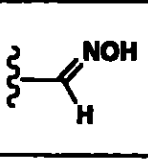
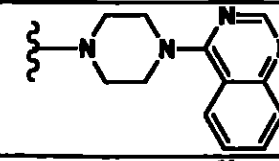
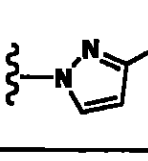
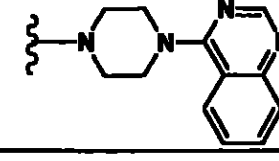
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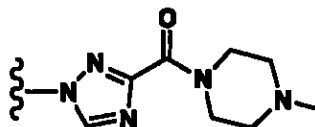
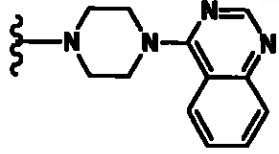
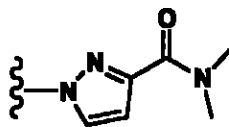
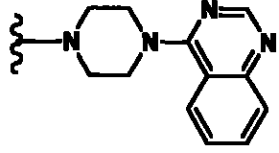
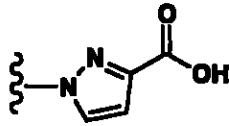
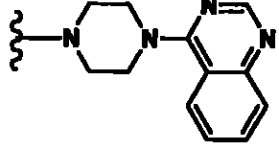
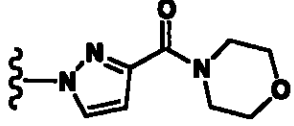
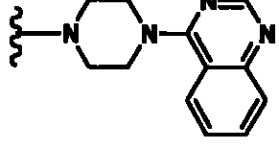
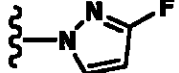
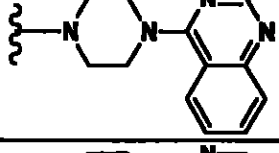
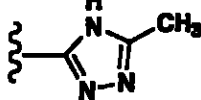
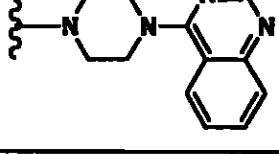
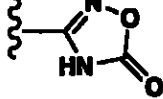
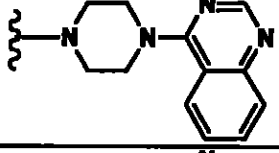
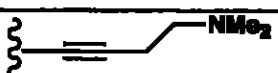
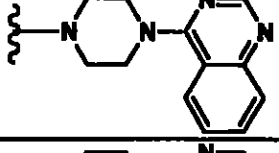
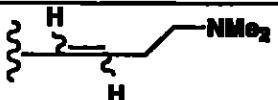
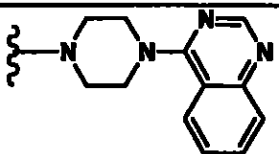
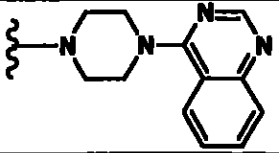
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The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations 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 sweeteners/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.



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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

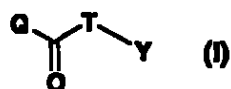
5 understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the

10 particular condition, and the host undergoing therapy.

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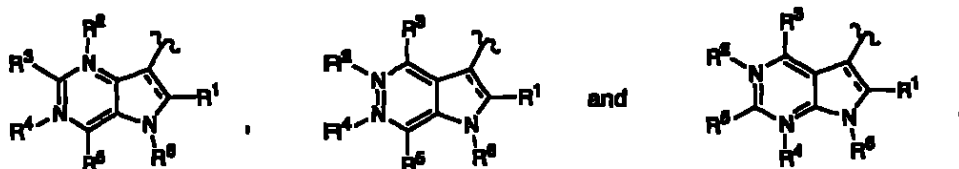
What is claimed is:

- 5 1. A compound of Formula I, including pharmaceutically acceptable salts thereof,



10 wherein:

Q is selected from the group consisting of



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T is  $-\text{C}(\text{O})-$  or  $-\text{CH}(\text{CN})-$ ;

$\text{R}^1$  is hydrogen or methyl;

- 20  $\text{R}^3$  and  $\text{R}^5$  are independently selected from the group consisting of hydrogen, halogen, cyano, nitro,  $\text{COOR}^8$ ,  $\text{XR}^9$  and B;

$\text{R}^2$  and  $\text{R}^4$  are independently O or do not exist with the proviso that only one of  $\text{R}^2$  and  $\text{R}^4$  are O;

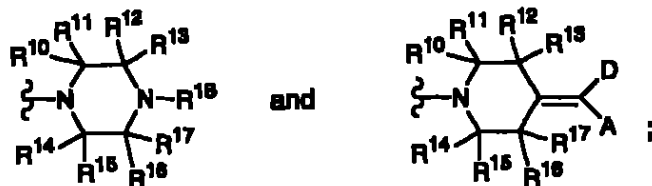
25

$\text{R}^6$  is  $(\text{CH}_2)_n\text{H}$ , wherein n is 0-1;

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

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-Y- is selected from the group consisting of



- 5  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or  $(C_{1-6})$ alkyl; wherein said  $(C_{1-6})$ alkyl may optionally be substituted with one to three same or different halogen, OH or CN;
- 10  $R^{18}$  is a member selected from the group consisting of C(O)-phenyl, C(O)-heteroaryl, pyridinyl, pyrimidinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalinyl, naphthyridinyl, phthalazinyl, azabenzofuryl and azaindolyl; wherein said member is optionally substituted with from one to two substituents selected from the group consisting of methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl and halogen;
- 15 D is selected from the group consisting of hydrogen, cyano,  $S(O)_2R^{24}$ , halogen,  $COOR^{20}$ ,  $C(O)NR^{21}R^{22}$ , phenyl and heteroaryl; wherein said phenyl or heteroaryl is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F (as defined below);
- 20 A is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;
- 25 B is selected from the group consisting of  $(C_{1-6})$ alkyl,  $C(O)NR^{21}R^{22}$ ,  $-C(O)CH_3$ ,  $-N(CH_2CH_2)_2NC(O)$ pyrazolyl, phenyl and heteroaryl; wherein said  $(C_{1-6})$ alkyl, phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

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heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl and triazolyl;

- 5 F is selected from the group consisting of (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkenyl, phenyl, pyridinyl, hydroxy, (C<sub>1-6</sub>)alkoxy, halogen, benzyl, -NR<sup>23</sup>C(O)-(C<sub>1-6</sub>)alkyl, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, and -CONR<sup>24</sup>R<sup>25</sup>; wherein said (C<sub>1-6</sub>)alkyl or phenyl are each optionally substituted with hydroxy, (C<sub>1-6</sub>)alkoxy, (C<sub>1-6</sub>)alkyl, CF<sub>3</sub>, dimethylamino or from one to three same or different halogen;

10

R<sup>8</sup>, R<sup>9</sup> and R<sup>26</sup> are each independently selected from the group consisting of hydrogen and (C<sub>1-6</sub>)alkyl;

X is selected from the group consisting of NR<sup>26</sup>, O and S;

15

R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup> and R<sup>25</sup> are independently selected from the group consisting of hydrogen, (C<sub>1-6</sub>)alkyl, phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different halogen or methyl; and

20

R<sup>27</sup> is piperazinyl, N-methyl piperazinyl, or 3-pyrazolyl.

2. A compound of claim 1 wherein T is  $\text{---}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{---}$ .

- 25 3. A compound of claim 2, wherein:

R<sup>1</sup> is hydrogen;

-- represents a carbon-carbon bond; and

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R<sup>2</sup> and R<sup>4</sup> do not exist.

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- D is selected from the group consisting of hydrogen, cyano,  $S(O)_2R^{24}$ , halogen,  $COOR^{20}$ ,  $C(O)NH_2$ , phenyl and heteroaryl; wherein said phenyl or heteroaryl is independently optionally substituted with one to three same or different halogens or a member selected from the group consisting of  $(C_{1-6})$ alkyl,  $(C_{1-6})$ alkenyl, hydroxy,  $(C_{1-6})$ alkoxy, halogen,  $-NR^{24}R^{25}$ ,  $-S(O)_2NR^{24}R^{25}$ ,  $COOR^{26}$  and  $-CONR^{24}R^{25}$ ; wherein said  $(C_{1-6})$ alkyl is optionally substituted with one to three same or different halogen or a hydroxy; and

- A is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole are independently optionally substituted with one to three same or different halogens or a member selected from the group consisting of  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkenyl,  $(C_{1-3})$ alkoxy, halogen and  $-NH_2$ ; wherein said  $(C_{1-4})$ alkyl is optionally substituted with one to three same or different halogens.

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4. A compound of claim 3 wherein:

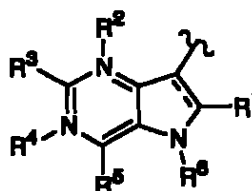
$R^6$  is hydrogen; and

- 20  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or methyl, with the proviso that a maximum of two of  $R^{10}$ - $R^{17}$  is a methyl.

5. A compound of claim 4 wherein:

- 25 Q is a member selected from groups (A), (B), and (C) consisting of

(A)

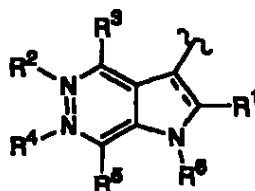


- 30 wherein  $R^3$  is hydrogen,  $C_1$ - $C_3$  alkoxy,  $-NR^{26}R^9$  or halogen;

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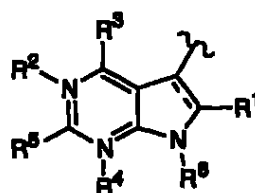
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(B)

wherein R<sup>3</sup> is hydrogen, methoxy or halogen; and

5

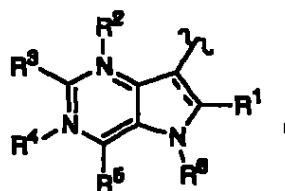
(C)

wherein R<sup>3</sup> is hydrogen, methoxy or halogen.

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6. A compound of claim 5 wherein:

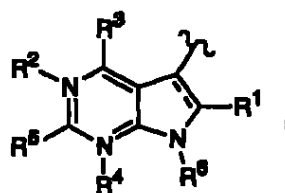
group(A) of Q is:



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wherein R<sup>3</sup> is hydrogen; and

group (C) of Q is:



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*DE* 170

wherein

$R^5$  is hydrogen.

5 7. A compound of claim 5 wherein:

Q is selected from group (A) or (B); and

10  $R^5$  is selected from the group consisting of hydrogen, halogen, heteroaryl, phenyl, cyano, methoxy,  $COOR^8$ ,  $C(O)NH_2$ ,  $C(O)NH$ heteroaryl, and  $C(O)NHCH_3$ ; wherein said  $C(O)NH$ heteroaryl, phenyl, and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F.

15 8. A compound of claim 7 wherein:

$R^5$  is selected from the group consisting of  $C(O)NH_2$ ,  $C(O)NHCH_3$  and  $C(O)NH$ heteroaryl; wherein said  $C(O)NH$ heteroaryl is optionally substituted with one to three same or different halogens or from one to three same or different  
20 substituents selected from F.

9. A compound of claim 7 wherein:

25  $R^5$  is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F.

10. A compound of claim 9 wherein:

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heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazoyl, pyrazolyl, tetrazolyl and triazolyl; wherein said heteroaryl is

independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F.

11. A compound of claim 5, wherein:

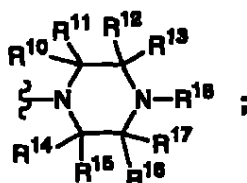
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$R^{18}$  is  $-C(O)$ phenyl or  $-C(O)$  heteroaryl; wherein said heteroaryl is pyridinyl, furanyl or thienyl; wherein heteroaryl is independently optionally substituted with a member selected from the group consisting of halogen, methyl, -amino, -NHMe, NMe<sub>2</sub> and hydroxymethyl.

10

12. A compound of claim 5 wherein:

-W- is



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$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or methyl, with the proviso that not more than one is methyl; and

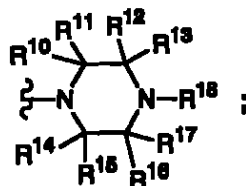
20  $R^{18}$  is selected from the group consisting of  $C(O)$ -phenyl and  $C(O)$ -heteroaryl; wherein each of  $C(O)$ -phenyl or  $-C(O)$ -heteroaryl may be optionally substituted with from one to two methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl or halogen.

25 13. A compound of claim 5 wherein:

-W- is



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$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or methyl, with the proviso that not more than one is methyl; and

5

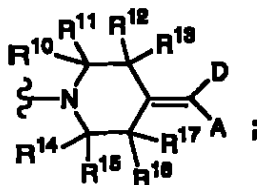
$R^{18}$  is selected from the group consisting of pyridinyl, pyrimidinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalinyl, naphthyridinyl, phthalazinyl, azabenzofuryl and azaindolyl, each of which may be optionally substituted with from one to two substituents selected from the group consisting of methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl and halogen.

10

14. A compound of claim 5 wherein:

-W- is

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$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or methyl, with the proviso that one is methyl;

20

D is selected from the group consisting of hydrogen, cyano,  $S(O)_2R^{24}$ , halogen,  $COOR^{20}$ ,  $C(O)NH_2$ , phenyl and heteroaryl; wherein said phenyl or heteroaryl is independently 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  $(C_{1-6})$ alkyl,  $(C_{1-6})$ alkenyl, hydroxy,  $(C_{1-6})$ alkoxy, halogen,  $-NR^{24}R^{25}$ ,  $-S(O)_2NR^{24}R^{25}$ ,  $COOR^{26}$  and  $-CONR^{24}R^{25}$ ; wherein said  $(C_{1-6})$ alkyl is optionally substituted with one to three same or different halogen or a hydroxy; and

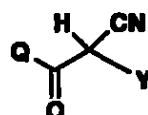
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A is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkenyl, (C<sub>1-3</sub>)alkoxy, halogen and -NH<sub>2</sub>; wherein said (C<sub>1-4</sub>)alkyl is optionally substituted with one to three same or different halogens.

15. A compound of claim 7 wherein:

10 Q is selected from Group (A).

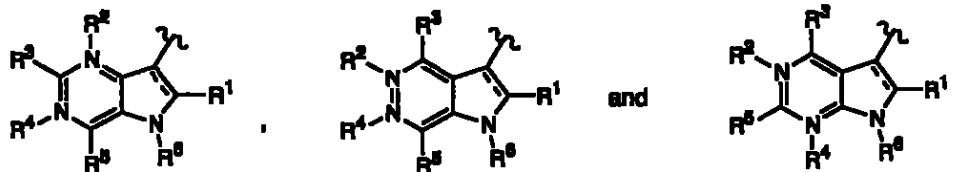
16. A compound of claim 1 including pharmaceutically acceptable salts thereof,



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wherein:

Q is selected from the group consisting of



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R<sup>1</sup> is hydrogen or methyl;

R<sup>3</sup> and R<sup>5</sup> are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, COOR<sup>8</sup>, XR<sup>9</sup> and B;

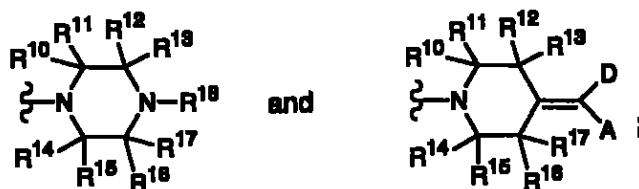
25

R<sup>2</sup> and R<sup>4</sup> are independently O or do not exist, with the proviso that only one of R<sup>2</sup> and R<sup>4</sup> are O;

R<sup>6</sup> is (CH<sub>2</sub>)<sub>n</sub>H, wherein n is 0-1;

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

-Y- is selected from the group consisting of



$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each independently H or  $(C_{1-6})$ alkyl; wherein said  $(C_{1-6})$ alkyl may optionally be substituted with one to three same or different halogen, OH or CN;

$R^{18}$  is a member selected from the group consisting of C(O)-phenyl, C(O)-heteroaryl, pyridinyl, pyrimidinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalinyl, naphthyridinyl, pthalazinyl, azabenzofuryl and azaindolyl; wherein said member is optionally substituted with from one to two substituents selected from the group consisting of methyl, -amino, -NHMe, -NMe<sub>2</sub>, methoxy, hydroxymethyl and halogen;

D is selected from the group consisting of hydrogen, cyano,  $S(O)_2R^{24}$ , halogen,  $COOR^{20}$ ,  $C(O)NR^{21}R^{22}$ , phenyl and heteroaryl; wherein said phenyl or heteroaryl is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

A is selected from the group consisting of phenyl, pyridinyl, furanyl, thienyl, isoxazole and oxazole; wherein said phenyl, pyridinyl, furanyl, thienyl, isoxazole or oxazole is independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

B is selected from the group consisting of  $(C_{1-6})$ alkyl,  $C(O)NR^{21}R^{22}$ , phenyl and heteroaryl; wherein said  $(C_{1-6})$ alkyl, phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl and triazolyl;

- 5 F is selected from the group consisting of (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkenyl, phenyl, pyridinyl, hydroxy, (C<sub>1-6</sub>)alkoxy, halogen, benzyl, -NR<sup>23</sup>C(O)-(C<sub>1-6</sub>)alkyl, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, and -CONR<sup>24</sup>R<sup>25</sup>; wherein said (C<sub>1-6</sub>)alkyl or phenyl are each optionally substituted with hydroxy, (C<sub>1-6</sub>)alkoxy, dimethylamino or from one to three same or different halogen;

10

R<sup>8</sup>, R<sup>9</sup> and R<sup>26</sup> are each independently selected from the group consisting of hydrogen and (C<sub>1-6</sub>)alkyl;

X is selected from the group consisting of NR<sup>26</sup>, O and S;

15

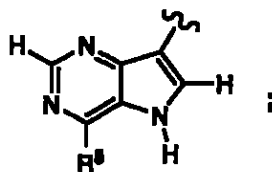
R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup> and R<sup>25</sup> are independently selected from the group consisting of hydrogen, (C<sub>1-6</sub>)alkyl, phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different halogen or methyl; and

20

R<sup>27</sup> is piperazinyl, N-methylpiperazinyl or 3-pyrazolyl.

17. A compound of claim 6 wherein:

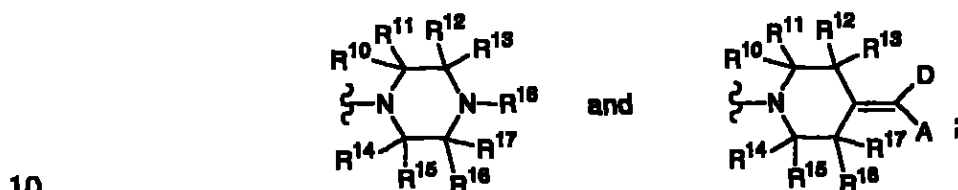
25 Q is



$R^5$  is selected from the group consisting of hydrogen, halogen, cyano,  ~~$XR^9$~~ , heteroaryl,  $-N(CH_2CH_2)_2NC(O)pyrazolyl$ , and  $-C(O)CH_3$ , wherein said heteroaryl is optionally substituted with one substituent selected from F;

- 5 heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, isoxazolyl, pyrazolyl, and triazolyl;

-Y- is selected from the group consisting of



$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are each hydrogen;

A is phenyl or pyridinyl;

15

$R^{18}$  is  $C(O)$ -phenyl, isoquinolyl or quinazolyl;

D is cyano or oxadiazolyl;

- 20 F is selected from the group consisting of  $(C_{1-6})alkyl$ , phenyl, pyridinyl,  $(C_{1-2})alkoxy$ ,  $-COOR^{26}$ ,  $-COR^{27}$  and  $-CONR^{24}R^{25}$ ; wherein said phenyl is optionally substituted with one group selected from methyl, methoxy, fluoro, or trifluoromethyl;

X is selected from the group consisting of O;

25

$R^9$  is  $(C_{1-2})alkyl$ ;

$R^{26}$  is hydrogen, methyl, or ethyl;

$R^{24}$  and  $R^{25}$  are independently selected from the group consisting of hydrogen and methyl; and

$R^{27}$  is piperazinyl, N-methyl piperazinyl, or 3-pyrazolyl.

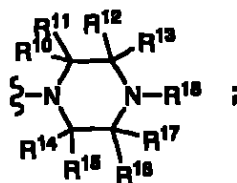
5

18. A compound of claim 17 wherein:

$R^5$  is heteroaryl optionally substituted with one halogen or one substituent selected from F;

10

-Y- is



$R^{18}$  is C(O)-phenyl, isoquinolyl or quinazolyl; and

15

F is (C<sub>1-6</sub>)alkyl.

19. A compound of claim 18 wherein  $R^{18}$  is C(O)-phenyl.

20. A compound of claim 18 wherein  $R^{18}$  is isoquinolyl or quinazolyl.

21. A compound of claim 17 wherein:

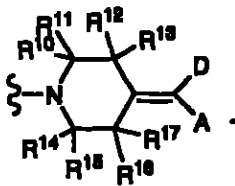
$R^5$  is heteroaryl optionally substituted with one substituent selected from F;

25

heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, isoxazolyl, pyrazolyl and triazolyl; and

-Y- is

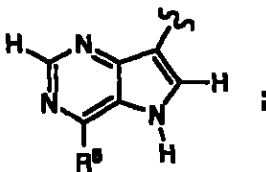
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~~178~~ 178

22. A compound of claim 17 wherein:

5 Q is



10 R<sup>5</sup> is heteroaryl optionally substituted with one substituent selected from F; and  
heteroaryl is selected from the group consisting of pyrazolyl and triazolyl.

23. A compound of claim 22 wherein:

15 F is selected from the group consisting of methyl and -CONR<sup>24</sup>R<sup>25</sup>; and

R<sup>24</sup> and R<sup>25</sup> are independently selected from the group consisting of hydrogen and methyl.

20 24. A compound of claim 23 wherein:

F is methyl.

25 25. A pharmaceutical composition which comprises an antiviral effective amount  
of a compound of Formula I, including pharmaceutically acceptable salts thereof, as  
claimed in claim 1, and one or more pharmaceutically acceptable carriers, excipients  
or diluents.

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26. The pharmaceutical composition of claim 25 which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

- 5                   (a) an AIDS antiviral agent;  
                  (b) an anti-infective agent;  
                  (c) an immunomodulator; and  
                  (d) HIV entry inhibitors.

10 27. A method for treating a mammal infected with the HIV 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, and one or more pharmaceutically acceptable carriers, excipients or diluents.

15 28. The method of claim 27 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, 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 an HIV  
20 entry inhibitor.



## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/5025 A61K31/519 A61P31/12 A61P31/18

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)

IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                     | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | US 2003/069266 A1 (WANG TAO ET AL)<br>10 April 2003 (2003-04-10)<br>cited in the application<br>examples                                                                                                                                                                                                                                               | 1-28                  |
| A          | FONT M ET AL: "Indoles and<br>pyridazino(4,5-b)indoles as nonnucleoside<br>analog inhibitors of HIV-1 reverse<br>transcriptase"<br>EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY,<br>EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR,<br>vol. 30, no. 12, 1995, pages 963-971,<br>XP002210360<br>ISSN: 0223-5234<br>cited in the application<br>the whole document | 1-28                  |

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

14/04/2005

Name and mailing address of the ISA

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Authorized officer

Fazzi, R

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/037213

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

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

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 27-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s) |               | Publication<br>date   |
|-------------------------------------------|----|---------------------|----------------------------|---------------|-----------------------|
| US 2003069266                             | A1 | 10-04-2003          | US                         | 2003207910 A1 | <del>06-11-2003</del> |
|                                           |    |                     | US                         | 2004110785 A1 | <del>10-06-2004</del> |
|                                           |    |                     | BG                         | 108021 A      | <del>30-04-2004</del> |
|                                           |    |                     | BR                         | 0206636 A     | <del>25-02-2004</del> |
|                                           |    |                     | CA                         | 2437524 A1    | <del>15-08-2002</del> |
|                                           |    |                     | CZ                         | 20032316 A3   | <del>14-01-2004</del> |
|                                           |    |                     | EE                         | 200300359 A   | <del>15-12-2003</del> |
|                                           |    |                     | EP                         | 1363705 A1    | <del>26-11-2003</del> |
|                                           |    |                     | HU                         | 0304062 A2    | <del>28-04-2004</del> |
|                                           |    |                     | JP                         | 2004522755 T  | <del>29-07-2004</del> |
|                                           |    |                     | MX                         | PA03006939 A  | <del>18-11-2003</del> |
|                                           |    |                     | NO                         | 20033436 A    | <del>01-10-2003</del> |
|                                           |    |                     | NZ                         | 527193 A      | <del>28-05-2004</del> |
|                                           |    |                     | SK                         | 9592003 A3    | <del>03-08-2004</del> |
|                                           |    |                     | WO                         | 02062423 A1   | <del>15-08-2002</del> |

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WO/2005/054247 A1

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A61K 31/5025, A61K 31/519, A61P 31/12, A61P 31/18

(21) Número de solicitud internacional: PCT/US2004/037213

(22) Fecha de presentación internacional:  
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(25) Idioma de Presentación: Inglés

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(71) Solicitante (para todos los estados designados excepto US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US)

(72) Inventores; y:

(75) Inventores/Solicitantes (para US solamente): BENDER, John, A. [US/US]; 21 Brookview Lane, Middletown, Connecticut 06457 (US) YANG, Zhong [CN/US]; 11-2 West Meadow Lane, Middletown, Connecticut 06457 (US) KADOW, John, F. [US/US]; 9 Quarry Run, Wallingford, Connecticut 06492 (US). MEANWELL, Nicholas, A. [GB/US]; 15 Valli Drive, East Hampton, Connecticut 06424 (US)

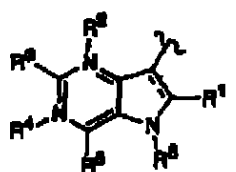
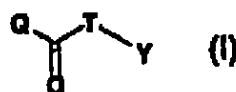
(74) Agentes: DUBOFF, Samuel et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

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

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

[Continúa en la siguiente página]

(54) Título: AGENTES ANTIVIRALES DE DIAZAINDOL-DICARBONIL-PIPERAZINILO



1205

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**Declaraciones bajo la Regla 4.17:**

- en cuanto al derecho del solicitante para aplicar y otorgar una patente (Regla 4.17(II)) para las siguientes designaciones AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), patente Eursidtica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- en cuanto al derecho del solicitante para aplicar y otorgar una patente (Regla 4.17(III)) para las siguientes designaciones AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR,

HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), patente Eursidtica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

**Publicada**

- Con reporte de búsqueda internacional.
- antes de la expiración del límite de tiempo para enmendar las reivindicaciones y volver a publicar en el evento de recepción las enmiendas

Para códigos de dos letras y otras abreviaciones, consulte "Notas Guía sobre Códigos y Abreviaciones" que aparecen al principio de cada emisión regular de la Gaceta del PCT.

**AGENTES ANTIVIRALES DE DIAZAINDOL-DICARBONIL-PIPERAZINILO****Campo de la Invención**

Esta invención proporciona compuestos que tienen  
5 propiedades de fármacos y bioafectoras, 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  
10 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  
15 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 el 2002, alrededor de 5.0 millones de nuevos  
infectados se reportaron, y 3.1 millones de personas murieron  
20 de SIDA. Los fármacos actualmente disponibles para el  
tratamiento de VIH incluyen diez inhibidores de transcriptasa  
inversa de nucleósido (RT) o combinaciones de píldora  
sencilla aprobadas (zidovudina o AZT (o Retrovir®), didanosina  
(o Videx®), estavudina (o Zerit®), lamivudina (o 3TC o  
25 Epivir®), zalcitabina (o DDC o Hivid®), succinato de abacavir

(o Ziagen®), sal de disoproxilfumarato de Tenofovir (o Viread®), Combivir® (contiene -3TC más AZT), Trizivir® (contiene abacavir, lamivudina, y zidovudina) y Emtriva® (emtricitabina); tres inhibidores de transcriptasa inversa no  
5 nucleósidos: nevirapina (o Viramune®), delavirdina (o Rescriptor®) y efavirenz (o Sustiva®), nueve inhibidores de  
proteasa péptidomiméticos o formulaciones aprobadas:  
saquinavir, indinavir, ritonavir, nelfinavir, amprenavir,  
lopinavir, Kaletra® (lopinavir y Ritonavir), Atazanavir  
10 (Reyataz®), Fosamprenavir® y un inhibidor de fusión el cual  
ataca al gp41 T-20 viral (FUZEON®). Cada uno de estos  
fármacos únicamente pueden detener transitoriamente la  
replica viral si se usan solos. Sin embargo, cuando se usan  
en combinación, estos fármacos tienen un efecto profundo en  
15 viremia y progreso de la enfermedad. De hecho, reducciones  
importantes en las tasas de mortalidad entre los pacientes  
con SIDA se han documentado recientemente como una  
consecuencia de una aplicación extendida de terapia de  
combinación. Sin embargo, a pesar de estos resultados  
20 impresionantes, del 30 hasta el 50% de los pacientes fallan  
de último momento a las terapias de fármaco de combinación.  
Potencia del fármaco insuficiente, no cumplimiento o apego,  
penetración de tejidos restringida y limitaciones específicas  
del fármaco dentro de ciertos tipos de células (por ejemplo,  
25 la mayoría de los análogos de nucleósido no se pueden

fosforilar en células en reposo), pueden contar para la supresión incompleta de virus sensibles. Adicionalmente, la alta tasa de replica y la rápida conversión de VIH-1 en combinación con la incorporación frecuente de mutaciones, conduce 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 transcriptasa inversa de nucleósido o por inhibidores peptidomiméticos de la proteasa. Los inhibidores de transcriptasa inversa no nucleósidos (NNRTI) actualmente han ganado un papel incrementadamente importante en la terapia de infecciones por VIH (Pedersen & Pedersen, Ref. 15). Al menos 30 diferentes clases de NNRTI se han descrito en la literatura (De Clercq, Ref. 16) y varios NNRTI se han evaluado en ensayos clínicos. 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  
5 a monoterapia. Como consecuencia, hay considerable interés  
en la identificación de NNRTI menos propensos al desarrollo  
de resistencia (Pedersen & Pedersen, Ref. 15). Ha aparecido  
una revisión reciente de inhibidores de transcriptasa inversa  
no nucleósidos: perspectivas sobre compuestos y estrategias  
10 terapéuticas novedosas para el tratamiento de la infección  
por VIH (Buckheit, referencia 99). Ha aparecido un repaso  
que cubre tanto a NRTI como NNRTIs (De Clercq, referencia  
100). Se ha publicado una revisión del estado actual de los  
fármacos para VIH (De Clercq, referencia 101).

15               Varios derivados de indol, que incluyen indol-3-  
sulfonas, indoles de piperazino, indoles de pirazino, y  
derivados de 5H-indolo[3,2-b][1,5]benzotiazepina se han  
reportado como inhibidores de transcriptasa inversa de VIH-1  
(Greenlee et al, Ref. 1; Williams et al, Ref. 2; Romero et  
20 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). Indol-2-carboxamidas también se han descrito como  
inhibidores de adhesión celular e infección por VIH  
(Boschelli et al, documento US 5,424,329, Ref. 4). Productos  
25 naturales de indol 3-sustituidos (semicocliodinol A y B;

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didemetilasterriquinona e isococliodinol) se han descrito como inhibidores de proteasa de VIH-1 (Fredenhagen et al, Ref. 22).

Derivados de amida de azaindol estructuralmente relacionados se han descrito previamente (Kato et al, Ref. 23(a); Levacher et al, Ref. 23(b); Dompe Spa, documento WO-09504742, Ref. 5(a); SmithKline Beecham PLC, documento WO-09611929, Ref. 5(b); Schering Corp., documento US-05023265, Ref. 5(c)). Sin embargo, estas estructuras difieren de aquellas reivindicadas en la presente, en que estas son mono-amida de monoaza-indol en vez de derivados de oxoacetamida, y no se hace mención del uso de estos compuestos para tratar infecciones virales, particularmente VIH.

Se necesitan nuevos fármacos para tratamiento del VIH, para tratamiento de pacientes que se vuelven resistentes a los fármacos actualmente aprobados antes descritos, que atacan la transcriptasa inversa o proteasa. Una aproximación para la obtención de estos fármacos es encontrar moléculas que inhiban nuevos y diferentes ataques de virus. Una clase general de inhibidores que están bajo estudio activo son los inhibidores de entrada de VIH. Esta clasificación general incluye fármacos dirigidos a diversos objetivos que incluyen inhibidores del receptor de quimiocina (CCR5 o CXCR4), inhibidores de fusión que atacan el gp41 viral, e inhibidores que evitan la unión del envoltente viral, gp120, su objetivo

celular humano CD4. Diversas revisiones o documentos generales sobre los inhibidores de entrada viral han aparecido recientemente y algunas referencias seleccionadas son:

5                    *Chemokine receptor antagonists as HIV entry inhibitors.* Expert Opinion on Therapeutic Patents (2004),  
: 14(2), 251-255.

*Inhibitors of the entry of HIV into host cells.*  
Meanwell, Nicholas A.; Kadow, John F. Current Opinion in  
10 Drug Discovery & Development (2003), 6(4), 451-461.

*Virus entry as a target for anti-HIV intervention.*  
Este, Jose A. Retrovirology Laboratory IrsiCaixa, Hospital  
Universitari Germans Trias i Pujol, Universitat Autònoma de  
Barcelona, Badalona, Spain. Current Medicinal Chemistry  
15 (2003), 10(17), 1617-1632.

*New antiretroviral agents.* Rachline, A.; Joly, V.  
Service de Maladies Infectieuses et Tropicales A, Hôpital  
Bichat-Claude Bernard, Paris, Fr. Antibiotiques (2003), 5(2),  
77-82.

20                    *New antiretroviral drugs.* Gulick, R. M. Cornell  
HIV Clinical Trials Unit, Division of International Medicine  
and Infectious Diseases, Weill Medical College of Cornell  
University, New York, NY, USA. Clinical Microbiology and  
Infection (2003), 9(3), 186-193.

25                    *Sensitivity of HIV-1 to entry inhibitors correlates*

- with envelope/coreceptor affinity, receptor density, and fusion kinetics. Reeves, Jacqueline D.; Gallo, Stephen A.; Ahmad, Navid; Miamidian, John L; Harvey, Phoebe E.; Sharron, Matthew; Pohlmann, Stefan; Sfakianos, Jeffrey N.; Derdeyn, Cynthia A.; Blumenthal, Robert; Hunter, Eric; Doms, Robert W. Department of Microbiology, University of Pennsylvania, Philadelphia, P A, USA. Proceedings of the National Academy of Sciences of the United States of America (2002), 99(25), 16249-16254. CODEN: PNASA6 ISSN: 0027-8424.
- 10                   *Opportunities and challenges in targeting HIV entry.* Biscone, Mark J.; Pierson, Theodore C.; Doms, Robert W. Department of Microbiology, University of Pennsylvania, Philadelphia, PA, USA. Current Opinion in Pharmacology (2002), 2(5), 529-533.
- 15                   *HIV entry inhibitors in clinical development.* O'Hara, Bryan M.; Olson, William C. Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA. Current Opinion in Pharmacology (2002), 2(5), 523-528.
- Resistance mutation in HIV entry inhibitors.*
- 20                   Hanna, Sheri L; Yang, Chunfu; Owen, Sherry M.; Lal, Renu B. HIV Immunology and Diagnostics Branch, Division of AIDS, STD, Atlanta, GA, USA. AIDS (London, United Kingdom) (2002), 16(12), 1603-1608.
- HIV entry: are all receptors created equal?*
- 25                   Goldsmith, Mark A.; Doms, Robert W. Genencor International,

192

Inc., Palo Alto, CA, USA. Nature Immunology (2002), 3(8),  
709-710. CODEN: NIAMCZ ISSN: 1529-2908.

*Peptide and non-peptide HIV fusion inhibitors.*

Jiang, Shibo; Zhao, Qian; Debnath, Asim K. The New York  
5 Blood Center, Lindsley F. Kimball Research Institute, New  
York, NY, USA. Current Pharmaceutical Design (2002), 8(8),  
: 563-580.

Una serie de publicaciones y divulgaciones  
recientes caracterizan y describen un compuesto etiquetado  
10 como BMS-806, un miembro inicial de una clase de inhibidores  
de entrada virales que atacan el gp-120 viral y evitan la  
unión del virus al CD<sup>4</sup> anfitrión.

*A small molecule HIV-1 inhibitor that targets the  
HIV-1 envelope and inhibits CD4 receptor binding.* Lin, Pin-  
15 Fang; Blair, Wade; Wang, Tao; Spicer, Timothy; Guo, Qi; Zhou,  
Nannan; Gong, Yi-Fei; Wang, H. -G. Heidi; Rose, Ronald;  
Yamanaka, Gregory; Robinson, Brett; Li, Chang-Ben; Fridell,  
Robert; Deminie, Carol; Demers, Gwendeline; Yang, Zheng;  
Zadjura, Lisa; Meanwell, Nicholas; Colonno, Richard.  
20 Proceedings of the National Academy of Sciences of the United  
States of America (2003), 100(19), 11013-11018.

*Biochemical and genetic characterizations of a  
novel human immunodeficiency virus type 1 inhibitor that  
blocks gp120-CD4 interactions.* Guo, Qi; Ho, Hsu-Tso; Dicker,  
25 Ira; Fan, Li; Zhou, Nannan; Friborg, Jacques; Wang, Tao;

McAuliffe, Brian V.; Wang, Hwei-gene Heidi; Rose, Ronald E.; Fang, Hua; Scarnati, Helen T.; Langley, David R.; Meanwell, Nicholas A.; Abraham, Ralph; Colonno, Richard J.; Lin, Pin-fang. *Journal of Virology* (2003), 77(19), 10528-10536.

5                    *Method using small heterocyclic compounds for treating HIV infection by preventing interaction of CD4 and gp120.* Ho, Hsu-Tso; Dalterio, Richard A.; Guo, Qi; Lin, Pin-Fang. *Sol. Int. PCT* (2003), WO 2003072028A2.

10                    *Discovery of 4-benzoyl-1-[(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)oxoacetyl]-2-(R)-methylpiperazine (BMS-378806): A Novel HIV-1 Attachment Inhibitor That Interferes with CD4-gp120 Interactions.* Wang, Tao; Zhang, Zhongxing; Wallace, Owen B.; Deshpande, Milind; Fang, Haiquan; Yang, Zheng; Zadjura, Lisa M.; Tweedie, Donald L;  
15                    Huang, Stella; Zhao, Fang; Ranadive, Sunanda; Robinson, Brett S.; Gong, Yi-Fei; Ricarrdi, Keith; Spicer, Timothy P.; Deminie, Carol; Rose, Ronald; Wang, Hwei-Gene Heidi; Blair, Wade S.; Shi, Pei-Yong; Lin, Pin-fang; Colonno, Richard J.; Meanwell, Nicholas A. *Journal of Medicinal Chemistry* (2003),  
20                    46(20), 4236-4239.

                    Indol, azaindol y otros derivados que contienen oxo amidas se han descrito en diversas solicitudes de patente diferentes PCT y Norteamericanas emitidas (Referencia 93-95, 106, 108, 109, 110, 111, 112, 113, y 114). Ninguna de estas  
25                    solicitudes describe compuestos de diazindol tal como se

describen en esta invención. El nitrógeno adicional de la  
clase de diazaíndol de moléculas proporciona propiedades  
alteradas, especialmente en combinación con sustituyentes  
específicos que son ventajosos y no están disponibles de  
5 azaiñdoles. Los diazaíñdoles son más fáciles de acceder y  
ofrecen así el potencial de proporcionar pacientes con  
tratamientos de menor costo. Una serie de Solicitudes  
Internacionales de Patente PCT de Bernd Nickel et al.  
(referencia 107a, b, y c) describe N-indolilglíoxamidas para  
10 el tratamiento de cáncer. Aunque algunos de estos compuestos  
contienen N-heteroarilo o N-arilo piperazinas, patrones de  
sustitución en otras posiciones están fuera del alcance de  
esta invención.

Diazaíñdoles estructuralmente similares con un  
15 grupo C-3 oxoacetilo también se han descrito previamente  
(Hutchison et al, Ref. 5(d); Resnyanskaya et al, Ref. 24 (a);  
Cook et al, Ref. 24(b)). Sin embargo, estas moléculas  
difieren de aquellas reivindicadas, en que no contienen  
porciones de piperazina o piperidina y no hay mención en el  
20 uso de estas moléculas como agentes antivirales,  
particularmente contra el VIH.

Nada en estas referencias se puede constituir para  
que describa o sugiera compuestos de novedad de esta  
25 invención y su uso para inhibir la infección por VIH.

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## REFERENCIAS CITADAS

Documentos de Patentes

1. Greenlee, W.J.; Srinivasan, P.C. Indole reverse transcriptase inhibitors. Patente Norteamericana 5,124,327.
- 5 2. Williams, T.M.; Ciccarone, T.M.; Saari, W. S.; Wai, J.S.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Theohrides, A.D. Indoles as inhibitors of HIV reverse transcriptase. Patente Europea 530907.
- 10 3. Romero, D.L.; Thomas, R.C.; Preparation of substituted indoles as anti-AIDS pharmaceuticals. PCT WO 93/01181.
4. Boschelli, D.H.; Connor, D.T.; Unangst, P.C. Indole-2-carboxamides as inhibitors de cell adhesion. Patente Norteamericana 5,424,329.
- 15 5. (a) Mantovanini, M.; Melillo, G.; Daffonchio, L. Tropyl 7-azaindol-3-ylcarboxyamides as antitussive agents. PCT WO 95/04742 (Dompe Spa). (b) Cassidy, F.; Hughes, I.; Rahman, S.; Hunter, D. J. Bisheteroaryl-carbonyl and carboxamide derivatives with 5HT 2C/2B antagonists activity. PCT WO 96/11929. (c) Scherlock, 20 M. H.; Tom, W. C. Substituted 1H-pyrrolopyridine-3-carboxamides. Patente Norteamericana 5,023,265. (d) Hutchison, D. R; Martinelli, M. J.; Wilson, T. M. Preparation or pyrrolo[2,3-d]pyrimidines as sPLA2 inhibitors 25 PCT WO 00/00201.



Otras Publicaciones

6. Larder, B.A.; Kemp, S.D. Multiple mutations in the HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science*, 1989, 246, 1155-1158.
- 5           7. Gulick, R.M. Current antiretroviral therapy: An overview. *Quality of Life Research*, 1997, 6, 471-474.
8. Kuritzkes, D.R. HIV resistance to current therapies. *Antiviral Therapy*, 1997, 2(Suplemento 3), 61-67.
9. Morris-Jones, S.; Moyle, G.; Easterbrook, P.J.
- 10 Antiretroviral therapies in HIV-1 infection. *Expert Opinion on Investigational Drugs*, 1997, 6(8), 1049-1061.
10. Schinazi, R.F.; Larder, B.A.; Mellors, J.W. Mutations in retroviral genes associated with drug resistance. *International Antiviral News*, 1997, 5,
- 15 129-142.
11. Vacca, J.P.; Condra, J.H. Clinically effective HIV-1 protease inhibitors. *Drug Discovery Today*, 1997, 2, 261-272.
12. Flexner, D. HIV-protease inhibitors. *Drug*
- 20 *Therapy*, 1998, 338, 1281-1292.
13. Berkhout, B. HIV-1 evolution under pressure of protease inhibitors: Climbing the stairs of viral fitness. *J. Biomed. Sci.*, 1999, 6, 298-305.
14. Ren, S.; Lien, E. J. Development of HIV
- 25 protease inhibitors: A survey. *Prog. Drug Res.*, 1998, 51;

~~205~~ 197

1-31.

15. Pedersen, O.S.; Pedersen, E.B. Non-nucleoside reverse transcriptase inhibitors: the NNRTI boom. *Antiviral Chem. Chemother.* **1999**, *10*, 285-314.

5                   16.           (a) De Clercq, E.       The role of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 infection. *Antiviral Research*, **1998**, *38*, 153-179.       (b) De Clercq, E.       Perspectives of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the  
10 therapy of HIV infection. *IL. Farmaco*, **1999**, *54*, 26-45.

17. Font, M.; Monge, A.; Cuartero, A.; Elorriaga, A.; Martinez-Irujo, J.J.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J.J.; Sarobe, P. and Borrás, F. Indoles and pyrazino[4,5-b]indoles as nonnucleoside analog inhibitors of  
15 HIV-1 reverse transcriptase. *Eur. J. Med. Chem.*, **1995**, *30*, 963-971.

18. Romero, D.L.; Morge, R.A.; Genin, M.J.; Biles, C.; Busso, M.; Resnick, L.; Althaus, I.W.; Reusser, F.; Thomas, R.C. and Tarpley, W.G. Bis(heteroaryl)piperazine  
20 (BHAP) reverse transcriptase inhibitors: structure-activity relationships of novel substituted indole analogues and the identification of 1-[(5-methanesulfonamido-1H-indol-2-yl)-carbonyl]-4-[3-[1-methylethyl)amino]-pyridinyl]piperazine  
momomethansulfonate (U-90152S), a second generation clinical  
25 candidate. *J. Med. Chem.*, **1993**, *36*, 1505-1508.

207  
198

19. Young, S.D.; Amblard, M.C.; Britcher, S.F.; Grey, V.E.; Tran, L.O.; Lumma, W.C.; Huff, J.R.; Schleif, W.A.; Emini, E.E.; O'Brien, J.A.; Pettibone, D.J. 2-Heterocyclic indole-3-sulfones as inhibitors of HIV-reverse transcriptase. *Bioorg. Med. Chem. Lett.*, 1995, 5, 491-496.
20. Genin, M.J.; Poel, T.J.; Yagi, Y.; Biles, C.; Althaus, I.; Keiser, B.J.; Kopta, L.A.; Friis, J.M.; Reusser, F.; Adams, W.J.; Olmsted, R.A.; Voorman, R.L.; Thomas, R.C. and Romero, D.L. Synthesis and bioactivity of novel bis(heteroaryl)piperazine (BHAP) reverse transcriptase inhibitors: structure-activity relationships and increased metabolic stability of novel substituted pyridine analogs. *J. Med. Chem.*, 1996, 39, 5267-5275.
21. Silvestri, R.; Artico, M.; Bruno, B.; Massa, S.; Novellino, E.; Greco, G.; Marongiu, M.E.; Pani, A.; De Montis, A and La Colla, P. Synthesis and biological evaluation of 5H-indolo[3,2-b][1,5]benzothiazepine derivatives, designed as conformationally constrained analogues of the human immunodeficiency virus type 1 reverse transcriptase inhibitor L-737,126. *Antiviral Chem. Chemother.* 1998, 9, 139-148.
22. Fredenhagen, A.; Petersen, F.; Tintelnot-Blomley, M.; Rosel, J.; Mett, H and Hug, P.J. Semicochliodinol A and B: Inhibitors of HIV-1 protease and EGF-R protein Tyrosine Kinase related to Asterriquinones

20x 199

produced by the fungus *Chrysosporium nardarium*.  
*Antibiotics*, 1997, 50, 395-401.

23. (a) Kato, M.; Ito, K.; Nishino, S.; Yamakuni, H.; Takasugi, H. New 5-HT<sub>3</sub> (Serotonin-3) receptor antagonists. *Chem. Pharm. Bull.*, 1995, 43, 1351-1357. (b) Levacher, V.; Benoit, R.; Duflos, J.; Dupas, G.; Bourguignon, J.; Queguiner, G. Broadening the scope of NADH models by using chiral and non chiral pyrrolo [2,3-b]pyridine derivatives. *Tetrahedron*, 1991, 47, 429-440.
24. (a) Resnyanskaya, E. V.; Tverdokhlebov, A. V.; Volovenko, Y. M.; Shishkin, O. V.; Zubatyuk, R. I. A simple synthesis of 1-acyl-3-aryl-3H-pyrrolo[2',3':4,5]pyrimido[6,1-b]benzothiazol-6-ium-2-olates: Betainic derivatives of a novel heterocyclic system. *Synthesis*, 2002, 18, 2717-2724. (b) Cook, P. D.; Castle, R. N. Pyrrolopyridazines. 1. Synthesis and reactivity of [2,3-d]pyridazine 5-oxides. *J. Het. Chem.* 1973, 10(4), 551-557.
25. Shadrina, L.P.; Dormidontov, Yu.P.; Ponomarev, V.G.; Lapkin, I.I. Reactions of organomagnesium derivatives of 7-aza- and benzoindoles with diethyl oxalate and the reactivity of ethoxalylindoles. *Khim. Geterotsikl. Soedin.*, 1987, 1206-1209.
26. Sycheva, T.V.; Rubtsov, N.M.; Sheinker, Yu.N.; Yakhontov, L.N. Some reactions of 5-cyano-6-chloro-7-

205 200

azaindoles and lactam-lactim tautomerism in 5-cyano-6-hydroxy-7-azaindolines. *Khim. Geterotsikl. Soedin.*, 1987, 100-106.

27. (a) Desai, M.; Watthey, J.W.H.; Zuckerman, M.  
5 A convenient preparation of 1-aroypiperazines. *Org. Prep. Proced. Int.*, 1976, 8, 85-86. (b) Adamczyk, M.; Fino, J.R.  
: Synthesis of procainamide metabolites. N-acetyl desethylprocainamide and desethylprocainamide. *Org. Prep. Proced. Int.* 1996, 28, 470-474. (c) Rossen, K.;  
10 Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. Asymmetric Hydrogenation of tetrahydropyrazines: Synthesis of (S)-piperazine 2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor Indinavir. *Tetrahedron Lett.*, 1995,  
15 36, 6419-6422. (d) Wang, T.; Zhang, Z.; Meanwell, N.A. Benzoylation of Dianions: Preparation of mono-Benzoylated Symmetric Secondary Diamines. *J. Org. Chem.*, 1999, 64, 7661-7662.

28. Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff,  
20 T.; Goodman, M. 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT): A new coupling reagent with remarkable resistance to racemization. *Organic Lett.*, 1999, 1, 91-93.

29. Harada, N.; Kawaguchi, T.; Inoue, I.; Ohashi,  
25 M.; Oda, K.; Hashiyama, T.; Tsujihara, K. Synthesis and

204 201

antitumor activity of quaternary salts of 2-(2'-oxoalkoxy)-9-hydroxyellipticines. *Chem. Pharm. Bull.*, 1997, 45, 134-137.

30. Schneller, S. W.; Luo, J.-K. Synthesis of 4-amino-1H-pyrrolo[2,3-b]pyridine (1,7-Dideazaadenine) and 1H-pyrrolo[2,3-b]pyridin-4-ol (1,7-Dideazahypoxanthine). *J. Org. Chem.*, 1980, 45, 4045-4048.

31. Shiotani, S.; Taniguchi, K. Furopyridines. XXII[1]. Elaboration of the C-substituents  $\alpha$  to the heteronitrogen atom of furo[2,3-b]-, -[3.2-b]-, -[2.3-c]- and -[3,2-c]pyridine. *J. Het. Chem.*, 1997, 34, 901-907.

32. Minakata, S.; Komatsu, M.; Ohshiro, Y. Regioselective functionalization of 1H-pyrrolo[2,3-b]pyridine via its N-oxide. *Synthesis*, 1992, 661-663.

33. Klemm, L. H.; Hartling, R. Chemistry of thienopyridines. XXIV. Two transformations of thieno[2,3-b]pyridine 7-oxide (1). *J. Het. Chem.*, 1976, 13, 1197-1200.

34. Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Crifantini, M.; Martelli, S. Synthesis of 4-amino-1- $\beta$ -D-ribofuranosyl-1H-pyrrolo[2,3-b]pyridine (1-Deazatubercidin) as a potential antitumor agent. *J. Med. Chem.*, 1982, 25, 1258-1261.

35. (a) Regnouf De Vains, J.B.; Papet, A.L.; Marsura, A New symmetric and unsymmetric polyfunctionalized 2,2'-bipyridines. *J. Het. Chem.*, 1994, 31, 1069-1077. (b) Miura, Y.; Yoshida, M.; Hamana, M. Synthesis of 2,3-fused

28 202

- quinolines from 3-substituted quinoline 1-oxides. Part II, *Heterocycles*, 1993, 36, 1005-1016. (c) Profft, V.E.; Rolle, W. Uber 4-merkaptoverbindungendes 2-metilpyridins. *J. Prakt. Chem.*, 1960, 283 (11), 22-34.
- 5 36. Nesi, R; Giomi, D.; Turchi, S.; Tedeschi, P., Ponticelli, F. A new one step synthetic approach to the isoxazolo[ 4,5-b ]pyridine system. *Synth. Comun.*, 1992, 22, 2349-2355.
- 10 37. (a) Walser, A.; Zenchoff, G.; Fryer, R.I. Quinazolines and 1,4-benzodiazepines. 75. 7-Hidroxyaminobenzodiazepines and derivatives. *J. Med. Chem.*, 1976, 19, 1378-1381. (b) Barker, G.; Ellis, G.P. Benzopyrone. Part I. 6-Amino- and 6-hydroxy-2-substituted chromones. *J. Chem. Soc.*, 1970, 2230-2233.
- 15 38. Ayyangar, N.R.; Lahoti, R.J.; Daniel, T. An alternate synthesis of 3,4-diaminobenzophenone and mebendazole. *Org. Prep. Proced. Int.*, 1991, 23, 627-631.
- 20 39. Mahadevan, I.; Rasmussen, M. Ambident heterocyclic reactivity: The alkylation of pyrrolopyridines (azaindoles, diazaindenes). *Tetrahedron*, 1993, 49, 7337-7352.
- 25 40. Chen, B.K.; Saksela, K.; Andino, R.; Baltimore, D. Distinct modes of human immunodeficiency type 1 proviral latency , revealed by superinfection of nonproductively infected cell lines with recombinant

208 203

luciferase-encoding viruses. *J. Virol.*, 1994, 68, 654-660.

41. Bodanszky, M.; Bodanszky, A. "The Practice of Peptide Synthesis" 2<sup>nd</sup> Ed., Springer-Verlag: Berlin Heidelberg, Alemania, 1994.

5 42. Albericio, F. et al. *J. Org. Chem.* 1998, 63, 9678.

43. Knorr, R. et al. *Tetrahedron Lett.* 1989, 30, 1927.

44. (a) Jaszay Z. M. et al. *Synth. Commun.*, 1998 10 28,2761 and references cited therein; (b) Bernasconi, S. et al. *Synthesis*, 1980, 385.

45. (a) Jaszay Z. M. et al. *Synthesis*, 1989, 745 and references cited therein; (b) Nicolaou, K. C. et al. *Angew. Chem. Int. Ed.* 1999, 38, 1669.

15 46. Ooi, T. et al. *Synlett.* 1999, 729.

47. Ford, R.E. et al. *J. Med. Chem.* 1986, 29, 538.

48. (a) Yeung, K.-S. et al. Bristol-Myers Squibb Unpublished Results. (b) Wang, W. et al. *Tetrahedron Lett.* 20 1999, 40, 2501.

49. Brook, M.A. et al. *Synthesis*, 1983, 201.

50. Yamazaki, N. et al. *Tetrahedron Lett.* 1972, 5047.

51. Barry A. Bunin "The Combinatorial Index" 1998 25 Academic Press, San Diego/London pages 78-82.



267 204

52. Richard C. Larock Comprehensive Organic Transformations 2nd Ed. 1999, John Wiley and Sons New York.
53. M.D. Mullican et al. *J. Med. Chem.* 1991, 34, 2186-2194.
- 5 54. Protective groups in organic synthesis 3rd ed. / Theodora W. Greene and Peter G.M. Wuts. New York: Wiley, 1999.
- 10 55. Katritzky, Alan R. Lagowski, Jeanne M. The principles of heterocyclic Chemistry New York: Academic Press, 1968.
56. Paquette, Leo A. Principles of modern heterocyclic chemistry New York: Benjamin.
- 15 57. Katritzky, Alan R.; Rees, Charles W.; Comprehensive heterocyclic chemistry: the structure, reactions, synthesis, and uses of heterocyclic compounds 1st ed. Oxford (Oxfordshire); New York: Pergamon Press, 1984. 8 v.
- 20 58. Katritzky, Alan R Handbook of heterocyclic 1st ed Oxford (Oxfordshire); New York: Pergamon Press, 1985.
59. Davies, David I Aromatic Heterocyclic Oxford; New York: Oxford University Press, 1991.
60. Ellis, G. P. Synthesis of fused Chichester [Sussex]; New York: Wiley, c1987-c1992. Chemistry of heterocyclic compounds; v. 47.
- 25 61. Joule, J. A Mills, K, Smith, G. F:

205

Heterocyclic Chemistry, 3rd ed London; New York Chapman & Hall, 1995.

62. Katritzky, Alan R., Rees, Charles W., Scriven, Eric F. V. Comprehensive heterocyclic chemistry II: a review of the literature 1982-1995.

63. The structure, reactions, synthesis, and uses of heterocyclic compounds 1st ed. Oxford; New York: Pergamon, 1996. 11 v. in 12: ill.; 28 cm.

64. Eicher, Theophil, Hauptmann, Siegfried. The chemistry of heterocycles: structure, reactions, syntheses, and applications Stuttgart; New York: G. Thieme, 1995.

65. Grimmett, M. R. Imidazole and benzimidazole Synthesis London; San Diego: Academic Press, 1997.

66. Advances in heterocyclic chemistry. Published in New York by Academic Press, inicia en 1963-a la fecha.

67. Gilchrist, T. L. (Thomas Lonsdale) Heterocyclic chemistry 3rd ed. Harlow, Essex: Longman, 1997, 414 p: ill.; 24 cm.

68. Farina, Vittorio; Roth, Gregory P. Recent advances in the Stille reaction; Adv. Met.-Org. Chem. 1996, 5, 1-53.

69. Farina, Vittorio; Krishnamurthy, Venkat; Scott, William J. The Stille reaction; org. React. (N. Y.) (1997), 50, 1-652.

70. Stille, J. K. Angew. Chem. Int. Ed. Engl.

229 206

- 1986, 25, 508-524.
71. Norio Miyaura and Akiro Suzuki *Chem Rev.* 1995, 95, 2457.
72. Home, D.A. *Heterocycles* 1994, 39, 139.
- 5 73. Kamitori, Y. et al. *Heterocycles*, 1994, 37(1), 153.
74. Shawali, J. *Heterocyclic Chem.* 1976, 13, 989.
75. a) Kende, A.S. et al. *Org. Photochem. Synth.* 10 1972, 1, 92. b) Hanks, L.V.; *Biochem. Prep.* 1966, 11, 63. c) *Synth. Meth.* 22, 837.
76. Hulton et al. *Synth. Comm.* 1979, 9, 789.
77. Pattanayak, B.K. et.al. *Indian J. Chem.* 1978, 16, 1030.
- 15 78. *Chemische Berichte* 1902, 35, 1545.
79. *Chemische Berichte* Ibid 1911, 44, 493.
80. Moubarak, I., Vessiere, R *Synthesis* 1980, Vol. 1,52-53.
81. *Ind J. Chem.* 1973, 11, 1260.
- 20 82. Roomi et.al. *Can J. Chem.* 1970, 48, 1689.
83. Sorrel, T.N. *J. Org. Chem.* 1994, 59, 1589.
84. Nitz, T.J. et.al. *J. Org. Chem.* 1994, 59, 5828-5832.
85. Bowden, K. et.al. *J. Chem. Soc.* 1946, 953.
- 25 86. Nitz, T.J. et al. *J. Org. Chem.* 1994, 59;

210 207

5828-5832.

87. Scholkopf et al. Angew. Int. Ed. Engl. 1971, 10(5), 333.

88. (a) Behun, J. D.; Levine, R. J. Org. Chem. 1961, 26, 3379. (b) Rossen, K.; Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. Asymmetric Hydrogenation of tetrahydropyrazines: Synthesis of (S)-piperazine 2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor Indinavir. 10 Tetrahedron Lett., 1995, 36, 6419-6422. (c) Jenneskens, L.W.; Mahy, J.; den Berg, E. M. M. de B.-v.; Van der Hoef, L.; Lugtenburg, J. Recl. Trav. Chim. Pays-Bas 1995, 114, 97.

89. Wang, T.; Zhang, Z.; Meanwell, N.A. 15 Benzoylation of Dianions: Preparation of mono-Benzoylated Symmetric Secondary Diamines. J. Org. Chem., 1999, 64, 7661-7662.

90. (a) Adamczyk, M.; Fino, J.R. Synthesis of procainamide metabolites. N-acetyl desethylprocainamide and 20 desethylprocainamide. Org. Prep. Proced. Int. 1996, 28, 470-474. (b) Wang, T.; Zhang, Z.; Meanwell, N.A. Regioselective mono-Benzoylation of Unsymmetrical Piperazines. J. Org. Chem., in press.

91. Masuzawa, K.; Kitagawa, M.; Uchida, H. Bull 25 Chem. Soc. Jpn. 1967, 40, 244-245.

ZH 200

92. Furber, M.; Cooper, M. E.; Donald, D. K.  
Tetrahedron Lett. 1993, 34, 1351-1354.

93. Blair, Wade S.; Deshpande, Milind; Fang,  
Haiquan; Lin, Pin-fang; Spicer, Timothy P.; Wallace, Owen B.;  
5 Wang, Hui; Wang, Tao; Zhang, Zhongxing; Yeung,  
Kap-sun. Preparation of antiviral indoleoxoacetyl piperazine  
derivatives Patente Norteamericana 6,469,006. Preparation of  
antiviral indoleoxoacetyl piperazine derivatives. Sol. Int.  
PCT (PCT/US00/14359), WO 0076521 A1, presentada el 24 de  
10 Mayo, 2000, publicada en diciembre 21, 2000.

94. Wang, Tao; Wallace, Owen B.; Zhang, Zhongxing;  
Meanwell, Nicholas A; Bender, John A Antiviral azaindole  
derivatives. Patente Norteamericana 6,476,034 and Wang, Tao;  
Wallace, Owen B.; Zhang, Zhongxing; Meanwell, Nicholas A.;  
15 Bender, John A Preparation of antiviral azaindole  
derivatives. Sol. Int. PCT (PCT/US01/02009), WO 0162255 A1,  
presentada en enero, 2001, publicada el 30 agosto, 2001.

95. Wallace, Owen B.; Wang, Tao; Yeung,  
Kap-Sun; Pearce, Bradley C.; Meanwell, Nicholas A; Qiu,  
20 Zhilei; Fang, Haiquan; Xue, Qiufen May; Yin, Zhiwei.  
Composition and antiviral activity of substituted  
indoleoxoacetic piperazine derivatives. Patente  
Norteamericana 6,573,262 que es una solicitud de continuación  
parcial de número de serie Norteamericana 09/888,686  
25 presentada el 25 de junio de 2001 (que corresponde a la sol:

212 209

Int. PCT (PCT/US01/20300), WO 0204440 A1, presentada el 26 de junio de 2001, publicada el 17 de enero de 2002.

96. J. L. Marco, S. T. Ingate, and P. M. Chinchon  
Tetrahedron 1999, 55, 7625-7644.

5 97. C. Thomas, F. Orecher, and P. Gmeiner Synthesis  
1998, 1491.

98. M. P. Pavia, S. J. Lobbstaël, C. P. Taylor, F.  
M. Hershenson, and D. W. Miskell.

99. Buckheit, Robert W., Jr. Expert Opinion on  
10 Investigational Drugs 2001, 10(8), 1423-1442.

100. Balzarini, J.; De Clercq, E.. Antiretroviral  
Therapy 2001, 31-62.

101. E. De clercq Journal of Clinical Virology,  
2001, 22, 73-89.

15 102. Merour, Jean-Yves; Joseph, Benoit. Curr. Org.  
Chem. (2001), 5(5), 471-506.

103. T. W. von Geldern et al. J. Med. Chem 1996,  
39, 968.

104. M. Abdaoui et al. Tetrahedron 2000, 56, 2427.

20 105. W. J. Spillane et al. J. Chem. Soc., Perkin  
Trans. 1, 1982, 3, 677.

106. Wang, Tao; Zhang, Zhongxing; Meanwell,  
Nicholas A.; Kadow, John F.; Yin, Zhiwei; Xue, Qiufen May.  
(USA). Composition and antiviral activity of substituted  
25 azaindoleoxoacetic piperazine derivatives. Sol. Pat. Publ:

217 210

(2003), US 20030207910 A1 publicada Nov 6, 2003 que es la Solicitud de Patente Norteamericana Número de Serie 10/214,982 presentada el 7 de agosto de 2002, que es una solicitud de continuación parcial de Número de Serie 5 Norteamericana 10/038,306 presentada el 2 de enero de 2002 (correspondiente a la Sol. Int. PCT (PCT/US02/00455), WO : 02/062423 A1, presentada el 2 de enero de 2002, publicada el 15 de agosto de 2002.

107. a) Nickel, Bernd; Szelenyi, Istvan; Schmidt, 10 Jurgen; Emig, Peter; Reichert, Dietmar; Gunther, Eckhard; Brune, Kay. Preparation of indolyglyoxilamides as antitumor agents. Sol. Int. PCT (1999), 47 pp. CODEN: PIXXD2 WO 9951224, b) Emig, Peter; Bacher, Gerald; Reichert, Dietmar; Baasner, Silke; Aue, Beate; Nickel, Bernd; Guenther, Eckhard. 15 Preparation of N-(6-quinolinyl)-3-indolyglyoxylamides as antitumor agents. Sol. Int. PCT (2002), 4WO 2002010152A2, c) Nickel, Bernd; Klenner, Thomas; Bacher, Gerald; Beckers, Thomas; Emig, Peter; Engel, Juergen; Bruyneel, Erik; Kamp, Guenter; Peters, Kirsten. Indolyl-3-glyoxilic acid 20 derivatives comprising therapeutically valuable properties. Sol. Int. PCT (2001), WO 2001022954A2.

108. Wang, Tao; Wallace, Owen B.; Meanwell, Nicholas A.; Zhang, Zhongxing; Bender, John A; Kadow, John F.; Yeung, Kap-Sun. Preparation of indole, azaindole, and 25 related heterocyclic piperazinecarboxamides for treatment of

211

AIDS. Sol. Int. PCT WO 2002085301A2, publicada el 31 de octubre de 2002; correspondiente a la Publicación de Patente Norteamericana 20030096825A1, publicada el 22 de Mayo de 2003.

5                   109. Kadow, John F.; Xue, Qiufen May; Wang, Tao; Zhang, Zhongxing; Meanwell, Nicholas A. Preparation of indole, azaindole and related heterocyclic pyrrolidine derivatives as antiviral agents. Sol. Int. PCT WO 2003068221A1, publicada el 21 de agosto de 2003; 10 correspondiente a la Publicación de Patente Norteamericana U.S. 20030236277A1.

                  110. Wang, Tao; Wallace, Owen B.; Meanwell, Nicholas A.; Kadow, John F.; Zhang, Zhongxing; Yang, Zhong. Preparation of piperazine derivatives as antiviral agents. 15 Sol. Int. PCT (2003), WO 2003092695 A1; correspondiente a la Publicación de Patente Norteamericana U.S. 20040009985A1, publicada el 15 de enero de 2004.

                  111. Kadow, John P.; Regueiro-Ren, Alicia; Xue, Qiufen May. Preparation of indolil-, azaindolil-, and 20 related heterocyclic sulfonylureidopiperazines for treatment of HIV and AIDS. Sol. Int. PCT (2003), WO 2004000210 A2; correspondiente a la Publicación de Patente Norteamericana U.S. 20040006090A1, publicada el 8 de enero de 2004.

                  112. Regueiro-Ren, Alicia; Xue, Qiufen May; Kadow, 25 John F.; Taylor, Malcolm. Preparation of indolil-;



212

azaindolil-, and related heterocyclic ureido and thioureido  
piperazines for treatment of HIV and AIDS. Sol. Int. PCT  
(2004), WO 2004011425 A2; correspondiente a la Publicación de  
Patente Norteamericana U.S. 20040063746A1, publicada el 1 de  
5 abril de 2004.

113. Wang, Tao; Zhang, Zhongxing; Meanwell,  
Nicholas A.; Kadow, John F.; Yin, Zhiwei; Xue, Qiufen May;  
Regueiro-Ren, Alicia; Matiskella, John D.; Ueda, Yasutsugu.  
Composition and antiviral activity of substituted  
10 azaindoleoxoacetic piperazine derivatives. Publ. Sol. Pat.  
E.U. (2004), US 2004110785 A1; publicada el 10 de junio de  
2004.

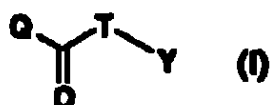
114. Wang, Tao; Kadow, John F.; Meanwell, Nicholas  
A.; Yeung, Kap-Sun; Zhang, Zhongxing; Yin, Zhiwei; Qiu,  
15 Zhilei; Deon, Daniel H.; James, Clint A.; Ruediger, Edward  
H.; Bachand, Carol. Preparation and pharmaceutical  
compositions of indole, azaindole and related heterocyclic  
4-alkenyl piperidine amides. Publ. Sol. Pat. E.U. (2004), US  
20040063744 A1; publicada el 1 de abril de 2004;  
20 correspondiente a la Sol. Int. PCT (2004), WO 2004/04337.

#### BREVE DESCRIPCION DE LA INVENCION

La presente invención comprende compuestos de  
fórmula I, sus formulaciones farmacéuticas y uso en pacientes  
25 que padecen o son susceptibles a un virus tal como el VIH:

Los compuestos de fórmula I, que incluyen sales farmacéuticamente aceptables no tóxicas de los mismos, tienen la fórmula y significado como se describe a continuación.

La presente invención comprende compuestos de fórmula I, que incluyen sales farmacéuticamente aceptables de los mismos, que son agentes antivirales efectivos, particularmente como inhibidores de VIH.

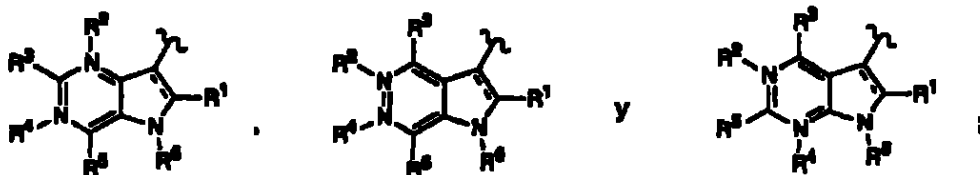


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en donde:

Q se selecciona del grupo que consiste de

15



T es  $-\text{C}(\text{O})-$  o  $-\text{CH}(\text{CN})-$ ;

$\text{R}^1$  es hidrógeno o metilo;

$\text{R}^3$  y  $\text{R}^5$  son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, ciano, nitro,  $\text{COOR}^8$ ,  $\text{XR}^9$  y B;

20

$\text{R}^2$  y  $\text{R}^4$  son independientemente 0 ó no existen con la condición de que solamente uno de  $\text{R}^2$  y  $\text{R}^4$  son 0;

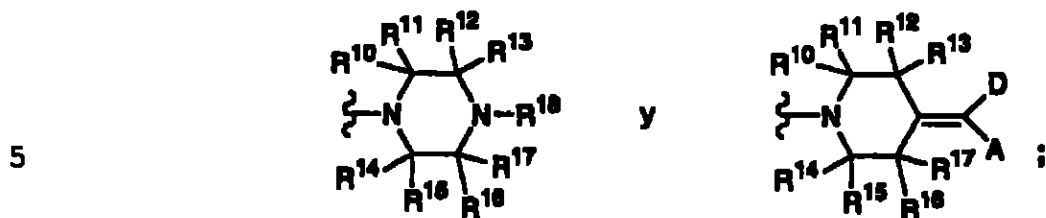
$\text{R}^6$  es  $(\text{CH}_2)_n\text{H}$ , en donde n es 0-1;

25

-- representa un enlace carbono-carbono o no

existe;

- Y - se selecciona del grupo que consiste de



10  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o alquilo( $C_{1-6}$ ); en donde alquilo( $C_{1-6}$ ) puede opcionalmente sustituirse con uno hasta tres halógenos iguales o diferentes, OH o CN;

15  $R^{18}$  es un miembro seleccionado del grupo que consiste de C(O)-fenilo, C(O)-heteroarilo, piridinilo, pirimidinilo, quinolilo, isoquinolilo, quinazolilo, quinoxalinilo, naftiridinilo, ftalazinilo, azabenzofurilo y azaindolilo; en donde el miembro es opcionalmente sustituido con uno o dos sustituyentes seleccionados del grupo que consiste de metilo, -amino, -NHMe, -NMe<sub>2</sub>, metoxi, hidroximetilo y halógeno;

20 D se selecciona del grupo que consiste de hidrógeno, ciano,  $S(O)_2R^{24}$ , halógeno,  $COOR^{20}$ ,  $C(O)NR^{21}R^{22}$ , fenilo y heteroarilo; en donde fenilo o heteroarilo es sustituido independientemente y opcionalmente con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres sustituyentes iguales o diferentes seleccionados de F (como se define a continuación);

25

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A se selecciona del grupo que consiste de fenilo, piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde fenilo, piridinilo, furanilo, tienilo, isoxazol o oxazol es sustituido independientemente y opcionalmente con uno hasta  
5 tres halógenos iguales o diferentes o desde uno hasta tres sustituyentes iguales o diferentes seleccionados de F;

B se selecciona del grupo que consiste de alquilo(C<sub>1-6</sub>), C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)CH<sub>3</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NC(O)pirazolilo, fenilo y heteroarilo; en donde alquilo(C<sub>1-6</sub>), fenilo y  
10 heteroarilo son sustituidos independientemente y opcionalmente con uno hasta tres halógenos iguales o diferentes, o desde uno o tres sustituyentes iguales o diferentes seleccionados de F;

Heteroarilo se selecciona del grupo que consiste de  
15 piridinilo, pirazinilo, piridazinilo, pirimidinilo, furanilo, tienilo, benztienilo, tiazolilo, oxazolilo, isoxazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, pirazolilo, tetrazolilo y triazolilo;

F se selecciona del grupo que consiste de  
20 alquilo(C<sub>1-6</sub>), alqueno(C<sub>1-6</sub>), fenilo, piridinilo, hidroxilo, alcoxi(C<sub>1-6</sub>), halógeno, bencilo, -NR<sup>23</sup>C(O)-alquilo(C<sub>1-6</sub>), -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, y -CONR<sup>24</sup>R<sup>25</sup>; en donde alquilo(C<sub>1-6</sub>) o fenilo son cada uno sustituido opcionalmente con hidroxilo, alcoxi(C<sub>1-6</sub>), alquilo(C<sub>1-6</sub>), CF<sub>3</sub>, dimetilamino o  
25 desde uno hasta tres halógenos iguales o diferentes;

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$R^8$ ,  $R^9$  y  $R^{26}$  son cada uno independientemente seleccionados del grupo que consiste de hidrógeno y alquilo ( $C_{1-6}$ );

X se selecciona del grupo que consiste de  $NR^{26}$ , O y S;

$R^{20}$ ,  $R^{21}$ ,  $R^{22}$ ,  $R^{23}$ ,  $R^{24}$  y  $R^{25}$  son independientemente seleccionados del grupo que consiste de hidrógeno, alquilo ( $C_{1-6}$ ), fenilo y heteroarilo; en donde fenilo y heteroarilo son sustituidos cada uno independientemente y opcionalmente con uno hasta tres halógenos o metilo iguales o diferentes; y

$R^{27}$  es piperazinilo, piperazinilo de N-metilo, o 3-pirazolilo.

Una modalidad preferida incluye los compuestos donde T es  $\text{---}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{---}$ .

Otra modalidad preferida de la invención son compuestos de fórmula I, que incluyen sales farmacéuticamente aceptables de los mismos

en donde:

$R^1$  es hidrógeno;

-- representa un enlace carbono-carbono; y

$R^2$  y  $R^4$  no existen.

D se selecciona del grupo que consiste de hidrógeno, ciano,  $S(O)_2R^{24}$ , halógeno,  $COOR^{20}$ ,  $C(O)NH_2$ , fenilo y heteroarilo; en donde fenilo o heteroarilo es sustituido independientemente y opcionalmente con uno hasta tres

halógenos iguales o diferentes o con un miembro seleccionado del grupo que consiste de alquilo(C<sub>1-6</sub>), alquenilo(C<sub>1-6</sub>), hidroxilo, alcoxi(C<sub>1-6</sub>), halógeno, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup> y -CONR<sup>24</sup>R<sup>25</sup>; en donde alquilo(C<sub>1-6</sub>) es sustituido opcionalmente con uno hasta tres halógenos o hidroxilo iguales o diferentes; y

A se selecciona del grupo que consiste de fenilo, piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde fenilo, piridinilo, furanilo, tienilo, isoxazol u oxazol son sustituidos independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o con un miembro seleccionado del grupo que consiste de alquilo(C<sub>1-4</sub>), alquenilo(C<sub>1-4</sub>), alcoxi(C<sub>1-3</sub>), halógeno y -NH<sub>2</sub>; en donde alquilo(C<sub>1-3</sub>) es opcionalmente sustituido con uno hasta tres halógenos iguales o diferentes.

Otra modalidad preferida son compuestos de fórmula I en donde:

R<sup>6</sup> es hidrógeno; y

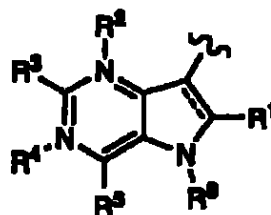
R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> son cada uno independientemente H o metilo con la condición de que un máximo de dos de R<sup>10</sup>-R<sup>17</sup> es un metilo.

Otra modalidad preferida de la invención son compuestos de fórmula I, que incluyen como anteriormente sales farmacéuticamente aceptables de los mismos

En donde:

Q es un miembro seleccionado de los grupos (A),  
(B), y (C) que consisten de  
(A)

5

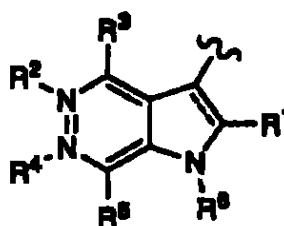


:

en donde  $R^3$  es hidrógeno, alcoxi  $C_1-C_3$ ,  $-NR^{26}R^9$  o  
halógeno;

10

(B)

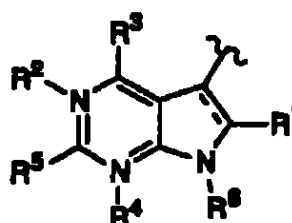


15

en donde  $R^3$  es hidrógeno, metoxi o halógeno; y

(C)

20



en donde  $R^3$  es hidrógeno, metoxi o halógeno.

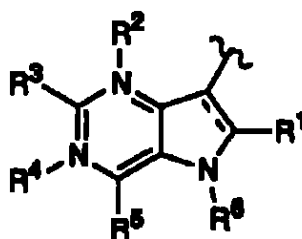
Otra modalidad preferida de la invención son  
compuestos de Fórmula I, como anteriormente incluyeron sales  
farmacéuticamente aceptables de los mismos, en donde:

25

grupo (A) de Q es:

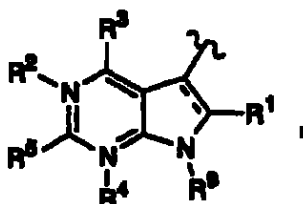
272 219

(A)



5

en donde  $R^3$  es hidrógeno; y  
grupo (C) de Q es:



10

en donde:

$R^5$  es hidrógeno.

En otra modalidad preferida de la invención, Q se  
15 selecciona del grupo de (A) o (B), y

$R^5$  se selecciona del grupo que consiste de  
hidrógeno, halógeno, heteroarilo, fenilo, ciano, metoxi,  
COOR<sup>6</sup>, C(O)NH<sub>2</sub>, C(O)NHheteroarilo, y C(O)NHCH<sub>3</sub>; en donde  
C(O)NHheteroarilo, fenilo, y heteroarilo son sustituidos  
20 independientemente de forma opcional con uno hasta tres  
halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F.

Otras modalidades preferidas son compuestos de  
formula I:

25 en donde heteroarilo se selecciona del grupo que



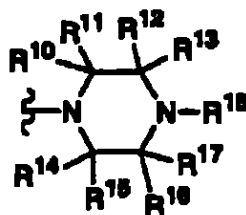
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consiste de piridinilo, pirazinilo, piridazinilo, pirimidinilo, furanilo, tienilo, tiazolilo, oxazolilo, isoxazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, pirazolilo, tetrazolilo y triazolilo; en donde heteroarilo es  
5 sustituido independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F;

$R^{18}$  es  $-C(O)$ fenilo o  $-C(O)$ heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; en donde  
10 heteroarilo es sustituido independientemente de forma opcional con un miembro seleccionado del grupo que consiste de halógeno, metilo, -amino, -NHMe, NMe<sub>2</sub> y hidroximetilo;

-W- es

15



20

$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o metilo con la condición de que no más  
de uno es metilo; y

25

$R^{18}$  se selecciona del grupo que consiste de  $C(O)$ -fenilo o  $C(O)$ -heteroarilo en donde cada uno de  $C(O)$ -fenilo o  $-C(O)$ -heteroarilo puede opcionalmente sustituirse con desde uno hasta dos grupos metilo, -amino, -NHMe, -NMe<sub>2</sub>, metoxi, hidroximetilo o halógeno; o

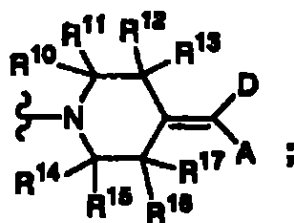
$R^{18}$  se selecciona del grupo que consiste de piridilo, pirimidinilo, quinolilo, isoquinolilo, quinazolilo, quinoxalinilo, naftiridinilo, ftalazinilo, azabenzofurilo y azaindolilo, cada uno de los cuales pueden

5 sustituirse con desde uno hasta dos grupos metilo, -amino, -NHMe, -NMe<sub>2</sub>, metoxi, hidroximetilo o halógeno.

En otra modalidad preferida:

-W- se selecciona del grupo que consiste de

10



15

$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o metilo, con la condición que uno es

metilo;

20

D se selecciona del grupo que consiste de hidrógeno, ciano,  $S(O)_2R^{24}$ , halógeno,  $COOR^{20}$ ,  $C(O)NH_2$ , fenilo, o heteroarilo; en donde fenilo o heteroarilo es sustituido independientemente de forma opcional con uno hasta tres

halógenos iguales o diferentes o desde uno hasta tres

sustituyentes iguales o diferentes seleccionados del grupo que consiste de alquilo( $C_{1-6}$ ), alquenilo( $C_{1-6}$ ), hidroxil, alcoxi( $C_{1-6}$ ), halógeno,  $-NR^{24}R^{25}$ ,  $-S(O)_2NR^{24}R^{25}$ ,  $COOR^{26}$  y  $-CONR^{24}R^{25}$ ; en donde alquilo( $C_{1-6}$ ) es opcionalmente sustituido

25 con uno hasta tres halógenos o un hidroxil; y

A se selecciona del grupo que consiste de fenilo, piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde fenilo, piridinilo, furanilo, tienilo, isoxazol u oxazol, es sustituido independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres sustituyentes iguales o diferentes seleccionados del grupo que consiste de alquilo(C<sub>1-4</sub>), alquenilo(C<sub>1-4</sub>), alcoxi(C<sub>1-3</sub>), halógeno y -NH<sub>2</sub>; en donde alquilo(C<sub>1-4</sub>) es opcionalmente sustituido con uno hasta tres halógenos iguales o diferentes.

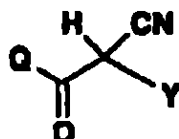
10

En otra modalidad preferida:

Q se selecciona del grupo (A).

Otra modalidad preferida son compuestos de fórmula I, que incluyen sales farmacéuticamente aceptables de los mismos,

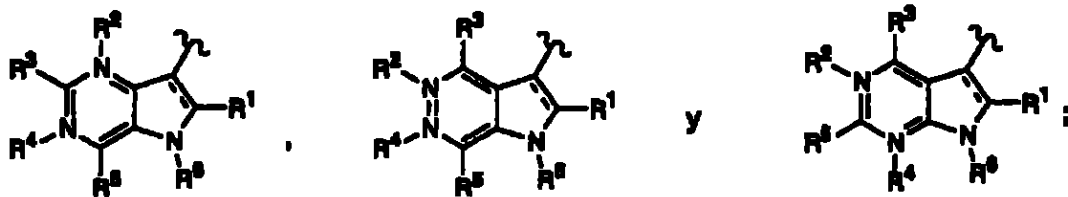
15



en donde:

Q se selecciona del grupo que consiste de

20



R<sup>1</sup> es hidrógeno o metilo;

25

R<sup>3</sup> y R<sup>5</sup> son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, ciano, nitro;

COOR<sup>8</sup>, XR<sup>9</sup> y B;

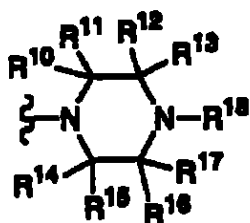
R<sup>2</sup> y R<sup>4</sup> son independientemente 0 ó no existen, con la condición de que solamente uno de R<sup>2</sup> y R<sup>4</sup> son 0;

R<sup>6</sup> es (CH<sub>2</sub>)<sub>n</sub>H en donde n es 0-1;

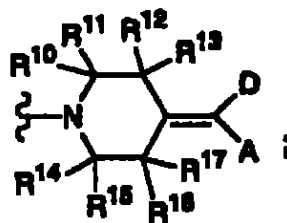
5 -- representa un enlace carbono-carbono o no existe;

-Y- se selecciona del grupo que consiste de

10



y



15

R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> y R<sup>17</sup> son cada uno independientemente H o alquilo(C<sub>1-6</sub>); en donde alquilo(C<sub>1-6</sub>) puede estar opcionalmente sustituido con uno hasta tres halógenos iguales o diferentes, OH o CN;

20

R<sup>18</sup> es un miembro seleccionado del grupo que consiste de C(O)-fenilo, C(O)-heteroarilo, piridinilo, pirimidinilo, quinolilo, isoquinolilo, quinazolilo, quinoxalinilo, naftiridinilo, ftalazinilo, azabenzofurilo y azaindolilo; en donde el miembro es opcionalmente sustituido con desde uno hasta dos sustituyentes seleccionados del grupo que consiste de metilo, -amino, -NHMe, -NMe<sub>2</sub>, metoxi, hidroximetilo y halógeno;

25

D se selecciona del grupo que consiste de

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hidrógeno, ciano,  $S(O)_2R^{24}$ , halógeno,  $COOR^{20}$ ,  $C(O)NR^{21}R^{22}$ ,  
fenilo y heteroarilo; en donde fenilo o heteroarilo es  
sustituido independientemente de forma opcional con uno hasta  
5 sustituyentes iguales o diferentes seleccionados de F;

A se selecciona del grupo que consiste de fenilo,  
piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde  
fenilo, piridinilo, furanilo, tienilo, isoxazol u oxazol es  
sustituido independientemente de forma opcional con uno hasta  
10 tres halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F;

B se selecciona del grupo que consiste de  
alquilo( $C_{1-6}$ ), cicloalquilo( $C_{3-6}$ ),  $C(O)NR^{21}R^{22}$ ,  $-C(O)CH_3$ ,  
 $-N(CH_2CH_2)_2NC(O)$ pirazolilo, fenilo y heteroarilo; en donde  
15 alquilo( $C_{1-6}$ ), fenilo y heteroarilo son sustituidos  
independientemente de forma opcional con uno hasta tres  
halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F;

heteroarilo se selecciona del grupo que consiste de  
20 piridinilo, pirazinilo, piridazinilo, pirimidinilo, furanilo,  
tienilo, tiazolilo, oxazolilo, isoxazolilo, imidazolilo,  
oxadiazolilo, tiadiazolilo, pirazolilo, tetrazolilo y  
triazolilo;

F se selecciona del grupo que consiste de  
25 alquilo( $C_{1-6}$ ), alquenilo( $C_{1-6}$ ), fenilo, piridinilo, hidroxil;

alcoxi(C<sub>1-6</sub>), halógeno, bencil, -NR<sup>23</sup>C(O)-alquilo(C<sub>1-6</sub>),  
 -NR<sup>24</sup>R<sup>25</sup>, -S(O)NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, y -CONR<sup>24</sup>R<sup>25</sup>; en donde  
 5      alquilo(C<sub>1-6</sub>) o fenilo son cada uno sustituidos opcionalmente  
 con hidroxilo, alcoxi(C<sub>1-6</sub>), dimetilo amino o desde uno hasta  
 tres halógenos iguales o diferentes;

R<sup>8</sup>, R<sup>9</sup> y R<sup>26</sup> son cada uno independientemente  
 1      seleccionados del grupo que consiste de hidrógeno y  
 alquilo(C<sub>1-6</sub>);

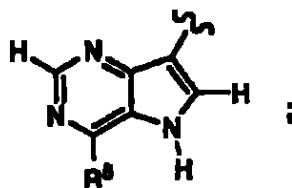
X se selecciona del grupo que consiste de NR<sup>26</sup>, O y  
 10      S;

R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup> y R<sup>25</sup> son independientemente  
 seleccionados del grupo que consiste de hidrógeno, alquilo  
 (C<sub>1-6</sub>), fenilo y heteroarilo; en donde fenilo y heteroarilo  
 son cada uno sustituidos independientemente de forma opcional  
 15      con uno hasta tres halógenos o metilo iguales o diferentes; y

R<sup>27</sup> es piperazinilo, N-metilpiperazinilo o  
 3-pirazolilo.

En otra modalidad, son compuestos de formula I, que  
 incluyen sales farmacéuticamente aceptables, en donde:

20      Q es



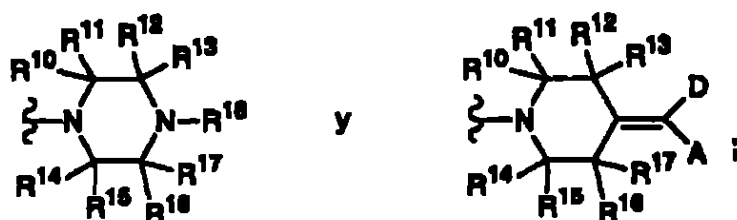
R<sup>5</sup> se selecciona del grupo que consiste de  
 25      hidrógeno, halógeno, ciano, XR<sup>9</sup>, heteroarilo;

-N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NC(O)pirazolilo, y -C(O)CH<sub>3</sub>, en donde heteroarilo es sustituido opcionalmente con un sustituyente seleccionado de F;

heteroarilo se selecciona del grupo que consiste de piridinilo, pirazinilo, piridazinilo, pirimidinilo, isoxazolilo, isoxazolilo, pirazolilo, y triazolilo;

-Y- se selecciona del grupo que consiste de

10



R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> y R<sup>17</sup> son cada uno hidrógeno;

15

A es fenilo o piridinilo;

R<sup>18</sup> es C(O)-fenilo, isoquinolilo o quinazolilo;

D es ciano o oxadiazolilo;

20

F se selecciona del grupo que consiste de alquilo(C<sub>1-6</sub>), fenilo, piridinilo, alcoxi(C<sub>1-2</sub>), -COOR<sup>26</sup> -COR<sup>27</sup> y -CONR<sup>24</sup>R<sup>25</sup>; en donde fenilo es opcionalmente sustituido con un grupo seleccionado de metilo, metoxi, fluoro, o trifluorometilo;

X se selecciona del grupo que consiste de O;

R<sup>9</sup> es alquilo(C<sub>1-2</sub>);

25

R<sup>26</sup> es hidrógeno, metilo, o etilo;

$R^{24}$  y  $R^{25}$  son independientemente seleccionados del grupo que consiste de hidrógeno y metilo; y

$R^{27}$  es piperazinilo, piperazinilo de N-metilo, o 3-pirazolilo.

5 Otra modalidad de la presente invención es un método para el tratamiento de mamíferos infectados con el virus, tal como el VIH, que comprende administrar al mamífero un cantidad efectiva antiviral de compuesto de Fórmula I, que incluye sales farmacéuticamente aceptable del mismo, y uno o  
10 más portadores, excipientes o diluyentes farmacéuticamente aceptables; opcionalmente el compuesto de fórmula I puede ser administrado en combinación con una cantidad efectiva antiviral de un agente de tratamiento de SIDA seleccionado del grupo que consiste de: (a) un agente antiviral de SIDA;  
15 (b) un agente anti-infección; (C) un inmunomodulador; y (d) inhibidores de entrada de VIH.

Otra modalidad de la presente invención es una composición farmacéutica que comprende una cantidad efectiva antiviral de un compuesto de fórmula I, que incluye sales  
20 farmacéuticamente aceptables del mismo, y uno o más portadores, excipiente, diluyentes farmacéuticamente aceptables y opcionalmente en combinación con una cantidad efectiva antiviral de un agente de tratamiento de SIDA seleccionado del grupo que consiste de: (a) un agente  
25 antiviral de SIDA; (b) un agente anti-infección; (C)



inmunomodulador; y (d) inhibidores de entrada de VIH.

#### DESCRIPCION DETALLADA DE LA INVENCION

5 Puesto que los compuestos de la presente invención  
pueden poseer centros asimétricos y por lo tanto presentarse  
como mezclas de diaestereómeros y enantiómeros, la presente  
invención incluye formas diaestereoisómericas y  
enantioméricas individuales de compuestos de Fórmula I,  
además de mezclas de los mismos.

10

#### DEFINICIONES

El término "alquilo C<sub>1-6</sub>" como se usa en la presente  
y en las reivindicaciones (salvo que se especifique de otra  
manera) significa grupos alquilo de cadena lineal o  
15 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 (es  
20 decir, anillos que comparten pares adyacentes de átomos de  
carbono) que tienen un sistema de electrones "pi" conjugado  
completamente. Ejemplos, sin limitación, de grupos arilo son  
fenilo, naftalenilo y antracenilo. El grupo arilo puede  
estar sustituido o no sustituido. Cuando se substituyen, los  
25 grupos sustituidos son preferiblemente uno o más

seleccionados de alquilo, cicloalquilo, arilo, heteroarilo, heteroalíciclico, hidroxí, alcoxi, ariloxi, heteroariloxi, heteroalícicloxí, tiohidroxí, tioariloxi, tioheteroariloxi, tioheteroalícicloxí, 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 heteroalíciclico de cinco o seis miembros.

Como se usa en la presente, un grupo "heteroarilo" se refiere a un grupo anillo monocíclico o fusionado (es decir, anillos que comparten un par adyacente de átomos) 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" conjugado completamente. a menos que se indique lo contrario, el grupo heteroarilo puede unirse en un átomo de carbono o nitrógeno dentro del grupo heteroarilo. Debe notarse que el término heteroarilo se pretende que abarque N-óxido del heteroarilo original si tal N-óxido es químicamente posible como se conoce en la técnica. Ejemplos, sin limitación, de grupos heteroarilo son furilo, tienilo, benzotienilo, tiazolilo, imidazolilo, oxazolilo, oxadiazolilo, tiadiazolilo, benzotiazolilo;

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230

triazolilo, tetrazolilo, isoxazolilo, isotiazolilo,  
pirrolilo, piranilo, tetrahidropiranilo, pirazolilo,  
piridilo, pirimidinilo, quinolinilo, isoquinolinilo,  
purinilo, carbazolilo, benzoxazolilo, benzimidazolilo,  
5 indolilo, isoindolilo, pirazinilo, diazinilo, pirazina,  
triazinil, triazina, tetrazinilo, y tetrazolilo. Cuando se  
substituyen, los grupos sustituidos son preferiblemente uno o  
más seleccionados de alquilo, cicloalquilo, arilo,  
heteroarilo, heteroalícíclico, hidroxilo, alcoxi, ariloxi,  
10 heteroariloxi, heteroalícícloxi, tioalcoxi, tiohidroxilo,  
tioariloxi, tioheteroariloxi, tioheteroalícícloxi, ciano,  
halógeno, nitro, carbonilo, O-carbamilo, N-carbamilo,  
C-amido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo,  
sulfonamido, trihalometilo, ureido, amino, y  $-NR^*R^y$ , en donde  
15  $R^*$  y  $R^y$  son como se define arriba.

Como se usa en la presente, un grupo  
"heteroalícíclico" 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,  
20 oxígeno y azufre. Los anillos se seleccionan de aquellos que  
proporcionan arreglos estables de enlaces y no se pretende  
que abarquen sistemas que no existirían. Los anillos también  
pueden tener uno o más enlaces dobles. Sin embargo, los  
anillos no tienen un sistema de electrón "pi" conjugado  
25 completamente. Ejemplos, sin limitación, de grupos

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heteroalíciclico son azetidínilo, piperídilo, piperazínilo, imidazolinilo, tiazolidínilo, 3-pirrolidin-1-ilo, morfolínilo, tiomorfolínilo y tetrahidropiránilo. Cuando se substituyen, los grupos sustituidos preferiblemente son uno o  
5 más seleccionados de alquilo, cicloalquilo, arilo, heteroarilo, heteroalíciclico, hidroxí, alcoxi, ariloxi, heteroariloxi, heteroalícicloxí, tiohidroxí, tioalcoxi, tioariloxi, tiorheteroariloxi, tiorheteroalícicloxí, ciano, halógeno, nitro, carbonilo, tiocarbonilo, O-carbámilo, N-carbámilo, O-tiocarbámilo, N-tiocarbámilo, C-amido, C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo, sililo, guanilo, guanidino, ureido, fosfonilo, amino y  $-NR^*R^y$ , en donde  $R^*$  y  $R^y$  son como se define  
10 arriba.

Un grupo "alquilo" se refiere a un hidrocarburo alifático saturado que incluye grupos de cadena lineal o ramificada. Preferiblemente, el grupo alquilo tiene 1 hasta 20 átomos de carbono alquilo (Cada vez que un intervalo numérico; por ejemplo, "1-20", se indique 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  
20 10 átomos de carbono. Más preferiblemente, es un alquilo  
25

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inferior que tiene 1 a 4 átomos de carbono. El grupo alquilo puede estar sustituido o no sustituido. Cuando se substituye, los grupos sustituidos son preferiblemente uno o más individualmente seleccionados de trihaloalquilo, 5 cicloalquilo, arilo, heteroarilo, heteroalícíclico, hidroxí, alcoxi, ariloxi, heteroariloxi, heteroalícícloxi, tiohidroxí, tioalcoxi, tioariloxi, tioheteroariloxi, tioheteroalícícloxi, ciano, halo, nitro, carbonilo, tiocarbonilo, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, 10 C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo, y combinados, un anillo heteroalícíclico de cinco o seis miembros.

Un grupo "cicloalquilo" se refiere a todos los 15 grupos de anillo monocíclico o fusionado de carbono (es decir, anillos que comparten un par adyacente de átomos de carbono) en donde uno o más anillos no tienen un sistema de electrón  $\pi$  conjugado completamente. Ejemplos, sin limitación, de grupos cicloalquilo son ciclopropano, 20 ciclobutano, ciclopentano, ciclopenteno, ciclohexano, ciclohexadieno, cicloheptano, cicloheptatrieno y adamantano. Un grupo cicloalquilo puede estar sustituido o no sustituido. Cuando se substituye, los grupos sustituyentes preferiblemente son uno o más individualmente seleccionados 25 de alquilo, arilo, heteroarilo, heteroalícíclico, hidroxí;

alcoxi, ariloxi, heteroariloxi, heteroalícicloxi, tiohidroxi,  
tioalcoxi, tioariloxi, tioleteroariloxi, tioleteroalícicloxi,  
ciano, halo, nitro, carbonilo, tiocarbonilo, O-carbamilo,  
N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido,  
5 C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo,  
sulfonilo, sulfonamido, trihalo-metansulfonamido,  
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,  
10 como se define en la presente, que consiste de al menos dos  
átomos de carbono y al menos un enlace doble de  
carbono-carbono.

Un grupo "alquinilo" se refiere a un grupo alquilo,  
como se define en la presente, que consiste de al menos dos  
15 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 tanto a un grupo  
-O-alquilo como a -O-cicloalquilo como se define en la  
20 presente.

Un grupo "ariloxi" se refiere tanto a un grupo  
-O-arilo como a -O-heteroarilo, como se define en la  
presente.

Un grupo "heteroariloxi" se refiere a un grupo  
25 heteroaril-O- con heteroarilo como se define en la presente.

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Un grupo "heteroalícicloxi" se refiere a un grupo heteroalíciclico-O- con heteroalíciclico como se define en la presente.

Un grupo "tiohidroxi" se refiere a un grupo -SH.

5 Un grupo "tioalcoxi" se refiere tanto a un grupo S-alquilo como a -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.

10 Un grupo "tioheteroariloxi" se refiere a un grupo heteroaril-S- con heteroarilo como se define en la presente.

Un grupo "tioheteroalícicloxi" se refiere a un grupo heteroalíciclico-S- con heteroalíciclico como se define en la presente.

15 Un grupo "carbonilo" se refiere a un grupo  $-C(=O)-R''$ , donde  $R''$  se selecciona del grupo que consiste de hidrógeno, alquilo, alquénilo, alquinilo, cicloalquilo, arilo, heteroarilo (enlazado a través de un anillo de carbono) y heteroalíciclico (enlazado a través de un anillo de carbono), como cada uno se define en la presente.

20 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.

25 Un grupo "ceto" se refiere a un grupo  $-CC(=O)C-$ , en

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donde el carbono en cualquiera o ambos lados de  $C=O$  puede ser alquilo, cicloalquilo, arilo o un carbono de un grupo heteroarilo o heteroalialcíclico.

5 Un grupo "trihalometancarbonilo" se refiere a un grupo  $Z_3CC(=O)-$  con Z que es 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.

10 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.

15 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.

20 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; es decir,  $-S(O)-$ .

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; es decir,  $-S(O)_2-$ .

25 Un grupo "S-sulfonamido" se refiere a un grupo  $-S(=O)_2NR^xR^y$ , con  $R^x$  y  $R^y$  como se define en la presente.



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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.

5 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.

10 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.

15 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.

20 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 "tioureido" se refiere a un grupo  $-NR^xC(=S)NR^yR^{y2}$  con  $R^x$  y  $R^y$  como se define en la presente y  $R^{y2}$  define el mismo como  $R^x$  y  $R^y$ .

25 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.

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Un grupo "guanilo" se refiere a un grupo  $R^*R^yNC(=N)-$ , con  $R^*$  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  
5 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  $-NR^*NR^yR^{y2}$   
con  $R^*$ ,  $R^y$  y  $R^{y2}$  como se define en la presente.

10 Cualquiera de dos grupos R adyacentes se puede  
combinar para formar un anillo arilo, cicloalquilo,  
heteroarilo o heterocíclico adicional fusionado al anillo que  
lleva inicialmente los grupos R.

Se conoce en la técnica que los átomos de nitrógeno  
15 en los sistemas heteroarilo pueden "participar en un 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 sustituirse como se  
20 entiende por los químicos en la técnica. La descripción y  
reivindicaciones de la presente invención se basan en los  
principios generales conocidos de enlace químico. Se  
entenderá que las reivindicaciones no abarcan estructuras  
conocidas que sean inestables o no capaces de existir con  
25 base en la literatura.

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Sales aceptables fisiológicamente y profármacos de compuestos descritos en la presente, están dentro del alcance de esta invención. El término "sal aceptable farmacéuticamente" como se usa en la presente y en las reivindicaciones, se pretende que incluya sales de adición de 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 carboxilato, con contraiones tal como amonio, sales de metal alcalino, particularmente sodio o potasio, sales de metal alcalinotérreo, particularmente calcio o magnesio, y sales con bases orgánicas apropiadas, tal como alquilaminas inferiores (metilamina, etilamina, ciclohexilamina, y similares) o con alquilaminas inferiores substituidas (por ejemplo, alquilaminas substituidas con hidroxilo, tal como dietanolamina, trietanolamina o tris(hidroximetil)-aminometano), o con bases tal como piperidina o morfolina.

En el método de la presente invención, el término

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"cantidad efectiva antiviral" significa la cantidad total de cada componente activo del método que es suficiente para mostrar un beneficio del paciente significativo, es decir, sanar las condiciones agudas caracterizadas por la inhibición de la infección de 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 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 presente y en las reivindicaciones, significan prevenir o aliviar enfermedades asociadas con la infección de VIH.

La presente invención también se dirige a combinaciones de compuestos con uno o más agentes útiles en el tratamiento de SIDA. Por ejemplo, los compuestos de esta invención pueden administrarse efectivamente, o en periodos de pre-exposición y/o post-exposición, en combinación con cantidades efectivas de antivirales de SIDA, inmunomoduladores, antiinfecciones o vacunas, tal como las de la siguiente tabla.

#### ANTIVIRALES

| <u>Nombre del Fármaco</u> | <u>Fabricante</u> | <u>Indicación</u>            |
|---------------------------|-------------------|------------------------------|
| 097                       | Hoechst/Byer      | infección por VIH, SIDA, ARC |

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|    |                                 |                                                 |                                                         |
|----|---------------------------------|-------------------------------------------------|---------------------------------------------------------|
|    |                                 |                                                 | (inhibidor de transcriptasa inversa (RT) no nucleósido) |
| 5  | Amprenivir<br>141 W94<br>GW 141 | Glaxo Wellcome                                  | Infección por VIH, SIDA, ARC (inhibidor de proteasa)    |
| 10 | Abacavir (1592U89)<br>GW 1592   | Glaxo Wellcome                                  | Infección por VIH, SIDA, ARC (inhibidor RT)             |
|    | Acemannan                       | Carrington Labs<br>(Irving, TX)                 | ARC                                                     |
| 15 | Acylovir                        | Burroughs<br>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                            |
| 20 | Adefovir dipivoxil<br>Al-721    | Gilead Sciences<br>Ethigen<br>(Los Angeles, CA) | Infección por VIH, ARC, PGL, VIH positivo, SIDA         |
| 25 | Alfa interferon                 | Glaxo Wellcome                                  | Sarcoma de Kaposi, VIH en combinación c/Retrovir        |

|    |                                                                        |                                             |                                                      |
|----|------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------|
|    | Ansamycin                                                              | Adria Laboratories                          | ARC                                                  |
|    | LM 427                                                                 | (Dublin, OH)                                |                                                      |
|    |                                                                        | Erbamont                                    |                                                      |
|    |                                                                        | (Stamford, CT)                              |                                                      |
| 5  | Anticuerpo que neutraliza el pH de interferón aberrante alfa inestable | Advance Biotherapy Concepts (Rockville, MD) | SIDA, ARC                                            |
| 10 | AR177                                                                  | Aronex Pharm                                | Infección por VIH, SIDA, ARC                         |
| 15 | Beta-fluoro-ddA                                                        | Nat'l Cancer Institute                      | Enfermedades asociadas con el SIDA                   |
| 20 | BMS-232623 (CGP-73547)                                                 | Bristol-Myers Squibb/Novartis               | Infección por VIH, SIDA, ARC (inhibidor de proteasa) |
| 25 | BMS-234475 (CGP-61755)                                                 | Bristol-Myers Squibb/Novartis               | Infección por VIH, SIDA, ARC (inhibidor de proteasa) |

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|    |                        |                                               |                                                   |
|----|------------------------|-----------------------------------------------|---------------------------------------------------|
|    | CI-1012                | Warner-Lambert                                | Infección por<br>VIH-1                            |
|    | Cidofovir              | Gilead Science                                | retinitis CMV,<br>herpes,<br>papilomavirus        |
| 5  | Sulfato de<br>curdlan  | AJI Pharma USA                                | Infección por<br>VIH                              |
|    | globina                | MedImmune                                     | Retinitis CMV                                     |
|    | Citomegalovirus        |                                               |                                                   |
| 10 | Inmuno<br>Cytovene     | Syntex                                        | Amenaza a la<br>visión                            |
|    | Ganciclovir            |                                               | CMV<br>Retinitis CMV<br>periférica                |
| 15 |                        |                                               |                                                   |
|    | Delaviridina           | Pharmacia-Upjohn                              | Infección por<br>VIH, SIDA, ARC<br>(inhibidor RT) |
| 20 |                        |                                               |                                                   |
|    | Sulfato de<br>dextrano | Ueno Fine Chem.<br>Ind. Ltd (Osaka,<br>Japón) | SIDA, ARC, VIH<br>asintomático<br>positivo        |
| 25 |                        |                                               |                                                   |

|    |                     |                  |                |
|----|---------------------|------------------|----------------|
|    | ddC                 | Hoffman-La Roche | Infección      |
|    | Didesoxicitidina    |                  | por VIH,       |
|    |                     |                  | SIDA, ARC      |
| 5  | ddI                 | Bristol-Myers    | Infección por  |
|    | Didesoxiinosina     | Squibb           | VIH, SIDA,     |
|    |                     |                  | ARC;           |
|    |                     |                  | combinación    |
|    |                     |                  | con AZT/d4T    |
| 10 | DMP-450             | AVID             | Infección por  |
|    |                     | (Camden, NJ)     | VIH, SIDA, ARC |
|    |                     |                  | (inhibidor de  |
|    |                     |                  | proteasa)      |
| 15 | Efavirenz           | DuPont Merck     | Infección por  |
|    | (DMP 266)           |                  | VIH, SIDA, ARC |
|    | (-)6-cloro-4-(S)-   |                  | (inhibidor RT  |
|    | ciclopropiletinil-  |                  | no nucleósido) |
|    | 4(S)-trifluoro-     |                  |                |
|    | metil-1,4,-dihidro- |                  |                |
| 20 | 2H-3,1-benzoxazin-  |                  |                |
|    | 2-ona, STOCRINE     |                  |                |
| 25 | EL10                | Elan Corp, PLC   | Infección por  |
|    |                     | (Gainesville,    | VIH            |
|    |                     | GA)              |                |



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|    |                                           |                                        |                                                                                                |
|----|-------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------|
|    | Famciclovir                               | Smith Kline                            | Herpes zoster,<br>Herpes simplex                                                               |
| 5  | FTC                                       | Emory University                       | Infección por<br>VIH, SIDA, ARC<br>(inhibidor de<br>transcriptasa<br>inversa)                  |
| 10 | GS 840                                    | Gilead                                 | Infección por<br>VIH, SIDA, ARC<br>(inhibidor de<br>transcriptasa<br>inversa)                  |
| 15 | HBY097                                    | Hoechst Marion<br>Roussel              | Infección por<br>VIH, SIDA, ARC<br>(inhibidor de<br>transcriptasa<br>inversa no<br>nucleósido) |
| 20 | Hypericin                                 | VIMRx Pharm.                           | Infección por<br>VIH, SIDA, ARC                                                                |
| 25 | Beta Interferón<br>Humano<br>Recombinante | Triton<br>Biosciences<br>(Alameda, CA) | SIDA, sarcoma<br>de Kaposi, ARC                                                                |

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|----|-------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
|    | Interferón alfa-<br>n3<br>Indinavir | Interferon<br>Sciences<br>Merck | ARC, SIDA<br><br>Infección por<br>VIH, SIDA, ARC,<br>VIH positivo<br>asintomático,<br>también en<br>combinación con<br>AZT/ddI/ddC |
| 5  |                                     |                                 |                                                                                                                                    |
| 10 | ISIS 2922                           | ISIS<br>Pharmaceuticals         | Retinitis CMV                                                                                                                      |
|    | KNI-272                             | Natl Cancer<br>Institute        | Enfermedades<br>asociadas con<br>VIH                                                                                               |
| 15 |                                     |                                 |                                                                                                                                    |
|    | Lamivudina, 3TC                     | Glaxo Wellcome                  | Infección por<br>VIH, SIDA, ARC<br>(inhibidor de<br>transcriptasa<br>inversa);<br>también con AZT                                  |
| 20 |                                     |                                 |                                                                                                                                    |
|    | Lobucavir                           | Bristol-Myers<br>Squibb         | Infección CMV                                                                                                                      |
| 25 |                                     |                                 |                                                                                                                                    |

|    |                                             |                                        |                                                                     |
|----|---------------------------------------------|----------------------------------------|---------------------------------------------------------------------|
|    | Nelfinavir                                  | Agouron<br>Pharmaceutical<br>s         | Infección por VIH,<br>SIDA, ARC<br>(inhibidor de<br>proteasa)       |
| 5  | Nevirapina                                  | Boeheringer<br>Ingleheim               | Infección VIH,<br>SIDA, ARC<br>(inhibidor RT)                       |
|    | Novapren                                    | Novaferon<br>Labs, Inc.<br>(Akron, OH) | Inhibidor de VIH                                                    |
| 10 | Secuencia de<br>Octapéptido de<br>Péptido T | Peninsula Labs<br>(Belmont, CA)        | SIDA                                                                |
| 15 | Fosfonoformiato<br>de trisodio              | Astra Pharm.<br>Products, Inc.         | Retinitis CMV,<br>infección por VIH,<br>otras infecciones<br>de CMV |
| 20 | PNU-140690                                  | Pharmacia-<br>Upjohn                   | Infección por VIH,<br>SIDA, ARC<br>(inhibidor de<br>proteasa)       |
|    | Probucol                                    | Vyrex                                  | Infección por VIH,<br>SIDA                                          |
| 25 | RBC-CD4                                     | Sheffield Med<br>Tech (Houston,<br>TX) | Infección por VIH,<br>SIDA, ARC                                     |

|    |                                                 |                                 |                                                               |
|----|-------------------------------------------------|---------------------------------|---------------------------------------------------------------|
|    | Ritonavir                                       | Abbott                          | Infección por<br>VIH, SIDA, ARC<br>(inhibidor de<br>proteasa) |
| 5  | Saquinavir                                      | Hoffman-La Roche                | Infección por<br>VIH, SIDA, ARC<br>(inhibidor de<br>proteasa) |
| 10 | Estavudina, d4T<br>dideshidrodesoxi<br>timidina | Bristol-Myers<br>Squibb         | Infección por<br>VIH, SIDA, ARC                               |
|    | Valaciclovir                                    | Glaxo Wellcome                  | Infecciones<br>Genital HSV &<br>CMV                           |
| 15 | Virazol<br>Ribavirin                            | Viratek/ICN<br>(Costa Mesa, CA) | VIH positivo<br>asintomático,<br>LAS, ARC                     |
| 20 | VX-478                                          | Vertex                          | Infección por<br>VIH, SIDA, ARC                               |
| 25 | Zalcitabina                                     | Hoffman-La Roche                | Infección por<br>VIH, SIDA,<br>ARC, con AZT                   |

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|    |                                                            |                         |                                                                                                |
|----|------------------------------------------------------------|-------------------------|------------------------------------------------------------------------------------------------|
|    | Zidovudina; AZT                                            | Glaxo Wellcome          | Infección por VIH,<br>SIDA, ARC, sarcoma<br>de Kaposi, en<br>combinación con<br>otras terapias |
| 5  | Sal de fumarato de<br>disoproxil de<br>Tenofovir (Viread®) | Gilead                  | Infección por VIH,<br>SIDA, (inhibidor de<br>transcriptasa<br>inversa)                         |
| 10 | Combivir®                                                  | GSK                     | Infección por VIH,<br>SIDA, (inhibidor de<br>transcriptasa<br>inversa)                         |
| 15 | Succinato de<br>abacavir (o Ziagen®)                       | GSK                     | Infección por VIH,<br>SIDA, (inhibidor de<br>transcriptasa<br>inversa)                         |
| 20 | Reyataz®<br>(o atazanavir)                                 | Bristol-Myers<br>Squibb | Infección por VIH,<br>SIDA, (inhibidor<br>de transcriptasa<br>inversa)                         |
| 25 | Fuzeon®<br>(o T-20)                                        | Roche/Trimeris          | Infección por VIH,<br>SIDA, inhibidor de<br>fusión viral                                       |

## INMUNOMODULADORES

|    | <u>Nombre del Fármaco</u> | <u>Fabricante</u>                        | <u>Indicación</u>                                                          |
|----|---------------------------|------------------------------------------|----------------------------------------------------------------------------|
|    | AS-101                    | Wyeth-Ayerst                             | SIDA                                                                       |
| 5  | Bropirimina               | Pharmacia-<br>Upjohn                     | SIDA avanzado                                                              |
|    | Acemannan                 | Carrington<br>Labs, Inc.<br>(Irving, TX) | SIDA, ARC                                                                  |
| 10 | CL246,738                 | American<br>Cyanamid<br>Lederle Labs     | SIDA, sarcoma<br>de Kaposi                                                 |
|    | EL10                      | Elan Corp, PLC<br>(Gainesville,<br>GA)   | Infección por<br>VIH                                                       |
| 15 | FP-21399                  | Fukui ImmunoPharm                        | Bloqueo de<br>fusión de VIH<br>con células<br>CD4+                         |
| 20 | Gamma Interferón          | Genentech                                | ARC, en<br>combinación<br>con w/TNF<br>(factor de<br>necrosis de<br>tumor) |
| 25 |                           |                                          |                                                                            |

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|    |                    |                  |                  |
|----|--------------------|------------------|------------------|
|    | Granulocito        | Genetics         | SIDA             |
|    | Factor de          | Institute Sandoz |                  |
|    | Etimulación de la  |                  |                  |
|    | Colonia de         |                  |                  |
| 5  | Macrófago          |                  |                  |
|    | Granulocito Factor | Hoechst-Roussel  | SIDA             |
|    | de Etimulación de  | Immunex          |                  |
|    | la Colonia de      |                  |                  |
|    | Macrófago          |                  |                  |
| 10 | Granulocito Factor | Schering-Plough  | SIDA,            |
|    | de Etimulación de  |                  | combinación con  |
|    | la Colonia de      |                  | w/AZT            |
|    | Macrófago          |                  |                  |
|    | Inmunoestimulante  | Rorer            | VIH seropositivo |
| 15 | de la partícula de |                  |                  |
|    | núcleo de VIH      |                  |                  |
|    | IL-2               | Cetus            | SIDA, en         |
|    | Interleucina-2     |                  | combinación con  |
|    |                    |                  | AZT              |
| 20 | IL-2               | Hoffman-La Roche | SIDA, ARC, VIH,  |
|    | Interleucina-2     | Immunex          | en combinación   |
|    |                    |                  | con AZT          |
|    | IL-2               | Chiron           | SIDA, incremento |
|    | Interleucina-2     |                  | en cuentas de    |
| 25 | (aldeslucina)      |                  | células CD4      |

|    |                    |                 |                |
|----|--------------------|-----------------|----------------|
|    | Inmuno globulina   | Cutter          | SIDA           |
|    | intravenosa        | Biological      | pediátrico, en |
|    | (humana)           | (Berkeley, CA)  | combinación    |
|    |                    |                 | con AZT        |
| 5  | IMREG-1            | Imreg           | SIDA, sarcoma  |
|    |                    | (New Orleans,   | de Kaposi,     |
|    |                    | LA)             | ARC. PGL       |
|    | IMREG-2            | Imreg           | SIDA, sarcoma  |
|    |                    | (New Orleans,   | de Kaposi,     |
| 10 |                    | LA)             | ARC. PGL       |
|    | Inmutiol dietil    | Merieux         | SIDA, ARC      |
|    | ditio carbamato    | Institute       |                |
|    | Alfa-2             | Schering Plough | Sarcoma de     |
|    | Interferon         |                 | Kaposi con     |
| 15 |                    |                 | AZT, SIDA      |
|    | Metionina-         | TNI             | SIDA, ARC      |
|    | encefalina         | Pharmaceutical  |                |
|    |                    | (Chicago, IL)   |                |
|    | MTP-PE Muramil-    | Ciba-Geigy      | Sarcoma de     |
| 20 | tripéptido         | Corp.           | Kaposi         |
|    | Factor estimulante | Amgen           | SIDA, en       |
|    | de la colonia de   |                 | combinación    |
|    | granulocitos       |                 | con AZT        |





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|    | Remune                           |    | Immune Response Corp.                            | Immunoterapéutico                                    |
|----|----------------------------------|----|--------------------------------------------------|------------------------------------------------------|
|    | rCD4                             |    | Genentech                                        | SIDA, ARC                                            |
| 5  | CD4 humano soluble recombinante  |    |                                                  |                                                      |
|    | Híbridos rCD4-IgG                |    |                                                  | SIDA, ARC                                            |
|    | CD4 humano soluble recombinante  |    | Biogen                                           | SIDA, ARC                                            |
| 10 | Interferón alfa 2a               |    | Hoffman-La Roche                                 | Sarcoma de Kaposi, SIDA, ARC, en combinación con AZT |
| 15 | SK&F106528 soluble               | T4 | Smith Kline                                      | Infección por VIH                                    |
|    | Timopentina                      |    | Immunobiology Research Institute (Annandale, NJ) | Infección por VIH                                    |
| 20 | Factor de Necrosis de Tumor; TNF |    | Genentech                                        | ARC, en combinación con gamma interferón             |
| 25 |                                  |    |                                                  |                                                      |

## ANTI-INFECCIOSOS

|    | <u>Nombre del</u><br><u>Fármaco</u>          | <u>Fabricante</u>              | <u>Indicación</u>                                    |
|----|----------------------------------------------|--------------------------------|------------------------------------------------------|
| 5  | Clindamicina con<br>Primaquina<br>Fluconazol | Pharmacia-Upjohn<br><br>Pfizer | PCP<br><br>Meningitis<br>criptococal,<br>candidiasis |
| 10 | Pastille,<br>Pastille Nystatin               | Squibb Corp.                   | Prevención de<br>candidiasis<br>oral                 |
|    | Ornidil<br>eflornitina                       | Merrell Dow                    | PCP                                                  |
| 15 | Pentamidina<br>Isetionato (IM y<br>IV)       | LyphoMed<br>(Rosemont, IL)     | Tratamiento de<br>PCP                                |
|    | Trimetoprim<br>Trimetoprim/sulfa             |                                | Antibacterial<br>Antibacterial                       |
| 20 | Piritrexim                                   | Burroughs<br>Wellcome          | Tratamiento de<br>PCP                                |
|    | Pentamidina<br>Isetionato para<br>Inhalación | Fisons<br>Corporation          | Prevención de<br>PCP                                 |
| 25 | Espiramicina                                 | Rhone-Poulenc<br>diarrea       | Criptosporidial                                      |

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|    |                                                                                |                                                          |                                                                                                           |
|----|--------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
|    | Intraconazol-<br>R51211                                                        | Janssen-Pharm                                            | Histoplasmosi<br>s;<br>cryptococcal                                                                       |
| 5  | Trimetrexato<br>Daunorubicin                                                   | Warner-Lambert<br>NeXstar, Sequus                        | PCP<br>Sarcoma de<br>Kaposi                                                                               |
| 10 | Eritropoietin<br>Humana<br>Recombinate                                         | Ortho Pharm.<br>Corp.                                    | Anemia severa<br>asociada con<br>terapia por<br>AZT                                                       |
| 15 | Hormona de<br>Crecimiento<br>Humano<br>Recombinante<br>Acetato de<br>Megestrol | Serono<br>Bristol-Myers<br>Squibb                        | Desgaste<br>relacionado<br>con el SIDA,<br>caquexia<br>Tratamiento<br>de anorexia<br>asociada con<br>SIDA |
| 20 | Testosterona<br>Nutrición<br>Enteral Total                                     | Alza, Smith<br>Kline<br>Norwich Eaton<br>Pharmaceuticals | Desgaste<br>relacionado<br>con el SIDA<br>Diarrea y<br>mala<br>absorción<br>relacionada<br>con SIDA       |

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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 entrada de VIH. Ejemplos de tales inhibidores de entrada de 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, May 2000, pp. 183-194 y en Inhibitors of the entry of HIV into host cells. Meanwell, Nicholas.; Kadow, John F. Current Opinion in Drug Discovery & Development (2003), 6(4), 451-461.

Específicamente los compuestos pueden utilizarse en combinación con otros inhibidores de enlace, inhibidores de fusión, y antagonistas receptores de quimiocina apuntados en el correceptor CCR5 ó CXCR4.

Se entenderá que el alcance de las combinaciones de los compuestos de esta invención con antivirales de SIDA, inmunomoduladores, anti-infecciones, inhibidores de entrada de VIH o vacunas, no se limita a la lista en la Tabla anterior, pero incluye en principio cualquier combinación con cualquier composición farmacéutica útil para el tratamiento de SIDA.

Las combinaciones preferidas son tratamientos simultáneos o alternativos con un compuesto de la presente invención y un inhibidor de proteasa de VIH y/o un inhibidor no nucleósido de transcriptasa inversa de VIH. Un cuarto

componente opcional en la combinaci3n es un inhibidor de nucle3sido de transcriptasa inversa de VIH, tal como AZT, 3TC, ddC o ddI. Un inhibidor preferido de proteasa de VIH es Reyataz® (ingrediente activo Atazanavir). Normalmente una

5 dosis de 300 hasta 600 mg se administr3 una vez al d3a. Esto puede ser co-administrado con una dosis baja de Ritonavir (50 hasta 500 mgs). Otro inhibidor preferido de proteasa de VIH es Kaletra®. Otro inhibidor 3til de proteasa de VIH es indinavir, que es la sal de sulfato de etanolato de N-(2(R)-

10 hidroxil-1-(S)-indanil)-2(R)-fenilmetil-4-(S)-hidroxil-5-(1-(4-(3-piridil-metil)-2(S)-N'-(t-butilcarboxamido)-piperazinil))-pentanamida, y se sintetiza de acuerdo con al documento U.S. 5,413,999. El indinavir generalmente se administra a una dosis de 800 mg tres veces al d3a. Otros inhibidores de

15 proteasa preferidos son nelfinavir y ritonavir. Otro inhibidor preferido de proteasa de VIH es saquinavir que se administra en una dosis de 600 o 1200 mg tid. Los inhibidores no nucle3sido preferidos de transcriptasa inversa de VIH incluyen efavirenz. La preparaci3n de ddC, ddI y AZT

20 tambi3n se describe en el documento EPO 0,484,071. Estas combinaciones pueden tener efectos inesperados en la limitaci3n de la propagaci3n y grado de infecci3n de VIH. Las combinaciones preferidas incluyen aquellas con indinavir con efavirenz siguiente (1), y opcionalmente, AZT y/o 3TC y/o

25 ddI y/o ddC; (2) indinavir, y cualquiera 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.

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#### 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 sigue:

|                                    |   |                        |
|------------------------------------|---|------------------------|
| h                                  | = | hora(s)                |
| rt                                 | = | temperatura ambiente   |
| mol                                | = | mol(es)                |
| mmol                               | = | milimol(es)            |
| 20 g                               | = | gramo(s)               |
| mg                                 | = | miligramo(s)           |
| mL                                 | = | mililitro(s)           |
| TFA                                | = | ácido trifluoroacético |
| DCE                                | = | 1,2-Dicloroetano       |
| 25 CH <sub>2</sub> Cl <sub>2</sub> | = | Diclorometano          |

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|    |                |   |                                                                   |
|----|----------------|---|-------------------------------------------------------------------|
|    | TPAP           | = | perrutenato de tetrapropilamonio                                  |
|    | THF            | = | Tetrahidrofurano                                                  |
|    | DEPBT=         |   | 3-(Dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona               |
| 5  | DMAP           | = | 4-dimetilaminopiridina                                            |
|    | P-EDC          | = | polímero soportado en 1-(3-dimetilaminopropil)-3-etilcarbodiimida |
|    | EDC            | = | 1-(3-dimetilaminopropil)-3-etilcarbodiimida                       |
| 10 | DMF            | = | N,N-dimetilformamida                                              |
|    | Base de Hunig  | = | N,N-Diisopropiletilamina                                          |
|    | MCPBA          | = | ácido meta-cloroperbenzoico                                       |
|    | azaíndol       | = | 1H-pirrólo-piridina                                               |
| 15 | 4-azaíndol     | = | 1H-pirrólo[3,2-b]piridina                                         |
|    | 5-azaíndol     | = | 1H-Pirrólo[3,2-c]piridina                                         |
|    | 6-azaíndol     | = | 1H-pirrólo[2,3-c]piridina                                         |
|    | 7-azaíndol     | = | 1H-pirrólo[2,3-b]piridina                                         |
|    | 4,6-diazaíndol | = | 5H-pirrólo[3,2-d]-pirimidina                                      |
| 20 | 5,6-diazaíndol | = | 1H-pirrólo[2,3-d]-piridazina                                      |
|    | 5,7-diazaíndol | = | 7H-pirrólo[2,3-d]-pirimidina                                      |
|    | PMB            | = | 4-Metoxibencilo                                                   |
|    | DDQ            | = | 2,3-Dicloro-5,6-diciano-1,4-benzoquinona                          |
| 25 | OTf            | = | Trifluorometansulfonoxi                                           |

|    |          |   |                               |
|----|----------|---|-------------------------------|
|    | NMM      | = | 4-metilmorfolina              |
|    | PIP-COPh | = | 1-benzoilpiperazina           |
|    | NaHMDS   | = | hexametildisilazida de sodio  |
|    | EDAC     | = | 1-(3-dimetilaminopropil)-3-   |
| 5  |          |   | etilcarbodiimida              |
|    | TMS      | = | Trimetilsililo                |
|    | DCM      | = | Diclorometano                 |
|    | DCE      | = | Dicloroetano                  |
|    | MeOH     | = | Metanol                       |
| 10 | THF      | = | Tetrahidrofurano              |
|    | EtOAc    | = | Acetato de etilo              |
|    | LDA      | = | Diisopropilamida de litio     |
|    | TMP-Li   | = | litio de 2,2,6,6-             |
|    |          |   | tetrametilpiperidinil         |
| 15 | DME      | = | Dimetoxietano                 |
|    | DIBALH   | = | hidruro de diisobutilaluminio |
|    | HOBT     | = | 1-hidroxibenzotriazol         |
|    | CBZ      | = | Benciloxicarbonilo            |
|    | PCC      | = | clorocromato de piridinio     |

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### Química

La presente invención comprende compuestos de  
Fórmula I, sus formulaciones farmacéuticas, y uso en  
pacientes que padecen de, o son susceptibles a, una infección  
25 por VIH. Los compuestos de Fórmula I incluyen sales



farmacéuticamente aceptables de los mismos.

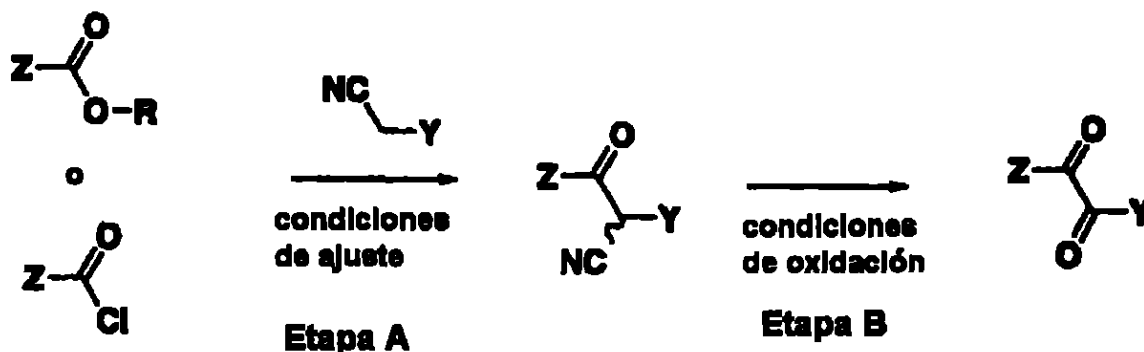
Los procedimientos de síntesis y actividades anti-VIH-1 de análogos que contienen diazaíndol oxoacético sustituido y piperidina, se describen abajo.

5 El esquema de reacción A detalla uno de los métodos preferidos para preparar los compuestos de la invención. En este método, como se muestra en la etapa A, un diazaíndol funcionalizado, el cual también es un éster de carboxi  
10 añadido a la posición 3, se condensó con un anión de acetonitrilo funcionalizado con Y para proporcionar los ejemplos alfa ciano cetona de la invención. La oxidación de estos compuestos como se muestra en la etapa B, proporciona compuestos adicionales de la invención.

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#### ESQUEMA DE REACCION A

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R se define en la descripción de la Etapa A

**Etapa A.** Los intermediarios de éster carboxílico Z-CO<sub>2</sub>R o más preferiblemente los cloruros ácidos Z-CO<sub>2</sub>Cl del  
25 Esquema de reacción A se condensan con un intermediario de

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cianometilo  $\text{YCH}_2\text{CN}$  bajo condiciones básicas para formar el intermediario  $\alpha$ -cianoceto  $\text{ZC(O)CH(CN)Y}$ . La base KHMDS en THF a temperatura ambiente se utiliza más frecuentemente, pero otras bases amida, tales como NaHMDS podrán utilizarse. El

5 solvente comúnmente utilizado es THF pero puede utilizarse DMF para moléculas menos solubles. Normalmente la reacción con un cloruro ácido  $\text{Z-CO}_2\text{Cl}$  se conduce con el matraz de reacción sumergido en un baño de enfriamiento de acetona y hielo seco ( $\sim -78^\circ\text{C}$ ) cuando THF es el solvente y un baño de

10 enfriamiento de acetonitrilo/acetona ( $\sim -42^\circ\text{C}$ ), cuando DMF es el solvente pero temperaturas entre  $-78^\circ$  y  $50^\circ\text{C}$  podrían utilizarse en casos apropiados. La reacción se agitó entre 1 hora y 1 día. Normalmente la reacción cuando se juzga que está completa por CCD o CL o CL/EM se mantiene a temperatura

15 fría y se agrega el oxidante directamente a la reacción como se describe en la Etapa B. Alternativamente la reacción podría permitirse que alcance temperatura ambiente y permitir que reaccione adicionalmente si es necesario y entonces enfriarse rápidamente, o enfriarse rápidamente en forma

20 inmediata con bicarbonato de sodio acuoso saturado. La mezcla podrá entonces extraerse con EtOAc, concentrarse y el intermediario  $\alpha$ -cianoceto  $\text{ZC(O)CH(CN)Y}$  podrá purificarse por CLAR preparativa. Cuando la misma reacción se lleva a cabo con un éster  $\text{Z-CO}_2\text{R}$  como reactivo, la reacción de alquilación

25 se inicia y entonces se permite usualmente que se entibie

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hasta temperatura ambiente para una reacción adicional. Normalmente R es metilo o etilo o menos idealmente otro grupo alquilo inferior. Los ésteres de fenoxi, pentafluorofenoxi, o Weinreb ( $R = -NH_2OMe$ ) pueden también utilizarse. Como se menciona arriba, en el evento en que los intermediarios de éster carboxílico  $Z-CO_2R$  son menos reactivos de lo deseado bajo condiciones de condensación estándar, pueden activarse por conversión inicial a un cloruro ácido  $Z-COCl$  (OR donde  $R = H$  se convierte a  $Cl$ ). Este es el método actualmente preferido para ésteres de diazaíndol de esta invención. La preparación de los cloruros ácidos de  $Z-CO_2R$  se realiza por hidrólisis inicial del éster al ácido carboxílico análogo  $Z-CO_2H$ . Un procedimiento normal involucra la agitación del éster con  $LiOH$  en THF y agua a  $100^\circ C$  durante 6 h hasta 2 días, concentrar la mezcla cruda y recristalizar el ácido carboxílico del agua. El ácido carboxílico  $Z-CO_2H$  se disuelve entonces o más normalmente se suspende en una suspensión en diclorometano y se agita con cloruro de oxalilo y una cantidad catalítica de DMF desde 4-24h pero normalmente durante la noche. Los solventes se eliminan *in vacuo* y el cloruro ácido se usa directamente. Los solventes alternativos posibles son benceno o tolueno. Un método alternativo posible para la conversión del ácido carboxílico a un cloruro ácido trae consigo la reacción de cloruro de tionilo en benceno a  $100^\circ C$  entre 2 h y 6 h con ácido en

presencia de DMF catalítico seguido por la concentración in vacuo para producir cloruro ácido  $Z\text{-CO}_2\text{Cl}$ . Como se menciona arriba, el cloruro ácido  $Z\text{-CO}_2\text{Cl}$  es el reactivo preferido para conducir la etapa A para la preparación de compuestos de diazindol de fórmula I. Alternativamente, el ácido puede convertirse en anhídridos ácidos los cuales también encuentran utilidad en la reacción de alquilación.

**Etapas B.** El método preferido para realizar la etapa B, la conversión del intermediario de  $\alpha$ -cianoceto  $ZC(O)CH(CN)Y$  a compuestos de diacarbonilo de fórmula I o intermediarios de cetoamida para preparar compuestos de fórmula I, es agregar 1-20 equivalentes pero más preferiblemente 5 equivalentes de una solución comercialmente disponible de ácido peracético al 32% en ácido acético acuoso diluido al matraz de reacción que contiene la reacción completa descrita en la Etapa A. La reacción es normalmente agitada a la misma temperatura a la cual se conduce la reacción de alquilación (para las reacciones de la Etapa A con cloruro ácido en THF  $\sim -78^\circ$  y para las reacciones de la etapa A en DMF  $\sim -42^\circ$ ) por un periodo de 1 hora y entonces permitir que se entibie hasta temperatura ambiente si no está aún a esa temperatura. La mezcla de reacción se permite entonces ya sea que reaccione adicionalmente o se diluya inmediatamente con cloruro de amonio acuoso saturado y EtOAc. Para productos ácidos relativamente insolubles que se

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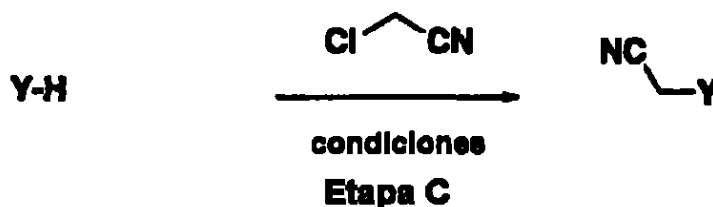
precipitan, el precipitado resultante se aísla por filtración como el producto oxoacetilo  $ZC(O)C(O)Y$ . Para productos de ácido soluble orgánico, el ácido se extrae en la capa orgánica y las capas se separan. La capa orgánica se concentra *in vacuo* y el producto se purifica vía CLAR preparativa. El intermediario  $\alpha$ -cianoceto  $ZC(O)CH(CH)Y$ , si aísla, se puede oxidar a un producto oxoacetilo  $ZC(O)C(O)Y$  usando una diversidad de oxidantes incluyendo mCPBA, NaOCl (blanqueador), ácido peracético o peróxido de níquel. En un procedimiento normal se agrega una solución de ácido peracético en ácido acético a una solución de intermediario  $\alpha$ -cianoceto  $ZC(O)CH(CN)Y$  en THF, y la reacción se agita entre temperatura ambiente y  $-70^{\circ}C$  por entre 30 minutos y 2 horas. Entonces se diluye la mezcla de reacción con cloruro de amonio acuoso saturado y EtOAc y se aísla el precipitado resultante por filtración como el producto oxoacetilo  $ZC(O)C(O)Y$ . Se puede combinar la etapa B y la etapa A en una reacción en un recipiente agregando el oxidante directamente al recipiente de reacción después de la terminación de la etapa A sin aislar el intermediario  $\alpha$ -cianoceto  $ZC(O)CH(CN)Y$ .

El esquema de reacción B detalla un método normal para la preparación de análogos de piperidina o piperazina de cianometilo utilizado en el esquema de reacción A. Dos referencias de literatura generales para parte de la química detallada en estos esquemas de reacción iniciales son

Takahashi, K; Shibasaki, K.; Ogura, K.; Iida, H.; Chem Lett. 1983, 859 o Yang; Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T.; Org. Lett. 2002, 4, 1103.

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## ESQUEMA DE REACCION B



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**Etapa C.** Amina secundaria de piperazina o piperidina funcionalizada se puede alquilar con haloacetoniitrilo bajo condiciones básicas, para producir un análogo de piperazina o piperidina de cianometilo. En un procedimiento normal se agrega piperizina de N-benzoil a una solución de cloroacetoniitrilo y TEA en THF y agita a temperatura ambiente por entre dos y cinco días. Se elimina el precipitado resultante por filtración, se concentra el filtrado *in vacuo* y el residuo es purificado por medio de cromatografía para producir el intermediario cianometilo  $\text{YCH}_2\text{CN}$ . La alquilación con haloacetoniitrilo también se puede llevar a cabo con una base alterna tal como 4-metilmorfolina o amina de diisopropiletil.

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Los coadyuvantes de condensación de éster diazaíndol carboxílico  $\text{Z-C(O)OR}$  utilizados en el esquema de reacción A se pueden preparar como se muestran en los

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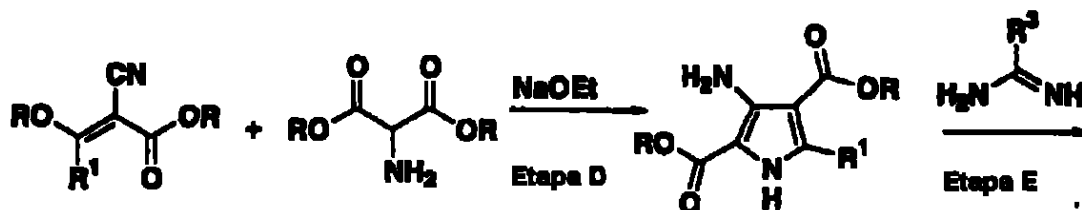
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siguientes esquemas de reacción:

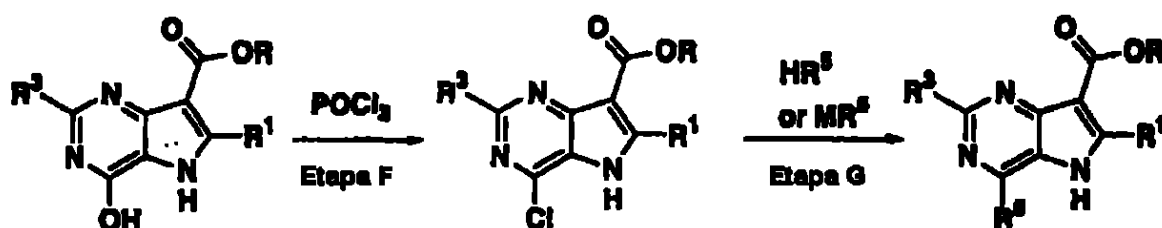
Un método preferido para la preparación de 4,6-diazaíndol se muestra en el esquema de reacción C.

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# ESQUEMA DE REACCION C



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R se define en la Etapa A

**Etapa D.** La reacción de (alquilmetileno)cianoacetato con un amino malonato bajo condiciones básicas se conoce para producir un éster-3-aminopirrol 2,4-dicarboxílico. Como se muestra en el esquema de reacción C, la etapa D se lleva acabo al reaccionar malonato de amino con 2-alcoxi 1-ciano acrilato en presencia de una base tal como etóxido de sodio. Para un ejemplo representativo ver; Elliot, A.J.; Montgomery, J. A., y Walsh, D.A. Tetrahedron Lett, 1996, 37(25), 4339-4340. Un procedimiento y condiciones normales se describen en la sección experimental.

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**Etapa E.** Éster 3-aminopirrol 2-carboxílico que resulta de la etapa D se puede ciclizar a 7-hidroxil-4,6-diazaíndol deseado usando diversos reactivos incluyendo formamidas dialquil acetal formamidas, nitrilos y formamidinas. En un procedimiento normal éster dietílico del ácido 3-aminopirrol-2,4-dicarboxílico y acetato de formamidina se calientan a reflujo en EtOH por 1 a 3 días. Se filtra en caliente la solución de reacción y el producto se cristaliza usualmente con enfriamiento y entonces se enjuaga con éter dietílico.

**Etapa F.** éster 3-carboxílico de 7-hidroxil-4,6-diazaíndol luego se puede convertir al análogo de 7 cloro por tratamiento con un reactivo de cloración tal como  $\text{POCl}_3$  o  $\text{SOCl}_2$ . En un procedimiento de reacción normal, 3-etiléster-7-hidroxil-4,6-diazaíndol y  $\text{POCl}_3$  se combinan y calientan a  $105^\circ\text{C}$  por entre 3 y 5 horas, se enfrían a temperatura ambiente y se diluyen con éter dietílico. Se recolecta el precipitado que se forma por filtración y se muestra que es 7-cloro-4,6-diazaíndol. Alternativamente, cuando se desea una mayor reactividad para una funcionalización adicional y para llevar a cabo la etapa G, el correspondiente 7-bromo-4,6-diazaíndol se puede preparar al sustituir  $\text{POBr}_3$  por agentes de cloración descritos arriba.

**Etapa G.** 7-cloro-4,6-diazaíndol se puede desplazar con una variedad de nucleófilos para formar los sustituyentes



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o intermediarios R<sup>5</sup> reivindicados a partir de los cuales los sustituyentes R<sup>5</sup> reivindicados se pueden formar. Se incluyen en estos cianuro, alcóxidos, aminas, alcoholes y varias especies metalizadas (cupratos, litiatos, zincatos, y reactivos de Grignard). En un procedimiento normal, 3-etiléster-7-cloro-4,6-diazaindol y 3-metil pirazol en EtOH se calientan entre 100°C y 140°C por 20 minutos hasta 1 hora. Al enfriar la reacción se concentra y se purifica por cromatografía en gel de sílice o por CLAR preparativa. Esta etapa también se puede llevar a cabo después de un acoplamiento inicial y las etapas de oxidación (etapas A y B) que se han realizado en el intermediario 3-etiléster-7-cloro-4,6-diazaindol. Se puede introducir una porción de ciano y convertirse a los ácidos, ésteres, amidas, amidatos, o heteroaromáticos. Se podría usar la metodología de acoplamiento de amida normal para preparar amidas a partir de ácidos. También se debe observar que la porción de halógeno se puede llevar a cabo hasta que se realicen los compuestos de la invención y entonces las condiciones descritas en la etapa G se pueden usar frecuentemente para usar compuestos adicionales de la invención.

Alternativamente, 7-cloro o 7-bromo-4,6-diazaindol se pueden acoplar a un heteroarilo estano o éster borónico por medio de una metodología Stille o Suzuki respectivamente. Otra metodología catalizada por metales tal como

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desplazamientos mediados por cobre se puede también usar para preparar derivados heteroaromáticos o heteroalíclicos enlazados a N. En general diazaíndoles sustituidos que contiene cloruro, bromuro, yoduro, triflato o fosfonato, se

5 deben someter a reacciones de acoplamiento con boronato (reacciones de tipo Suzuki) o estano para proporcionar diazaíndoles sustituidos. Estanos y boronatos, se preparan por medios de procedimientos de literatura estándar o como se describe en la sección experimental de esta solicitud.

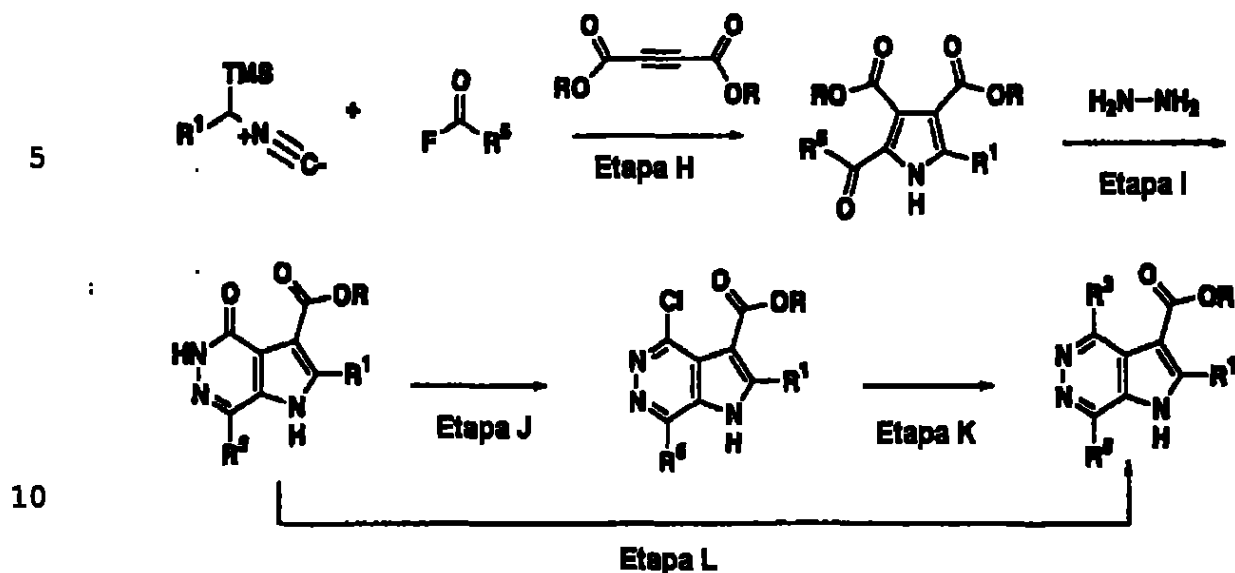
10 Bromuros, cloruros, triflatos, o fosfonatos de vinilo se pueden someter a acoplamiento mediado por metal para proporcionar compuestos de fórmula W-H. Son particularmente útiles los acoplamientos de Stille o Suzuki. Una discusión detalla de las referencias y mejores condiciones para estos

15 tipos de acoplamiento mediado por metal se describe más adelante en esta solicitud en donde la discusión se combina con una descripción de cómo se puede también usar estos tipos de reacciones para funcionalizar diazaíndoles. Además las solicitudes incorporadas en su totalidad en cualquier otra

20 parte en esta solicitud, contienen métodos para la preparación de heteroarilos a partir de grupos funcionales añadidos a indoles y azaíndoles. Esta metodología también es aplicable a diazaíndoles.

Un método potencial para la preparación de 5,6-  
25 diazaíndoles QCOOR se muestra en el esquema de reacción D.

## ESQUEMA DE REACCION D



R se define en la Etapa J

15 **Etapa H.** TMS-isocianuro reaccionaria con fluoruro ácido en presencia de dialquil acetileno bicarboxilato para formar pirrol sustituido. Para ejemplos representativos ver: Livinghouse, T.; Smith, R.; J. Chem. Soc., Chem. Commun 1983, 5, 210. En procedimiento normal, isocianuro de trimetilsililmetilo (generado a partir de la litiación de isiocianuro de metilo, seguido por sililación con TMSCl) se

20 agitaría con un fluoruro ácido de arilo y dimetilacetilenbicarboxilato en tolueno a 80°C. Después de una preparación estándar, un pirrol funcionalizado en donde R<sup>1</sup> es hidrógeno y R<sup>5</sup> es arilo se realizaría.

25 **Etapa I.** Una mezcla de ceto-diéster-pirrol y

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diclorohidrato de hidrazina en etanol calentada a reflujo debería resultar en la formación de 4-hidroxil-5,6-diazaíndol deseado. Alternativamente, ceto-diéster-pirrol, hidrato de hidrazina y una cantidad catalítica de ácido p-toluensulfónico se pueden calentar hasta reflujo en tolueno o benceno en presencia de una trampa Dean-Stark y con deshidratación, se debería formar 4-hidroxil-5,6-diazaíndol deseado.

**Etapas J, Etapa K y Etapa L.** Un intermediario 4-hidroxil-5,6-diazaíndol se puede convertir a intermediarios en los cuales  $R^3$  se modifica por funcionalización directa del grupo hidroxilo o por conversión del grupo hidroxilo a un grupo de partida (halógeno o triflato) seguido por un desplazamiento nucleofílico o un acoplamiento mediado por metal (Pd o Cu). Estas etapas podrían también llevarse a cabo después de las etapas de oxidación y acoplamiento iniciales (etapas A y B) que se han realizado en el intermediario 4-hidroxil-5,6-diazaíndol. Las condiciones descritas para la etapa G también se podrían utilizar para este sistema.

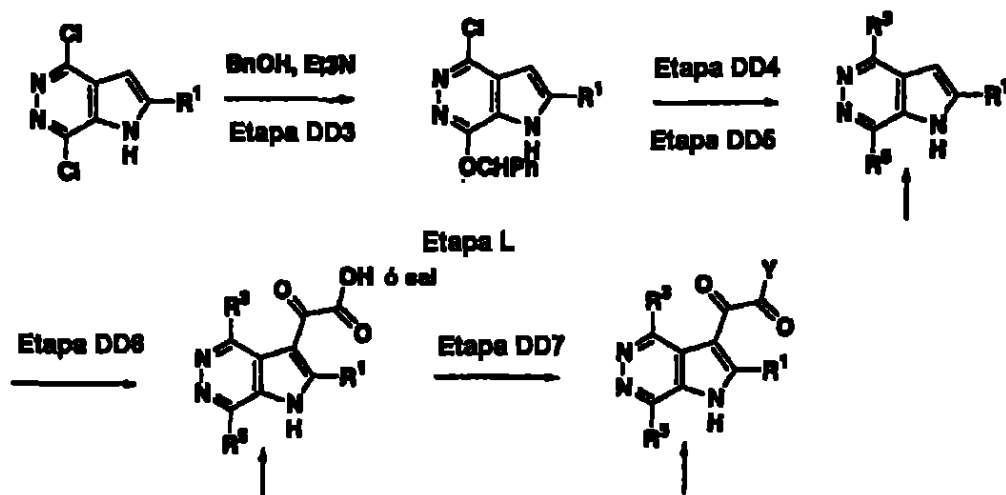
## ESQUEMA DE REACCION DD



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R se define en la Etapa J

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Como se muestra en el esquema de reacción DD etil éster de pirrol 2,3-di-carboxílico preparado como en cualquiera de las siguientes dos referencias: Roeder, Erhard; Wiedenfeld, Helmut; Bourauel, Thomas. Synthesis of ethil 2,3-bis(ethoxycarbonil)-1H-pyrrole-1-propionate. Liebigs Annalen der Chemie (1987), (12), 1117-19. y Swan, George A.; Waggott, A. Chemistry of melanins. VI. Syntheses of 3-carboxypyrrole-2-acetic acid, 3,5-dicarboxypyrrole-2-acetic acid, and related compounds. Journal of the Chemical Society [Section] C: Organic (1970), (2), 285-90, puede reaccionar con hidracina en etanol entre temperatura ambiente y reflujo para proporcionar el producto ciclizado de la etapa DD1. La reacción con cloruro de fosforilo (2.2 hasta 5 equivalentes deberá proporcionar dicloruro como se muestra en la etapa DD2. En la etapa DD3 la reacción selectiva de cloruro C-7

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podria ocurrir usando alcohol bencílico y trietilamina en un cosolvente tal como THF. En la etapa DD4, el grupo 4-cloro podria ser desplazado entonces con metóxido de sodio o potasio en solventes tales como metanol o tolueno o una  
5 mezcla. Se puede agregar yoduro de cobre I estequiométrico para acelerar reacciones lentas. En la etapa DD5, la  
hidrogenación selectiva del grupo bencilo usando de 5 hasta 10% de Pd/C en EtOH bajo una presión de globo de hidrogeno proporciona el compuesto 7-hidroxi. Alternativamente el  
10 grupo bencilo se puede dividir selectivamente con TMSI en acetonitrilo a temperaturas de 0 hasta 65°C o usando HBr en 1,2,dicloroetano a temperaturas desde -20 a 50°C. Una preparación alternativa es para hacer reaccionar el intermediario de dicloro anterior con metóxido mas que con  
15 alcohol bencílico y luego dividir selectivamente éter C-7 usando condiciones descritas para la división de bencilo. Al hacer reaccionar el grupo hidroxi C-7/tautómero de amida con POC13 o POBr3 generaría cloruro o bromuro selectivamente que se puede funcionalizar como se describe en la etapa G del  
20 esquema de reacción C para 4,6-diazindoles. La etapa DD6 describe la acilación del intermediario funcionalizado y se hace usando los mismos procedimientos descritos en la etapa O del esquema de reacción F. Etapa DD7, acoplamiento de amida con piperazina o piperidina se lleva a cabo de acuerdo a los  
25 procedimientos generales descritos en la etapa P del esquema

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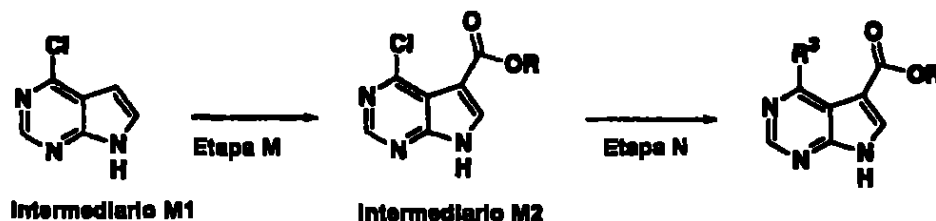
de reacción F, para proporcionar compuestos de la invención. Se debe entender que el orden de las etapas DD5-DD7 se puede intercambiar para determinar cual orden proporciona mejores producciones.

5                    5,7-diazaindol se puede preparar como se muestra en el esquema de reacción E. El intermediario M1 es un  
10 : compuesto conocido cuya síntesis se ha descrito en la literatura en las siguientes referencias: Olsen, David B.; Lafemina, Robert L; Eldrup, Anne B.; Bera, Sanjib. Methods  
of inhibiting orthopoxvirus replication with nucleoside  
compounds. PCT Int. Appl. (2003), 99 pp. WO 2003068244A1  
Mekouar, Khalid; Deziel, Robert; Mounir, Samir; Iyer,  
Radhakrishnan P. Preparation of 7-deaza L-nucleosides as  
antiviral agents against the hepatitis B virus. PCT Int.  
15 Appl. (2003), WO 2003055896A2 Carroll, Steven S.; Lafemina,  
Robert L; Hall, Dawn L; Himmelberger, Amy L; Kuo, Lawrence  
C.; Maccoss, Malcolm; Olsen, David B.; Rutkowski, Carrie A.;  
Tomassini, Joanne E.; An, Haoyun; Bhat, Balkrishen; Bhat,  
Neelima; Cook, Phillip Dan; Eldrup, Anne B.; Guinasso,  
20 Charles J.; Prhavc, Marija; Prakash, Thazha P. Preparation  
of nucleoside derivatives as inhibitors of RNA- dependent RNA  
viral polymerase. PCT Int. Appl. (2002), 235 pp CODEN:  
PIXXD2 WO 2002057425A2 Carroll, Steven S.; Maccoss, Malcolm;  
Olsen, David B.; Bhat, Balkrishen; Bhat, Neelima; Cook,  
25 Phillip Dan; Eldrup, Anne B.; Prakash, Thazha P.; Prhavc,

Marija; Song, Quanlai. Preparation of nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase. PCT Int. Appl. (2002), WO 2002057287 A2.

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## ESQUEMA DE REACCION E



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**Etapa M.** acilación Friedel-Crafts de diazindol.

El intermediario M2 en donde R es etilo es un compuesto conocido que se puede preparar como se describe en las siguientes tres referencias de la literatura:

Ugarkar, Bheemarao G.; DaRe, Jay M.; Kopcho, Joseph J.; Browne, Clinton E., III; Schanzer, Juergen M.; Wiesner, James B.; Erion, Mark D. Adenosine Kinase Inhibitors. 1. Synthesis, Enzyme Inhibition, and Anti-seizure Activity of 5-Iodotubercidin Analogues. Journal of Medicinal Chemistry (2000), 43(15), 2883-2893.

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Firestein, Gary Steven; Ugarkar, Bheemarao Ganapatrao; Miller, Leonard Paul; Gruber, Harry Edward; Bullough, David Andrew; Erion, Mark David; Castellino, Angelo John. Preparation of adenosine kinase-inhibiting purine nucleoside analogs as antiinflammatory agents. PCT Int. Appl. WO 9417803A1.

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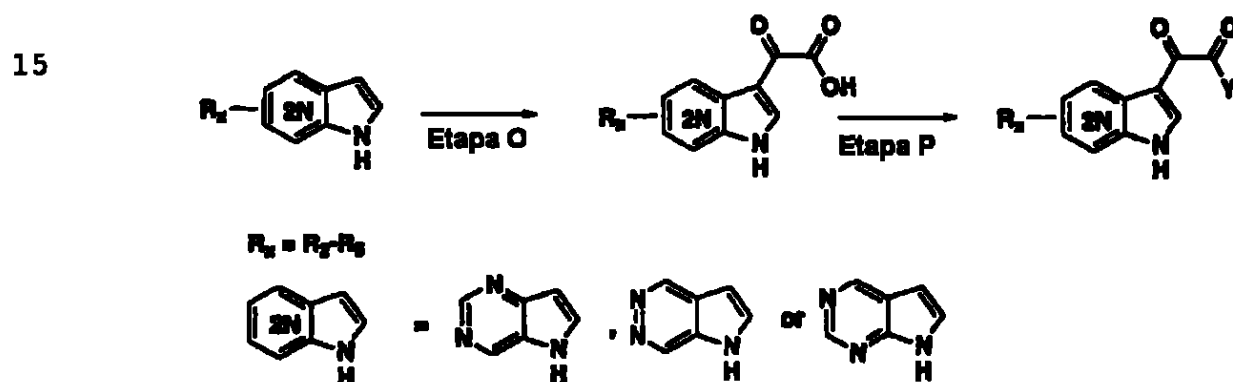
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Browne, Clinton E.; Ugarkar, Bheemarao G.; Mullane, Kevin M.; Gruber, Harry E.; Bullough, David A.; Erion, Mark D.; Castellino, Angelo. Adenosine kinase inhibitors. Eur. Pat. Appl. EP 496617 A1.

5 **Etapla N.** La sustitución nucleofílica o catalizada por metal de 4-cloro-5,7-diazaindol producirá los sustituyentes  $R^3$  de la reivindicación 1.

El núcleo de diazaíndol se puede acoplar a la piperidina o piperazina funcionalizada a través de un oxoacetato o a través de un proceso de acilación/amidación  
10 como se muestra en el esquema de reacción F.

#### ESQUEMA DE REACCION F



**Etapla O.** La conversión de 3H-diazaindol específico a cetoácido detallado se podría lograr por diversos métodos. **Método A para la etapa O:** Un método exitoso ha sido usar condiciones de acilación Fridel-Crafts mediadas por un  
25 líquido iónico. En particular el líquido iónico

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cloroaluminato de 1-alquil-3-alquilimidazol es generalmente útil para promover una asilación de tipo Friedel-Crafts y trabaja con algunos diazandoles. El líquido iónico se genera al mezclar cloruro de 1-aqluil-3-alquilimidazolio con cloruro de aluminio a temperatura ambiente con agitación vigorosa. Se prefiere una relación molar de 1:2 o 1:3 de cloruro de 1-alquil-3-alquilimidazolio a cloruro de aluminio. Un cloroaluminato de imidazol particularmente útil para la acilación de diazaídoles con clorooxoacetato de metilo o etilo sería el cloroaluminato de 1-etil-3-metilimidazol. La reacción se realizaría normalmente a temperatura ambiente y el éster de diazaíndolglioxilo se esperaría que se aislara. El éster resultante entonces se puede hidrolizar usando métodos de hidrólisis para la etapa O abajo descrita.

15 Mas convenientemente es probable que éster de glioxilo se pueda hidrolizar in situ a temperatura ambiente con un tiempo de reacción prolongado (normalmente durante la noche) para dar el ácido de glioxilo correspondiente que estaría listo para la formación de amida.

20 Un procedimiento experimental representativo es como sigue: cloruro de 1-etil-3-metilimidazolio (2 equivalentes adquiridos de TCI, que se pesan bajo una corriente de nitrógenos) se agitaría en una matraz de fondo redondo secado al horno a temperatura ambiente bajo una atmósfera de nitrógeno, y luego cloruro de aluminio (6

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equivalentes; polvo anhidro empacado bajo argón en ampollitas adquiridas de Aldrich preferidas, se agregaría, después de pesarlas bajo una corriente de nitrógeno). La mezcla se agitaría vigorosamente para formar un líquido, al cual entonces se agregaría diazaíndol (1 equivalente) seguido por agitación hasta que resulte una mezcla homogénea. Luego se agregaría a la mezcla de reacción gota a gota cloroacetato de etilo o de metilo (2 equivalentes) y luego continuaría la agitación a temperatura ambiente por 2 a 24 horas probablemente aproximadamente 16 horas. Después de que se termina la agitación, la mezcla en un baño de agua con hielo y la reacción se enfriarían rápidamente al agregar cuidadosamente agua en exceso. Se filtraría los precipitados, se lavan con agua y se secan bajo alto vacío para dar el ácido diazaíndolglioxílico. Para algunos ejemplos, se puede requerir 3, o equivalentes uniformes de cloruro 1-etil-3-metilimidazolio y cloroacetato. Una referencia mas extensa con ejemplos análogos sin diazaíndoles pero con condiciones que se utilizarían con diazaíndoles esta contenida en: Yeung, Kap-Sun; Farkas, Michelle E.; Qiu, Zhilei; Yang, Zhong. Friedel-Crafts acylation of indoles in acidic imidazolium chloroaluminate ionic liquid at room temperature. Tetrahedron Letters (2002), 43(33), 5793-5795.4 Related references: (1) Welton, T. Chem Rev. 1999, 99, 2071; (2) Surette, J. K. D.; Green, L; Singer, R. D. Chem. Commun.

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1996, 2753; (3) Saleh, R. Y. WO 00/15594.

**Etapas O, método B.** Diazaindol se puede tratar con un reactivo de Grignard tal como MeMgI (metil magnesio yoduro), metil magnesio bromuro o etil magnesio bromuro y entonces un halogenuro de zinc tal como ZnCl<sub>2</sub> (Cloruro de zinc) o bromuro de zinc seguido por la adición de monoéster de cloruro de oxalilo tal como ClCOCOOME (clorooxoacetato de metilo) u otro éster como el anterior, para producir éster de glioxil de diazaindol. Ésteres de ácido oxálico tal como el oxalato de metilo, oxalato de etilo o anteriores se usan. Solventes apróticos tales como CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, benceno, tolueno, DCE, THF, dioxano o similares se pueden usar potencialmente solos o en combinación para esta secuencia.

**Etapas O, método C.** Una reacción Friedel-Crafts catalizada por ácido Lewis bajo condiciones estándar con un cloroacetoacetato de alquilo se podría utilizar. Esto se puede seguir por hidrólisis in situ de éster por el método abajo descrito para formar ácido cetocarboxílico de diazaindol (citar las patentes previas). Así, los precursores de cetoéster de diazaindol para el ácido detallado se pueden preparar por reacción de diazaindoles con un exceso de ClCOCOOME en presencia de AlCl<sub>3</sub> (cloruro de aluminio). Algunas descripciones adicionales de los procedimientos exactos para llevar a cabo esta reacción pero sobre índoles o azaindoles están contenidas en Zhang, Zhongxing; Yang, Zhong;

Wong, Henry; Zhu, Juliang; Meanwell, Nicholas A.; Kadow, John F.; Wang, Tao. "An Effective Procedure for the Acylation of Azaindoles at C-3." J. Org. Chem. 2002, 67(17), 6226-6227; b) Tao Wang et al. Patente Norteamericana 6,476,034 B2

5 "Antiviral Azaindole derivatives" publicado el 5 de noviembre de 2002; c) W. Blair et al. Solicitud de patente PCT WO 00/76521 A1 publicada el 21 de diciembre de 2000; d) O. Wallace et al. solicitud PCT WO 02/04440A1 publicada el 17 de enero de 2002. Algunas reacciones de 5-ciano-6-cloro-7-

10 azaindoles y tautomerismo de lactama-lactima en 5-ciano-6-hidroxi-7-azaindolines. Khim. Geterotsikl. Soedin., 1987, 100-106). Normalmente un solvente inerte tal como CH<sub>2</sub>Cl<sub>2</sub> se usaría pero otros tales como THF, Et<sub>2</sub>O, DCE, dioxano, benceno o tolueno pueden encontrar la aplicación ya sea solos o en

15 mezclas. Otros ésteres de oxalato tal como monoésteres de etilo o bencilo de ácido oxálico pueden también ser suficientes para el método arriba mostrado. La mayoría de ésteres lipofílicos facilitan el aislamiento durante extracciones acuosas. Los catalizadores ácidos de Lewis tal

20 como tetracloruro de estaño, cloruro de titanio IV y cloruro de aluminio se pueden utilizar con esta transformación con cloruro de aluminio siendo el más preferido.

**Métodos de hidrólisis para la Etapa :** La hidrólisis de metiléster de cetodiazindol daría una sal de

25 potasio del producto ácido que se muestra como el producto

para la Etapa O en el esquema de reacción F, y esta entonces estaría lista para el acoplamiento con aminas como se muestra en la siguiente etapa. La acidificación durante la preparación, normalmente con HCl acuoso proporcionaría productos ácidos de la etapa O como se muestran. Algunas condiciones normales utilizan hidróxido de sodio metanólico o etanólico seguido por una acidificación cuidadosa con ácido clorhídrico acuoso de una molaridad variable pero se prefiere HCl 1M. No se utiliza la acidificación en muchos casos como se describe arriba para las condiciones preferidas. El hidróxido de litio o hidróxido de potasio también se pueden utilizar y se pueden agregar cantidades variables de agua a alcoholes. También se pueden usar butanoles o propanoles como solventes. Temperaturas elevadas hasta puntos de ebullición de los solventes se pueden utilizar sino son suficientes las temperaturas ambiente. Alternativamente la hidrólisis se puede llevar a cabo en un solvente no polar tal como  $\text{CH}_2\text{Cl}_2$  o THF en presencia de Triton B. Las temperaturas de  $-78^\circ\text{C}$  hasta el punto de ebullición del solvente se pueden utilizar pero se prefiere  $-10^\circ\text{C}$ . Otras condiciones para la hidrólisis de éster se enlistan en la referencia 41 y ambas de estas referencias y muchas condiciones para la hidrólisis de éster son bien conocidas por los químicos de experiencia promedio en la técnica.

**Etapa P.** Se puede acoplar ácido cetocarboxílico

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con piperidinas o piperazinas funcionalizadas usando diversos reactivos de acoplamiento que forman un enlace péptido o enlace amida estándar. El intermediario ácido Z-C(O)(O)OH del esquema de reacción F se puede acoplar con una piperazina o piperadina substituida, H-Y usando reactivos de acoplamientos que forman el enlace de péptido o el enlace de amida. La combinación de EDAC y trietilamina en tetrahidrofurano o BOPCl y diisopropil etil amina en cloroformo se puede utilizar pero DEPBT u otros reactivos de acoplamiento tales como PyBop se pueden utilizar. Otra condición de acoplamiento útil utiliza HATU (L.A. Carpino et al. J. Chem. Soc. Chem. Comm. 1994,201-203; A. Virgilio et al. J. Am. Chem. Soc. 1994, 116, 11580-11581). Un procedimiento general para usar este reactivo es ácido (1 equivalente) y H-Y o H-W-Boc o sal de HCl (2 equivalente) en DMF, son agitados a temperatura ambiente por entre una hora y 2 días. Se agrega HATU (2 equivalentes) en una porción y entonces DMAP (3 equivalentes). La reacción se puede agitar a temperatura ambiente por 2 a 15 horas (progreso de reacción monitoreado por métodos estándar es decir CCD, CL/EM). La mezcla se filtra a través de papel filtro para recolectar el sólido. Se concentra el filtrado y se agrega agua. Se filtra nuevamente la mezcla y se lava el sólido con agua. Se combina el sólido y se lava con agua. Se conocen muchos reactivos para acoplamiento de enlace de amida por un químico

orgánico experto en la técnica y casi todos ellos se aplican para realizar productos de amida acoplados.

DEPBT (3-(dietoxifosfiriloxi)-1,2,3-benzotriazin-4(3H)-ona) y N,N-diisopropiletilamina, comúnmente conocidos como base de Hunig, representan otro método eficiente para formar el enlace de amida (etapa P). DEPBT se adquiere de Adrich o se prepara de acuerdo al procedimiento de Ref. 28, Li, H.; Jiang, X.; Ye, Y.- H.; Fan, C.; Romoff, T.; Goodman, M. Organic Lett., 1999, 1, 91-93. Normalmente se usa un solvente inerte tal como DMF o THF pero se pueden usar otros solventes apróticos.

La reacción de construcción de enlace de amida, se puede llevar a cabo usando las condiciones preferidas antes descritas, condiciones EDC abajo descritas, otras condiciones de acoplamiento descritas en esta solicitud o alternativamente al aplicar las condiciones o reactivos de acoplamiento para la construcción del enlace de amida descritas en las solicitudes incorporadas para la construcción de sustituyentes R<sub>2</sub>-R<sub>5</sub> en indoles o azaindoles. Se dan en esta solicitud algunos ejemplos no limitantes específicos.

Alternativamente, el ácido se puede convertir a metilo éster usando diazometano en exceso en THF/éter. Éster de metilo en THF seco puede hacer reaccionar con amida de litio del intermediario H-Y. La amida de litio de H-Y, Li se



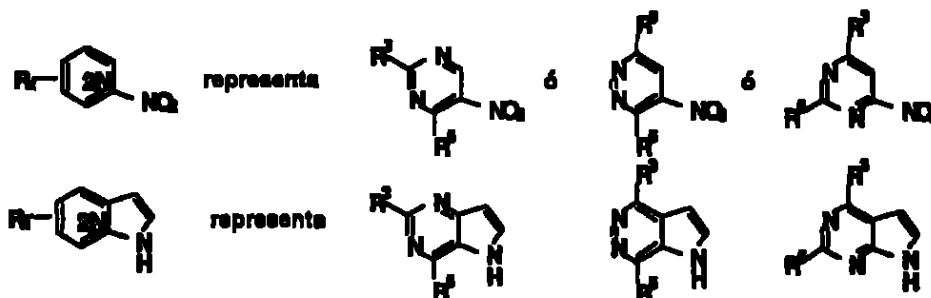
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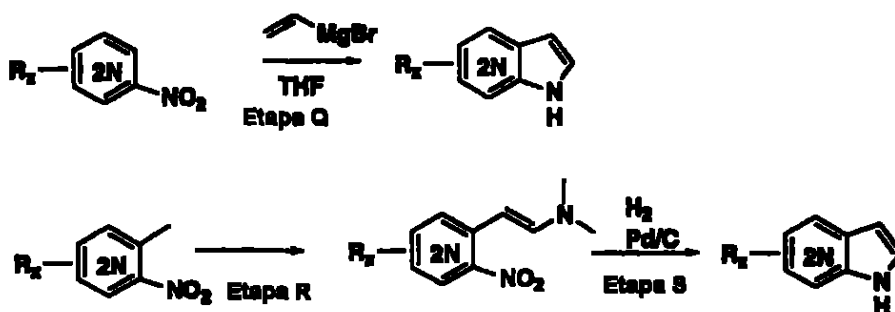
forma al hacer reaccionar H-Y con bistrimetilsililamida de litio en THF por 30 minutos en un baño de enfriamiento de agua con hielo. Se pueden formar similarmente amidas de sodio o potasio y utilizarse si se desea una reactividad adicional. Se pueden utilizar otros ésteres tal como etilo, fenilo o pentafluorofenilo y se formarían utilizando la metodología estándar.

Además, el ácido se puede convertir a cloruro de ácido usando cloruro de oxalilo en un solvente tal como benceno o cloruro de tionilo ya sea puro o que contiene una cantidad catalítica de DMF. Se pueden utilizar temperaturas entre 0°C y reflujo dependiendo del sustrato. Se pueden obtener compuestos de fórmula I a partir de compuestos resultantes de fórmula Z-C(O)(O)Cl por la reacción con H-Y adecuado en presencia de amina terciaria (3-10 equivalentes) tal como trietilamina o diisopropiletilamina en un solvente aprótico anhidro tal como diclorometano, dicloroetano, éter de dietilo, dioxano, THF, acetonitrilo, DMF o similares a temperaturas que van desde 0°C hasta reflujo. Son más preferidos diclorometano, dicloroetano o THF. La reacción se puede monitorear por CL/EM. También se pueden preparar 3H-diazaíndoles bajo condiciones de reacción de Bartoli o Liemgruber-Batchko como se muestra en el esquema de reacción G. Las condiciones para llevar a cabo estas reacciones están contenidas en las solicitudes de patentes incorporadas.

NOTA: Para propósitos de brevedad, el siguiente símbolo se toma para representar los siguientes sistemas:



### ESQUEMA DE REACCION G



$R_1 = H$

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Etapa Q. La etapa Q en el esquema de reacción G detalla una síntesis potencial de un intermediario de diazaindol por medio de la reacción de Bartoli bien conocida en la cual el bromuro de vinil magnesio reacciona con grupos nitro de arilo o heteroarilo para formar un anillo que contiene nitrógeno de 5 miembros como se muestra. Algunas referencias para la transformación anterior para formar un anillo de indol incluyen Bartoli et al. a) Tetrahedron Lett. 1989, 30, 2129. b) J. Chem. Soc. Perkin Trans. 1 1991, 2757.

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c) J. Chem. Soc. Perkin Trans. II 1991, 657. d) SynLett

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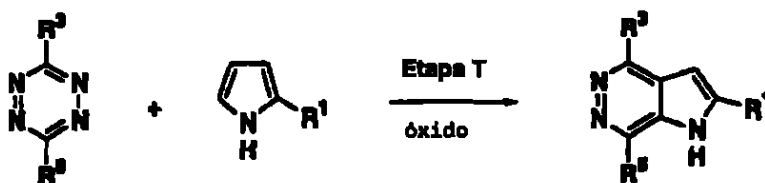
(1999), 1594. En el procedimiento preferido, que se puede aplicar a la síntesis de diazaindol, se agrega una solución de bromuro de vinil magnesio en THF (normalmente 1.0M pero desde 0.25 a 3.0M) gota a gota a una solución de nitropiridina en THF a  $-78^{\circ}$  bajo una atmósfera inerte de ya sea nitrógeno o argón. Después de que se termina la adición, la temperatura de reacción se deja entibiar hasta  $-20^{\circ}$  y entonces se agita por aproximadamente 12 horas antes de enfriar rápidamente con una solución de cloruro de amonio acuosa al 20%. La reacción se extrae con acetato de etilo y entonces se prepara con una forma típica usando un agente de secado tal como sulfato de magnesio anhidro o sulfato de sodio. Los productos se purifican generalmente usando cromatografía sobre gel de sílice. Se alcanzan generalmente mejores resultados usando bromuro de vinil magnesio recientemente preparado. En algunos casos el cloruro de vinil magnesio se puede sustituir por bromuro de vinil magnesio.

**Etapas R.** La reacción con dimetilformamida dimetil acetal en un solvente inerte o bajo condiciones puras para formar precursores Batcho-Leimgruber proporcionaría el precursor de ciclización 33 como se muestra. Una condición normal utilizaría 20% de DMF dimetil acetal en DMF calentado a  $105-110^{\circ}\text{C}$ . Aunque la etapa se anticipa para trabajar como se muestra, la piridina se puede oxidar a N-óxido previo a la

reacción usando un perácido tal como MCPBA o un oxidante más potente tal como ácidos meta-trifluorometilo o meta nitro peroxibenzoico.

**Etapas S.** Reducción del grupo nitro usando por ejemplo hidrogenación sobre un catalizador de platino sobre carbono en un solvente tal como MeOH, EtOH o EtOAc podría proporcionar el producto ciclisado. Generalmente se requeriría solo una presión positiva ligera de hidrogeno (una corriente) pero se pueden necesitar presiones superiores (1.5 atm). Alternativamente la reducción se puede llevar a cabo usando, dicloruro de estaño y HCl, hidrogenación sobre níquel Raney u otros catalizadores o al usar otros métodos para la reducción nitro tal como se describe en alguna otra parte en esta solicitud.

Otro método posible para la preparación de 5,6-diazaíndoles se muestra en el esquema de reacción H.



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**Etapas T.** 1,2,3,4-tetrazinas han mostrado reaccionar con pirrol y pirroles sustituidos para formar productos de 5,6-diazaíndol. Esta reacción procede a través de un ciclo adición [4+2] seguida por una retrociclo adición [4+2] para liberar el gas de nitrógeno y una oxidación

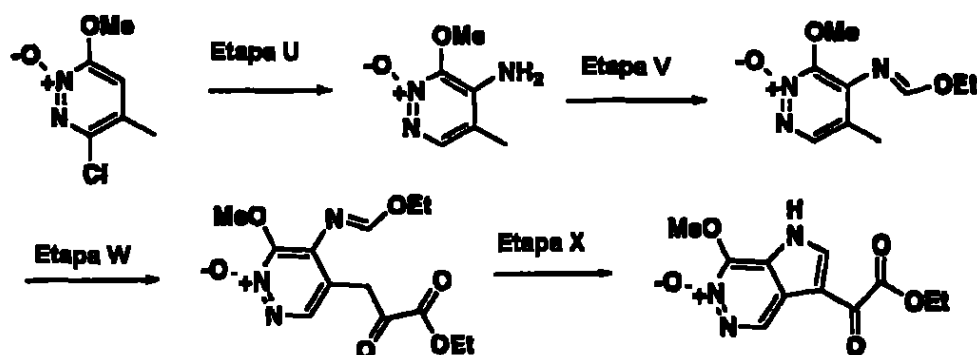
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adicional para establecer aromaticidad. Para ejemplos representativos ver: Seitz, Z.; Kaempchen, T.; Arch. Pharm. 1978, 311, 728. Takahashi, M; Ishida, H.; Kohmoto, M. Bull. Chem. Soc. Japan 1976, 49, 1725. Benson, S. C.; Palabrica, C. A.; Snyder, J. K. J. Org. Chem. 1987, 52, 4610. Gonzalez, J. C.; Lobo-Antunes, J; Perez-Lourido, P.; Santana, L; Uriate, E. Synthesis 2002, 4, 475-478.

Otro método posible para la preparación de 5,6-diazaindol con oxoacetato C-3 se muestra en el esquema de reacción I (Cook, P. D.; Castle, R. N. J. Het. Chem. 1973, 10, 551).

#### ESQUEMA DE REACCION I

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**Etapa U.** El N-óxido de piridazina de inicio, se nitraría inicialmente y el grupo nitro resultante entonces se reduciría bajo condiciones estándar a una amina. El cloro entonces se eliminaría bajo condiciones de hidrogenación. Alternativamente, el cloro puede permanecer en la molécula y

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llevarse a través de las etapas posteriores. Esto debe permitir la formación de 4-cloro-5,6-diazaindol. El cloro entonces se puede convertir a un grupo metoxi o amino por desplazamiento nucleofílico o acoplamiento asistido catalizado por cobre. Esto resultaría en un intermediario que se puede convertir a moléculas reivindicadas dentro de esta solicitud por medio del acoplamiento de enlace de amida previamente descrito.

**Etapas V.** La amina se puede entonces funcionalizarse con ortoformiato de etilo bajo condiciones ácidas para formar etoxiimina. En un procedimiento normal la amina y ortoformiato de trietilo se disolvieron en una solución de DMF y etanol que se había ajustado a pH 1 con cloruro de hidrogeno anhidro. La reacción entonces se calienta a 150-160°C y se recolecta el etanol por destilación resultando en la reacción de etoxiimina deseada.

**Etapas W.** Desprotonación del grupo metilo seguida por acilación con oxalato de dietilo produciría un intermediario de cetoéster que se puede usar para formar un 3-oxoacetato-5,6-diazaindol (Etapas X) o se puede usar para hacer un 2-carboxilato-5,6-diazaindol por hidrólisis de la imina, seguido por la condensación de la amina sobre la acetona de cinco centros alejados.

**Etapas X.** El cetoéster entonces se puede ciclisar en etoximina bajo condiciones básicas para llegar a

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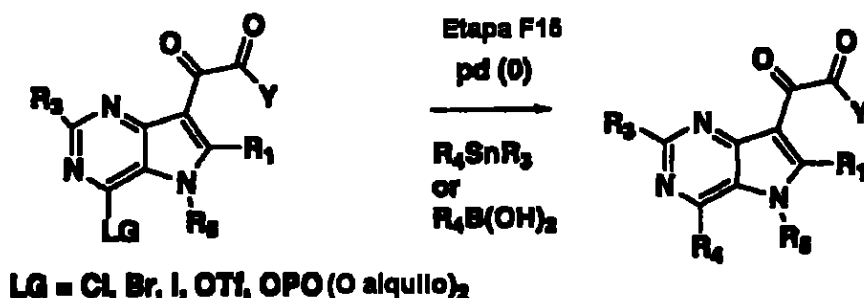
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3-oxoacetato-5,6-diazaindol. Para formar las moléculas de esta reivindicación, la piperazina o piperadonas funcionalizadas se pueden acoplar al éster a través de reacciones que forma enlace de amida estándar. Este esquema de reacción general también se debe permitir para la preparación de otros intermediarios de 5,6-diazaindol con diferentes sustituyentes  $R^3$  y  $R^5$  por el desplazamiento o acoplamiento al cloro o desplazamiento de metoxi en algún punto en la secuencia.

Preparaciones de piperazinas y piperidinas funcionalizadas se describen después en la solicitud.

#### ESQUEMA DE REACCION 15

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#### Etapa F15

Como se muestra anteriormente en el esquema de reacción 15, etapa F15, diazaindoles sustituidos que contienen cloruro, bromuro, yoduro, triflato o fosfonato se pueden someter a reacciones de acoplamiento con boronato

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zac

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(reacciones de tipo Suzuki) o estanano para proporcionar diazandoles sustituidos. Estananos y boronatos se preparan por medio de procedimientos estándar en la literatura o como se describe en la sección experimental de esta solicitud.

- 5 Diazaindoles sustituidos se pueden someter a un acoplamiento mediado por metales para proporcionar compuestos de fórmula I : en donde  $R^4$  es por ejemplo arilo, heteroarilo, o heteroalíclico. Los intermediarios de bromo o cloro diazaíndol (o triflatos o yoduros de diazaíndol) se pueden
- 10 someter a un acoplamiento de tipo Stille con heteroarilestananos como se muestra en el esquema de reacción 15. Las condiciones para esta reacción son bien conocidas en la técnica y las siguientes son 3 referencias de ejemplo: a) Farina, V.; Roth, G.P. Recent advances in the Stille
- 15 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 las condiciones de acoplamiento generales también están
- 20 en la referencia de Richard C. Larock Comprehensive Organic Transformations 2nd Ed. 1999, John Wiley and Sons New York. Todas estas referencias proporcionan condiciones numerosas a la disposición a los expertos en la técnica además de ejemplos específicos proporcionados en el ejemplo 15 y en
- 25 modalidades específicas. También se puede reconocer bien que



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un estanano de diazaíndol también se puede acoplar a un haluro o triflato de arilo o heterocíclico para construir compuestos de fórmula I. El acoplamiento de Suzuki (Norio Miyaúra and Akiro Suzuki Chem. Rev. 1995, 95, 2457.) entre un intermediario de diazaíndol de triflato, bromo o cloro y un boronato adecuado se puede también utilizar y están contenidos algunos ejemplos específicos en esta solicitud. Los acoplamientos catalizados por paladio de estananos y boronatos entre intermediarios de diazaíndol de cloro también son factibles y se han utilizado ampliamente para esta invención. Los procedimientos preferidos para este acoplamiento de diazaíndol de cloro y estanano utilizan dioxano, estequiométrico o un exceso de reactivo estaño (hasta 5 equivalente), 0.1 a 1 eq de tetraquis trifenil fosfina paladio (0) en dioxano calentado por 5 hasta 15 horas a 110 a 120°C. Otros solventes tales como DMF, THF, tolueno o benceno se pueden utilizar. Los procedimientos preferidos para el acoplamiento de Suzuki de diazaíndol de cloro y boronato utilizan 1:1 DMF agua como solvente, 2 equivalentes de carbonato de potasio como base estequiométrica o un exceso de reactivo de boro (hasta 5 equivalentes), 0.1 a 1 eq de tetraquis trifenil fosfina paladio (0) calentado de 5 a 15 horas a 110 a 120°C. Algunas referencias (y las referencias en ellas) que describen catalizadores que son útiles para el acoplamiento con cloruro de arilo y heteroarilo son: Littke;

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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. documento WO 0002887 5 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; 10 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.

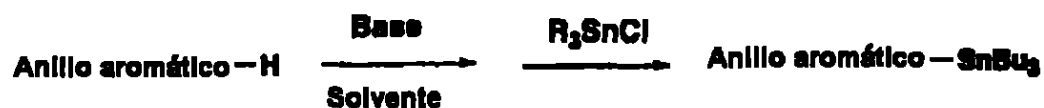
Alternativamente, el boronato o estanano se puede 15 formar potencialmente sobre el diazaíndol por medio de métodos conocidos en la técnica, y el acoplamiento realizado en forma inversa con halógenos o triflatos basados en arilo o heteroarilo.

Los agentes conocidos de boronato o estanano se 20 pueden adquirir de recursos comerciales o prepararse siguiendo los documentos descritos. Los ejemplos adicionales para la preparación de reactivos de estaño o reactivos de boronato están contenidos en la sección experimental.

Los agentes novedosos de estanano se pueden 25 preparar a partir de una de las siguientes rutas.

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## ESQUEMA DE REACCION Tin-01



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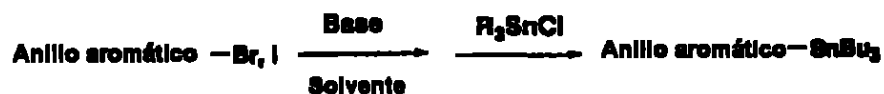
Base = LDA, TMP-Li, n-BuLi, S-BuLi, t-BuLi

Solvente = THF, éter, DME

R = Me, Bu

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## ESQUEMA DE REACCION Tin-02



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

Solvente = THF, éter, DME

R = Me, Bu

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## ESQUEMA DE REACCION Tin-03

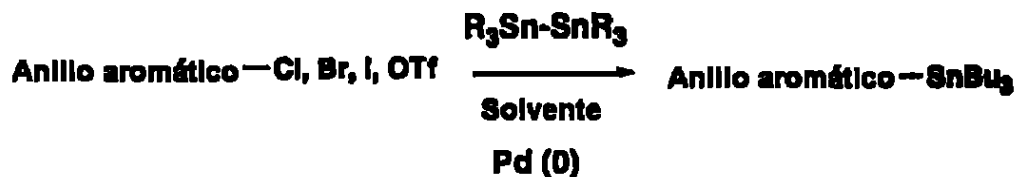


Solvente = THF, éter, DME

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R = Me, Bu

## ESQUEMA DE REACCION Tin-04



Solvente = Dioxano, Tolueno

R = Me, Bu

## ESQUEMA DE REACCION Tin-05

E = Electrófilo = R'-haluro, R'COCl, R'OCOCi, R'R'NCOCi, RSO<sub>2</sub>Cl, R'NCO, R'NSO, R'NCNR'Solvente = CH<sub>2</sub>Cl<sub>2</sub>, THF, éter, DMF

R = Me, Bu

Base = NaH, BuLi, LDA, K<sub>2</sub>CO<sub>3</sub>, Et<sub>3</sub>N, DBU, DMAP, NaHMDS

Los reactivos de boronato se preparan como se describe en la referencia 71. La reacción de los reactivos de litio o Grignard con boratos de triaalkilo genera boronato. Alternativamente, los acoplamientos catalizados por paladio de los reactivos de diboroalquilo o diboroalcoxi con haluros de arilo o heteroarilo pueden proporcionar reactivos de boro para su uso en acoplamientos tipo Suzuki. Algunas condiciones de ejemplos para el acoplamiento de haluro con

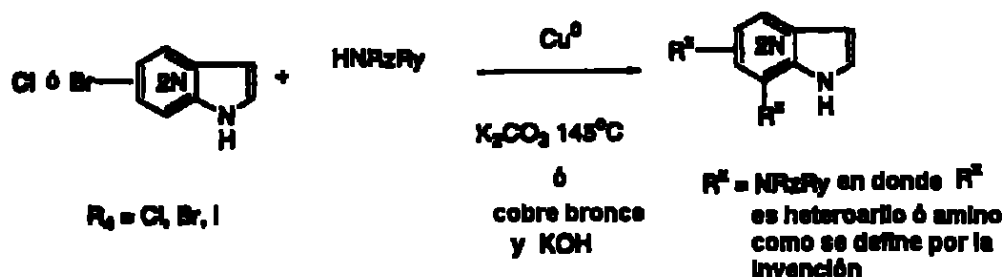
(MeO)BB(OMe)<sub>2</sub> utilizan PdCl<sub>2</sub>(dppf), KOAc, DMSO a 80°C hasta que esta completa la reacción cuando es seguida por un análisis CLAR o CCD.

Se proporcionan ejemplos relacionados en la siguiente sección experimental.

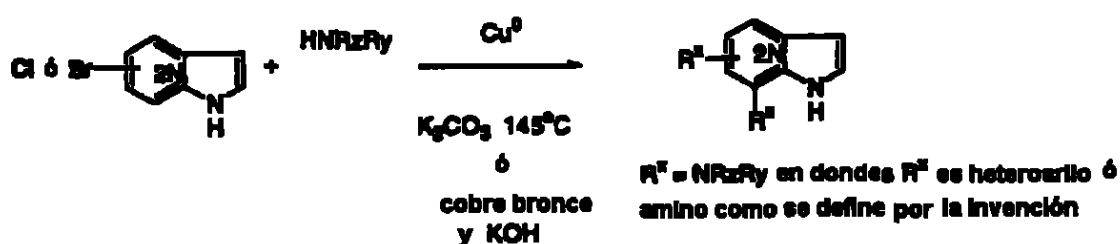
Los métodos para la adición directa de reactivos organometálicos de arilo o heteroarilo a heterociclos que contienen cloro nitrógeno alfa o N-óxidos de nitrógeno que contienen heterociclos se conocen y aplican a diazainadoles. Algunos ejemplos son Shiotani et al. J. heterocyclic Chem. 1999, 34(3), 901-907; Fourmigue et al. J. Org. Chem. 1991, 56(16), 4858-4864.

#### ESQUEMA DE REACCION 15aa

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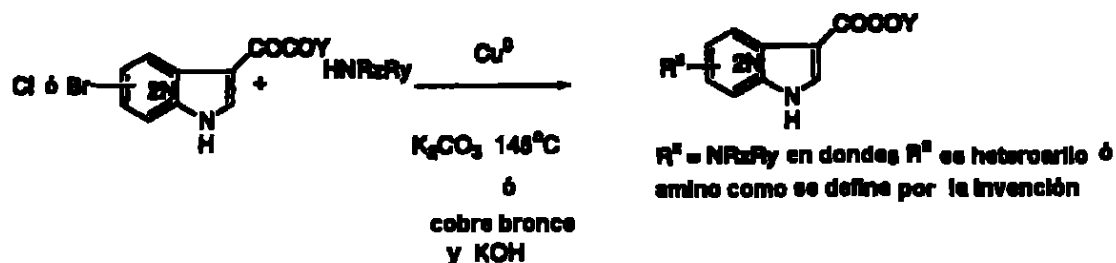
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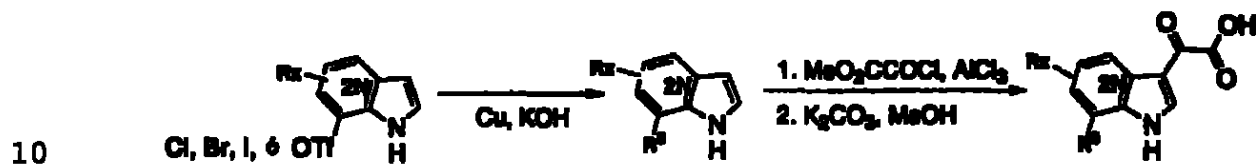
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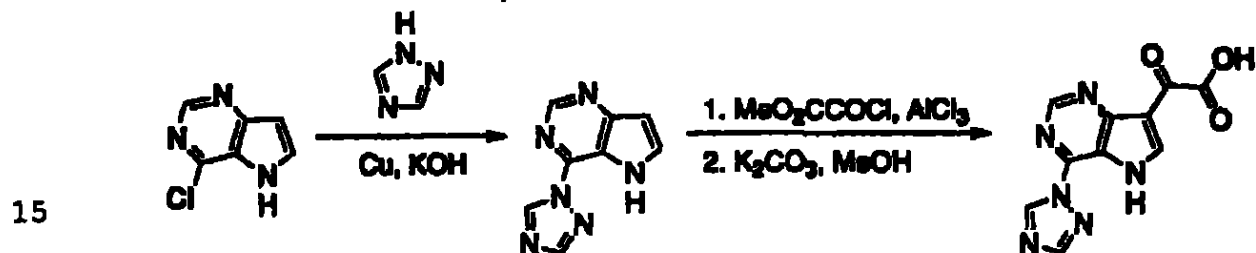
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## ESQUEMA DE REACCION 15bb



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( $\text{R}^1\text{H}$  es un heteroarilo ó amino con N-H libre)



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Ejemplo propuesto

Los desplazamientos directos para instalar amina o los sustituyentes heteroarilo enlazados a N también podrán usarse para preparar los compuestos de fórmula I. Como se muestra en los esquema de reacción 15aa y 15bb, una mezcla del intermediario halo-diazaindol, 1-2 equivalentes de polvo de cobre; 1-2 equivalentes de carbonato de potasio, y 2-30 equivalentes del correspondiente reactivo heterocíclico, con 10 equivalentes preferidos; se calientan a 135-160°C durante

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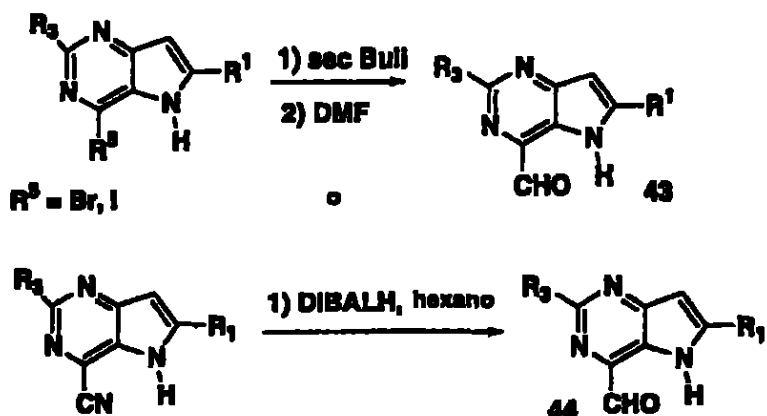
4 a 9 horas. La mezcla de reacción se enfría hasta temperatura ambiente y se filtra a través de un papel filtro. El filtrado se diluye con metanol y se purifica ya sea por CLAR preparativa o gel de sílice. En muchos casos, no es  
5 necesaria la cromatografía, el producto puede obtenerse por cristalización con metanol.

: Alternativamente, la instalación de aminas o heteroarilos enlazados a N podrá llevarse a cabo al calentar 1 hasta 40 equivalentes de amina apropiada y un equivalente  
10 de diazaíndol de cloruro, bromuro o yoduro apropiado con bronce de cobre (desde 0.1 hasta 10 equivalentes (preferiblemente alrededor de 2 equivalentes) y desde 1 hasta 10 equivalentes de hidróxido de potasio finamente pulverizado (preferiblemente alrededor de 2 equivalentes). Pueden  
15 utilizarse temperaturas de 120°C hasta 200°C con 140-160°C generalmente preferidas. Para materiales de inicio volátiles puede utilizarse un reactor sellado. La reacción muy frecuentemente se aplicara cuando el halógeno que se desplaza esta en la posición 7 del diazaíndol pero el método podría  
20 trabajar cuando el halógeno esta en una posición diferente (posición posible 4-7). Como se muestra arriba, la reacción podrá utilizarse en diazaíndoles no sustituidos en la posición 3 o en intermediarios que contienen dicarbonilo o urea o tiourea de bicarbonilo piperacina intactos que están  
25 contenidos en los compuestos de fórmula I.

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## ESQUEMA DE REACCION 16



10 Una posible preparación de un intermediario de  
 aldehído importante, 43, usando un procedimiento adaptado del  
 método de Gilmore et al. Synlett 1992, 79-80 se muestra en  
 el esquema de reacción 16 anterior. el sustituyente aldehído  
 se muestra solo en una posición por la razón de claridad, y  
 no se considerara como una limitación de la metodología. El  
 15 intermediario de bromuro o yoduro podrá convertirse en un  
 intermediario aldehído, 43, por intercambio de metal-halógeno  
 y la reacción posterior con dimetilformamida en un solvente  
 aprótico apropiado. Las bases normales usadas podrían  
 incluir, pero no podrán limitarse a, bases de alquil litio  
 20 tales como n-butilitio, sec-butilitio o terc-butilitio o un  
 metal tal como metal de litio. Un solvente aprótico  
 preferido en THF. Normalmente, la transmetalación podrá  
 iniciarse a  $-78^{\circ}\text{C}$  y permitirá que reaccione con  
 dimetilformamida (lo que permite que la reacción se entibie  
 25 lo que se puede requerir para hacer posible la reacción



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completa) para proporcionar un aldehído que se elabora para los compuestos de fórmula I. Otros métodos para la introducción de un grupo aldehído para formar intermediarios de fórmula 43 incluyen reacciones de carbonilación catalizada por metal de transición de diazaíndoles de bromo, sulfonilo de trifluorometal, o estanilo apropiados.

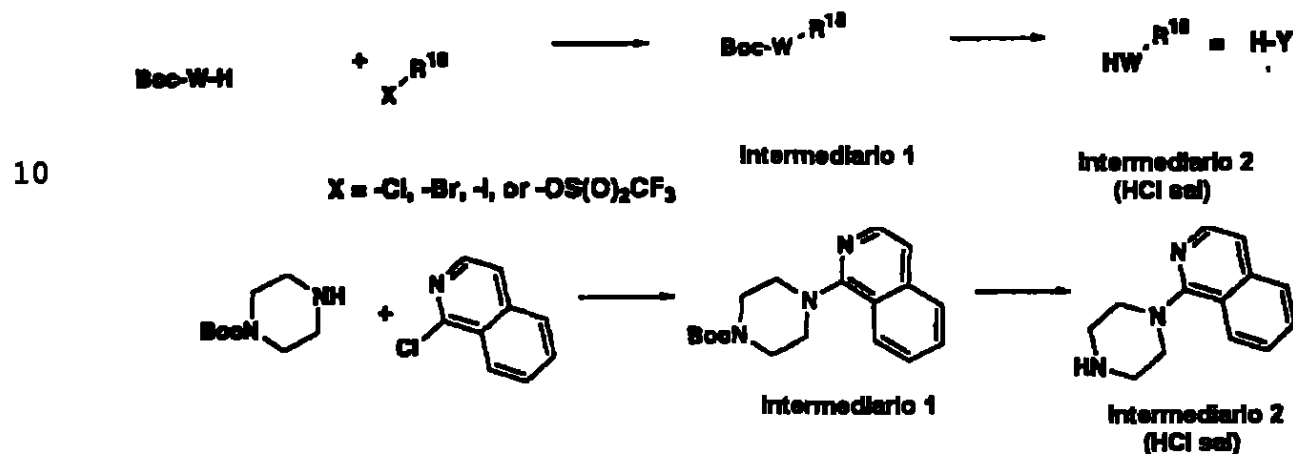
Como se muestra en el esquema de reacción 52, las piezas HW-R<sup>18</sup> pueden prepararse por un número de métodos diferentes, una forma útil es hacer reaccionar una piperazina monoprotegida con cloruro, bromuro, yoduro o triflato de heteroarilo. Esta reacción se lleva a cabo normalmente a temperaturas elevadas (50 hasta 250°C) en un solvente tal como etilenglicol, DME, dioxano, NMP o DMF. Una base de amina terciaria tal como amida de trietilo o amina de diisopropilo se utiliza normalmente y usualmente 2 hasta 4 equivalentes se utilizan. Al menos 2 equivalentes son usados si una sal de HW R<sup>18</sup> se utiliza. La piperazina se monoproteje normalmente con un grupo BOC ya que este material esta comercialmente disponible. La eliminación del grupo BOC se da normalmente usando HCl (normalmente 1 hasta 6N) en dioxano para proporcionar la sal de HCl. También puede usarse TFA para generar la sal de TFA. Alternativamente, las condiciones para acoplamiento de heterociclos usando catalizador de cobre se discute previamente en el esquema de reacción 12 pueden usarse para acoplar W a R<sup>18</sup> por medio del

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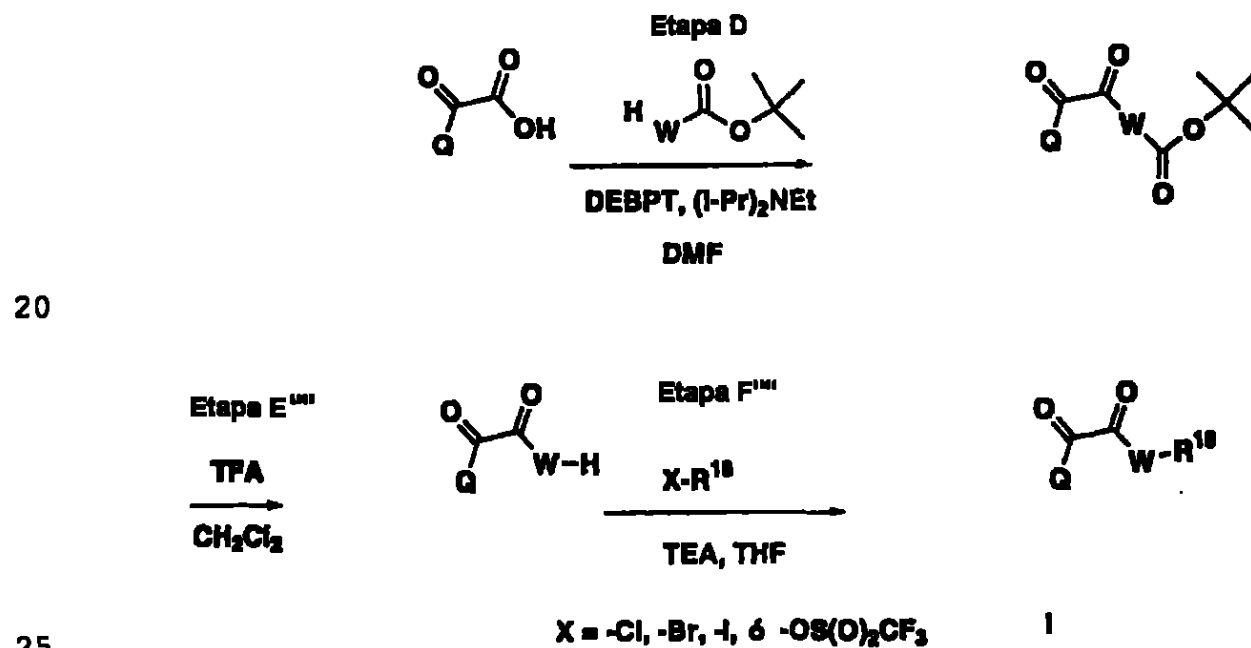
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desplazamiento de X en X-R<sup>18</sup>. Alternativamente, la catálisis de paladio en presencia de un catalizador bidentado por medio del procedimiento de Buchwald o del uso de un catalizador de ferrocenilo por medio de los métodos de Hartwig, podrá usarse para acoplar la piperazina al hetroarilo (R<sup>18</sup>).

## ESQUEMA DE REACCION 52



## ESQUEMA DE REACCION 53



El esquema de reacción 53 describe como puede acoplarse una piperazina protegida a Q-COOH por medio de metodología estándar. Las condiciones para eliminar el grupo protector amina podrían ser tBoc u otros grupos, es proteger al grupo específico. Como se muestra en el esquema de reacción 53 donde tBoc es el grupo protector preferido usado para ejemplificar la estrategia, las condiciones estándar para eliminar tal como TFA en diclorometano o alternativamente HCl acuoso, pueden proporcionar amina libre. La amina libre se acopla al R<sup>18</sup> heteroaromático usando las condiciones descritas en el esquema de reacción 52 para la etapa F'''.

#### Esquemas de Reacción Generales:

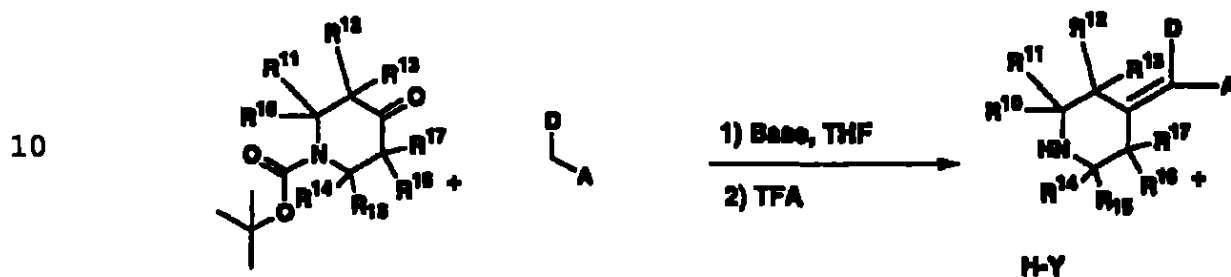
El esquema de reacción D1 describe un método posible para preparar los compuestos descritos por H-W donde Y es como se define la descripción y las reivindicaciones de la invención. Normalmente, esta metodología trabajara mejor cuando D es un grupo que reduce el PKA de los hidrógenos en la porción metileno adyacente. Por ejemplo, ciano, sulfonilo, amido y similares como se especifica en la reivindicación. Preferiblemente podrán ser porciones arilo o heteroarilo como se describe en la reivindicación 1. También podrán ser otros grupos descritos en la reivindicación 1. Las bases de alcóxido de alcoholes C1 hasta C4 pueden

30<sup>th</sup>30<sup>th</sup>

utilizarse, pero otras bases tales como dialquil amidas de litio, sodio ó potasio o las correspondientes distrimetilsilil amidas también podrán utilizarse.

## 5 Preparación de Intermediarios:

### ESQUEMA DE REACCION D1

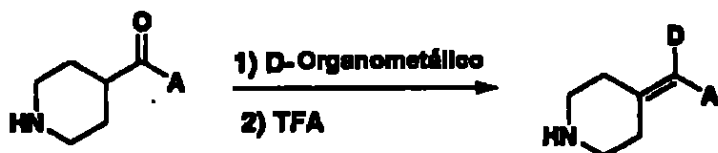


Notar como se muestra en el esquema de reacción D1, la porción piperazina o piperidina de Y puede sustituirse como se define por la invención. En el interés de claridad, las piperidinas y piperazinas no substituidas se usan en los esquemas de reacción para mantenerlas legibles. Se entenderá que podrá incorporarse sustituyentes.

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### ESQUEMA DE REACCION E1



D = heteroarilo, arilo, alquilo

Intermediario 1

Organometálico = MgBr, Li, CoCl<sub>2</sub>, ZnBr

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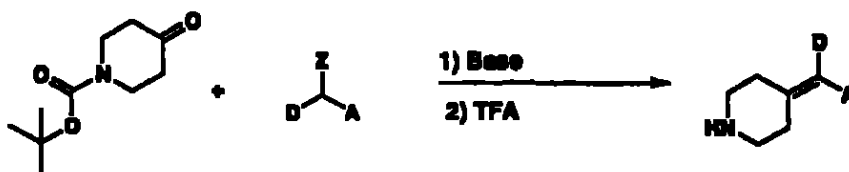
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Como se muestra en el esquema de reacción E1, la adición de un reactivo organometálico a una cetona puede proporcionar un alcóxido terciario intermediario que se somete a protonación y la eliminación del catalizador ácido para formar el enlace doble deseado. Un número de reactivos organometálicos será suficiente como se muestra, pero un equivalente extra (al menos un total de dos) podrá necesitarse para compensar la desprotección del nitrógeno de amina en muchos casos.

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## ESQUEMA DE REACCION F1



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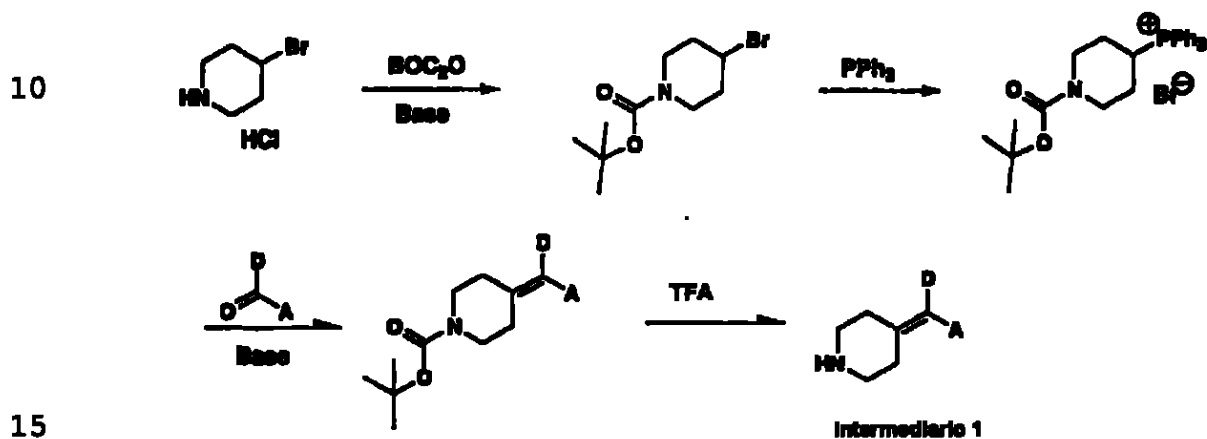


Las condiciones de olefinación estándar basadas en tal como Wittig, Horner Emmons, Petersen or Arsenic podrán usarse para convertir la acetona a los productos deseados.

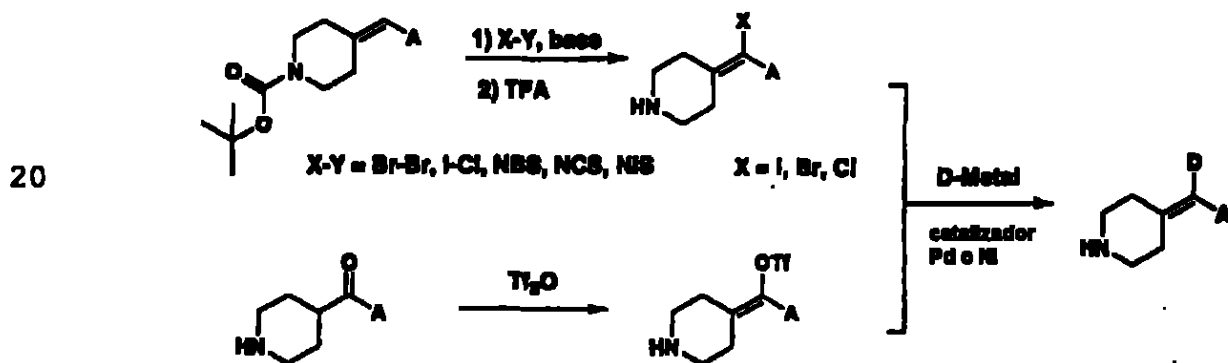
Algunas revisiones generales de esta metodología de direcciones para uso están contenidas en las siguientes referencias: Wadsworth, W.S., Jr., in "Organic Reactions", Dauben, W.G., Ed., Wiley, New York, 1977, 25, 73. McMurry, J.E. Acct. Chem. Res. 1983, 16, 405. Cushman, M., et al. Bloorg. Med. Chem. 2002, 10, 2807. Cuando

Z=trifenilfosfina, butilitio o LDA podrán usarse para generar  
 iluro de fósforo en THF y entonces iluro se haga reaccionar  
 con la acetona para proporcionar el producto deseado. Los  
 reactivos con base en óxido de fosfinato o fosfina podrán  
 5 usarse con bases similares o con metóxido o etóxido de sodio  
 o potasio en los solventes de alcohol correspondientes.

## ESQUEMA DE REACCION G1



## ESQUEMA DE REACCION H1



Metal =  $\text{SnR}_2$ ,  $\text{B(OH)}_2$ ,  $\text{AlR}_2$ ,  $\text{MgBr}$ , y similares

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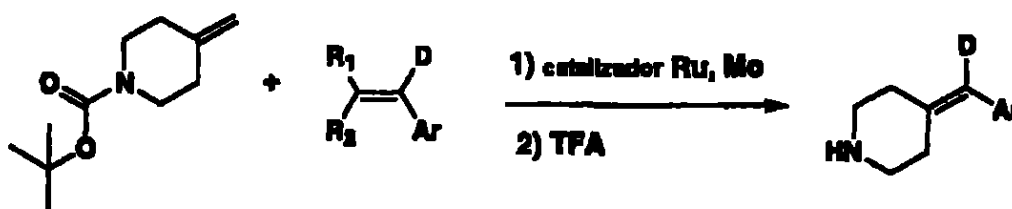
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Como se muestra anteriormente en el esquema de  
reacción H1, un cloruro, bromuro, yoduro, triflato, o  
fosfonato se somete a reacciones de acoplamiento con un  
boronato (reacciones tipo Suzuki). Los estananos y boronatos  
se preparan por medio de los procedimientos estándar en la  
literatura o como se describe en las sección experimental de  
esta solicitud. Bromuros, cloruros, triflatos, o fosfonatos  
de vinilo pueden someterse a acoplamiento mediado por metal  
para proporcionar compuestos de fórmula W-H. Los  
acoplamientos de Stille o Suzuki son particularmente útiles.  
Una discusión detallada de las referencias y las mejores  
condiciones para estos tipos de acoplamiento mediado por  
metal se describen después en esta solicitud donde la  
discusión se combina con una descripción de cómo estos tipos  
de reacciones también pueden usarse para funcionalizar  
diazaindoles.

Cuando Ar es benceno, los materiales de inicio  
están disponibles comercialmente.

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## ESQUEMA DE REACCION J1



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Alternativamente, los compuestos Y-H podrán potencialmente prepararse por medio de metatesis de olefina usando catalizadores de rodio altamente activos. El material de inicio de metileno puede prepararse por medio de metilenación Wittig simple de la acetona precursora que se prepara por medio de métodos de la literatura. La metátesis de olefina se lleva acabo preferiblemente usando 1% de catalizador de imidasolideno rutenio bencilideno descrito en la siguiente referencia. La reacción se lleva acabo iniciando a temperaturas baja ( $-40^{\circ}$ ) o similares. El material de metileno de inicio se mezcla con un exceso de olefina (5 hasta 100 equivalentes) y la reacción se calienta hasta  $\sim 40^{\circ}\text{C}$ . Synthesis of Symmetrical Trisubstituted olefins by Cross Metathesis. Chatterjee, Arnab K., Sanders, Daniel P.; Grubbs, Robert H. Organic Letters ACS ASAP.

Las referencias adicionales se enlistan a continuación las cuales muestran condiciones adicionales y sustratos que podrán usarse con este catalizador.

Diversidad de grupo funcional por metátesis cruzada de olefina catalizada por rutenio. Toste, F. Dean; Chatterjee, Arnab K.; Grubbs, Robert H.. The Arnold y Mabel Beckman Laboratory of Chemical Synthesis, Division of



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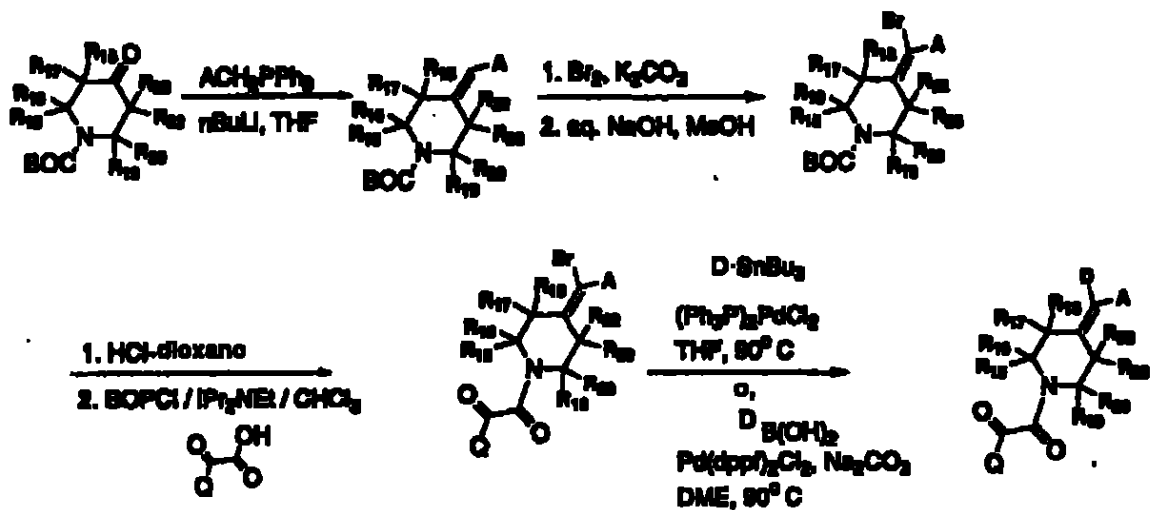
Chemistry y Chemical Engineering, California Institute of Technology, Pasadena, CA, USA. Pure and Applied Chemistry (2002), 74(1), 7-10. A Versatile Precursor for the Synthesis of New Ruthenium Olefin Metathesis Catalysts. Sanford, Melanie S.; Love, Jennifer A.; Grubbs, Robert H.. Arnold y Mabel Beckman Laboratories for Chemical Synthesis Division of Chemistry y Chemical Engineering, California Institute of Technology, Pasadena, CA, USA. Organometallics (2001), 20(25), 5314-5318. Olefin metathesis with 1,1-difluoroethylene. Tinka, Tina M.; Day Michael W.; Grubbs, Robert H.. Arnold y Mabel Beckman Lab. Of Chemical Synthesis, California Institute of Technology, Pasadena, CA, USA. Angewandte Chemie, International Edition (2001), 40(18), 3441-3444.

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El esquema de reacción K1 muestra una secuencia en la cual piperidona se convierte a olefina monofuncionalizada por medio de olefinación Wittig. Bromación y deshidrobromación proporciona un intermediario de bromuro de vinilo versátil. Este intermediario se acopla al ácido  $QC(O)C(O)OH$  con  $BOPCl$  para proporcionar un compuesto de fórmula I. Este intermediario se funcionaliza entonces usando acoplamientos mediados por paladio para ya sea boronatos o estananos. Las condiciones para estos acoplamientos se describen en esta solicitud.

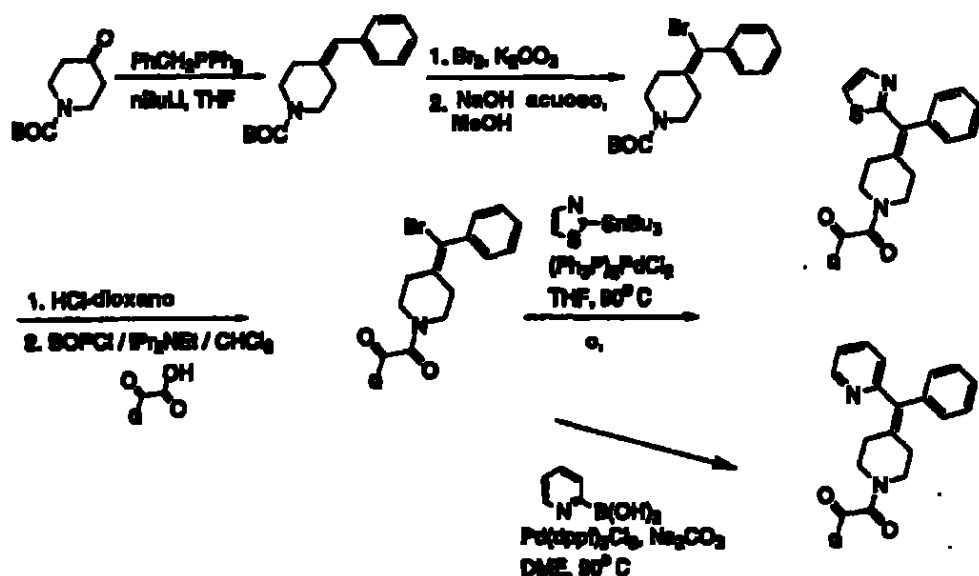
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## ESQUEMA DE REACCION K1



El esquema de reacción L1 muestra ejemplos específicos del esquema de reacción general K1 que son alguno de aquellos descritos en la sección experimental.

## ESQUEMA DE REACCION L1



El esquema de reacción M1 muestra como un bromuro de vinilo protegido puede convertirse a ácido carboxílico por

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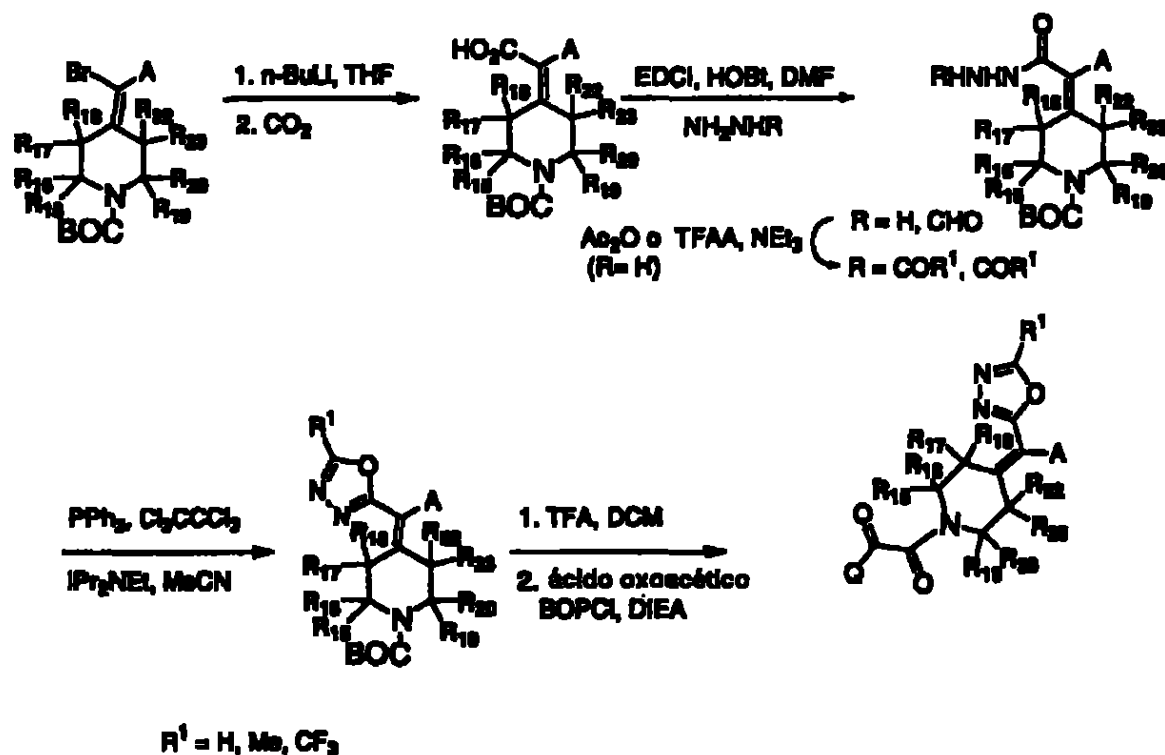
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medio de intercambio de bromuro de litio y la reacción con dióxido de carbono. Como se describe en esta solicitud e incorpora, ácidos carboxílicos que son excelentes precursores para muchos heterociclos o amidas. El resto del esquema de reacción M1 muestra la conversión a oxadiazoles funcionales. Otra química descrita en esta solicitud detalla otros métodos para convertir ácidos a grupos de otros compuestos de la invención.

## ESQUEMA DE REACCION M1

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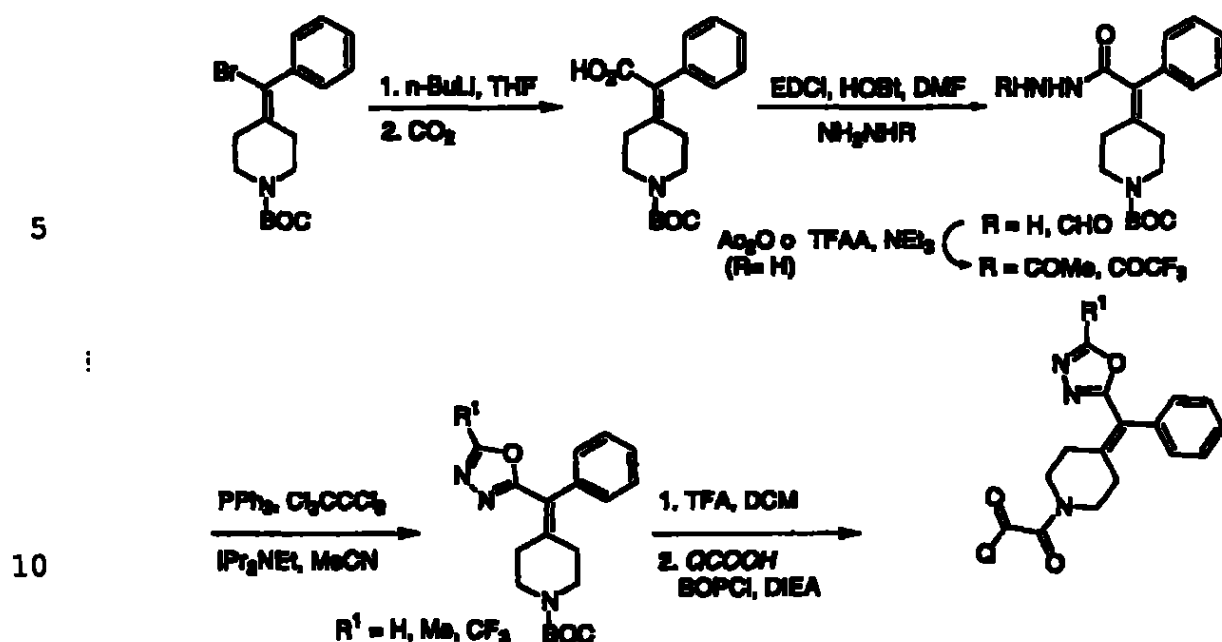


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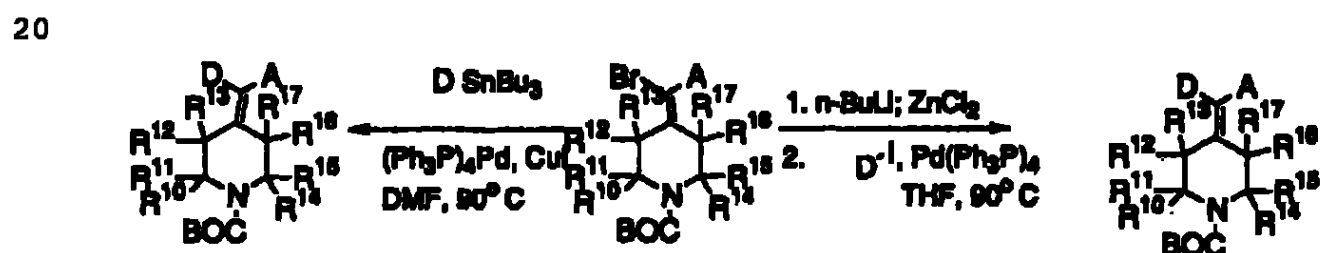
El esquema de reacción N1 detalla un ejemplo más específico del esquema de reacción M1.

## ESQUEMA DE REACCION N1



El esquema de reacción P detalla métodos para la funcionalización del bromuro de vinilo para colocar a los grupos D (o A). Ya sea detener una modificación de acoplamiento o un acoplamiento mediante zinc se describen. Los detalles de estas transformaciones se describen posteriormente en la sección metales de acoplamiento.

## ESQUEMA DE REACCION P

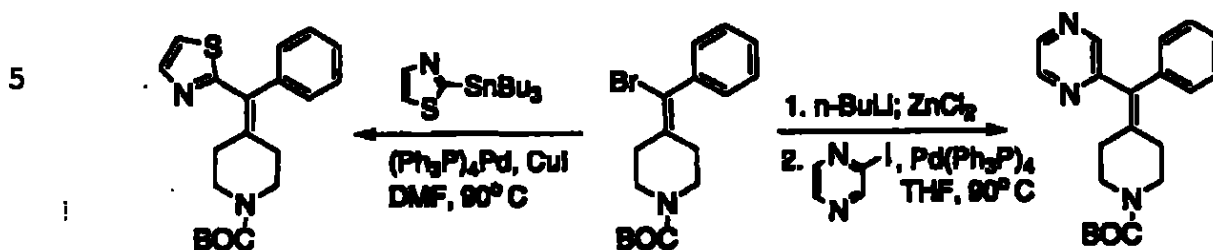


El esquema de reacción Q detalla algunos ejemplos

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específicos del esquema de reacción P.

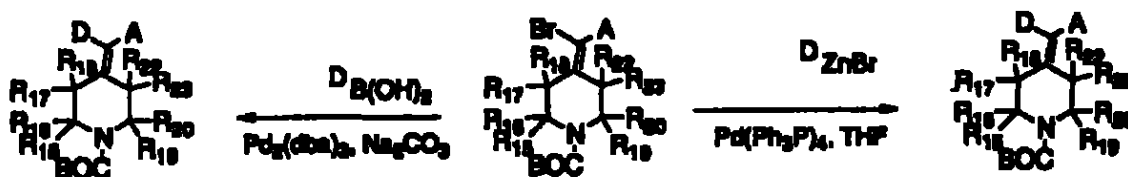
### ESQUEMA DE REACCION Q



El esquema de reacción R detalla los métodos para la funcionalidad del bromuro de vinilo para instalar los grupos D (o A). Ya sea acoplamiento Stille modificado, acoplamiento mediado por zinc, o un acoplamiento de ácido borónico Suzuki se detallan. Se muestra un método para convertir el bromuro de vinilo a yoduro de vinilo. Si el bromuro de vinilo no puede someter una reacción eficiente, el yoduro más reactivo puede prepararse como un mejor coadyuvante. Los detalles de estas transformaciones se discuten posteriormente en la sección de acoplamiento de metal.

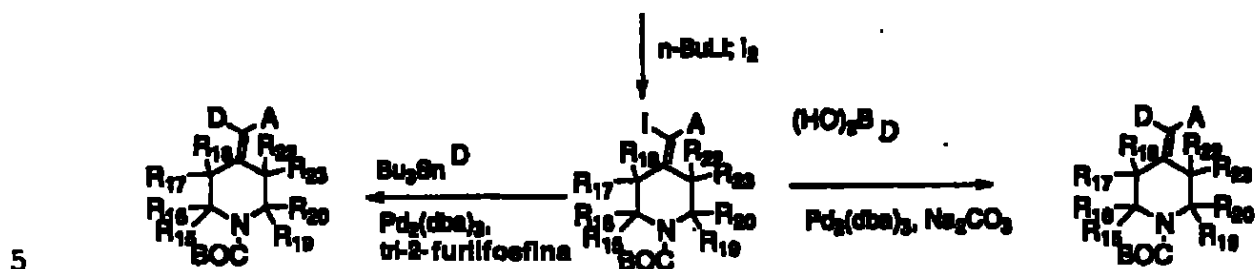
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### ESQUEMA DE REACCION R



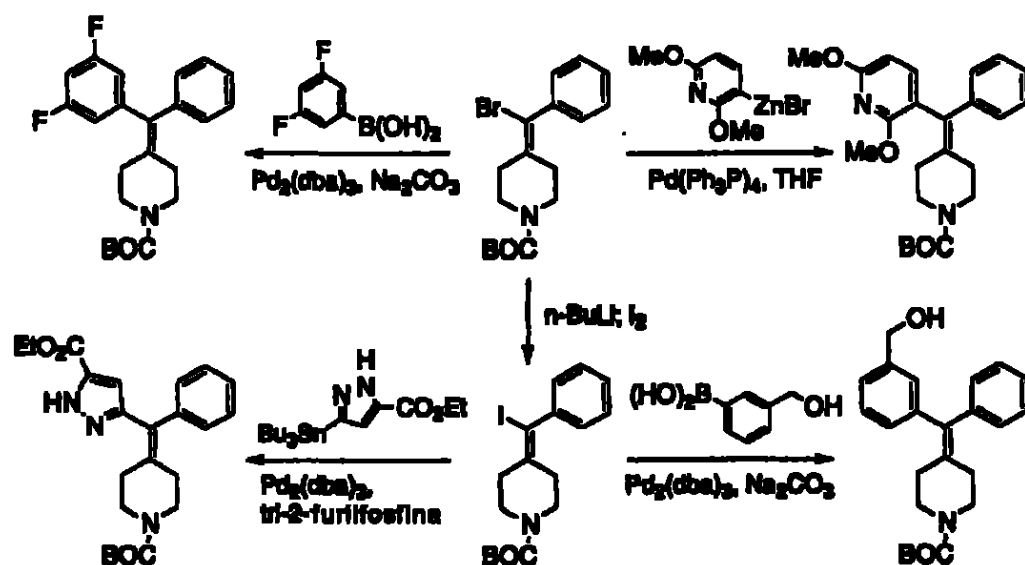
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El esquema de reacción S proporciona ejemplos específicos del esquema de reacción R.

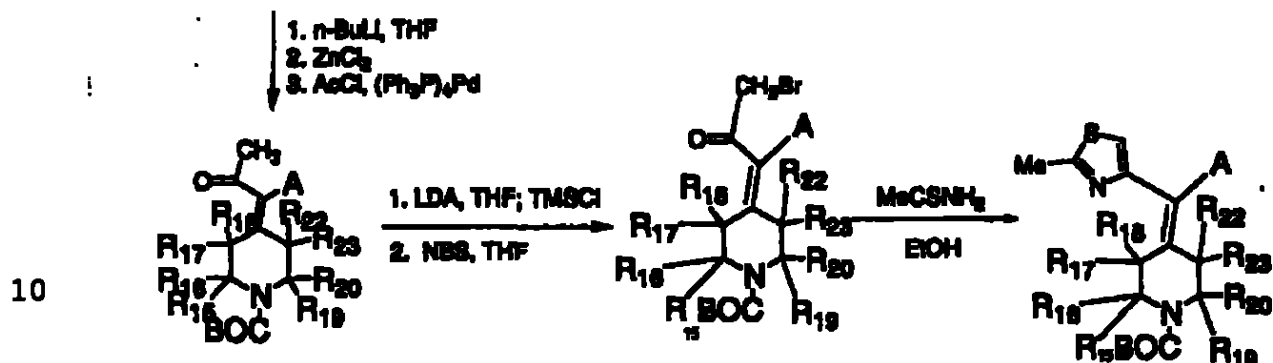
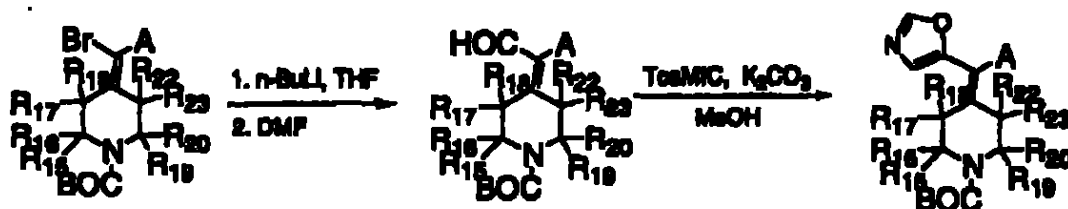
# ESQUEMA DE REACCION S



El esquema de reacción T muestra métodos para convertir bromuro de vinilo en más grupos funcionarizados D (o A). Un intermediario aldehído clave se genera del bromuro de vinilo y puede usarse para generar heteroarilos tales como oxazol por medio de una reacción Tosmic.

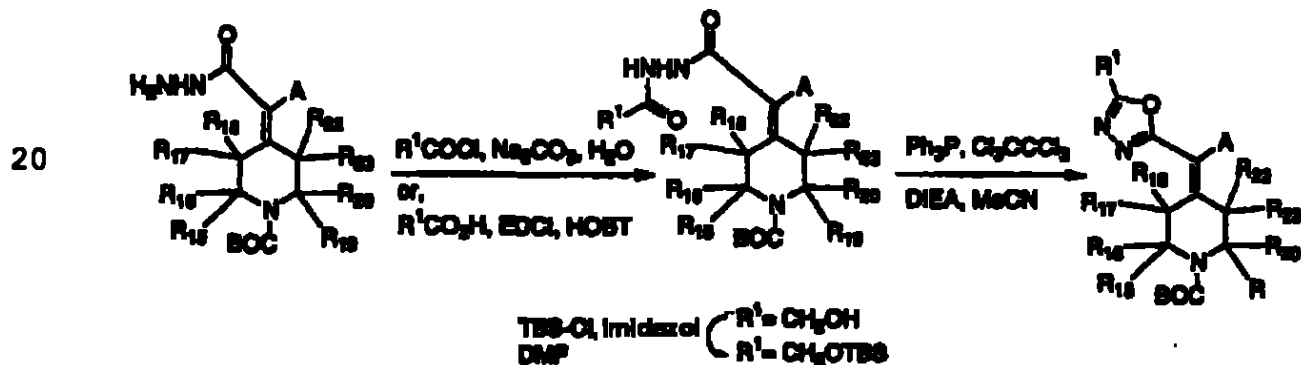
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## ESQUEMA DE REACCION T



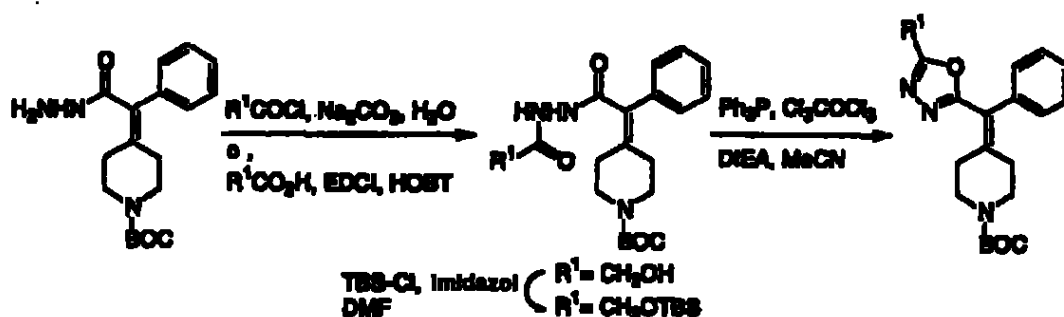
El esquema de reacción U mostró como una hidrazida (generada del ácido) puede usarse para preparar oxadiazoles con diferentes sustituyentes.

## ESQUEMA DE REACCION U



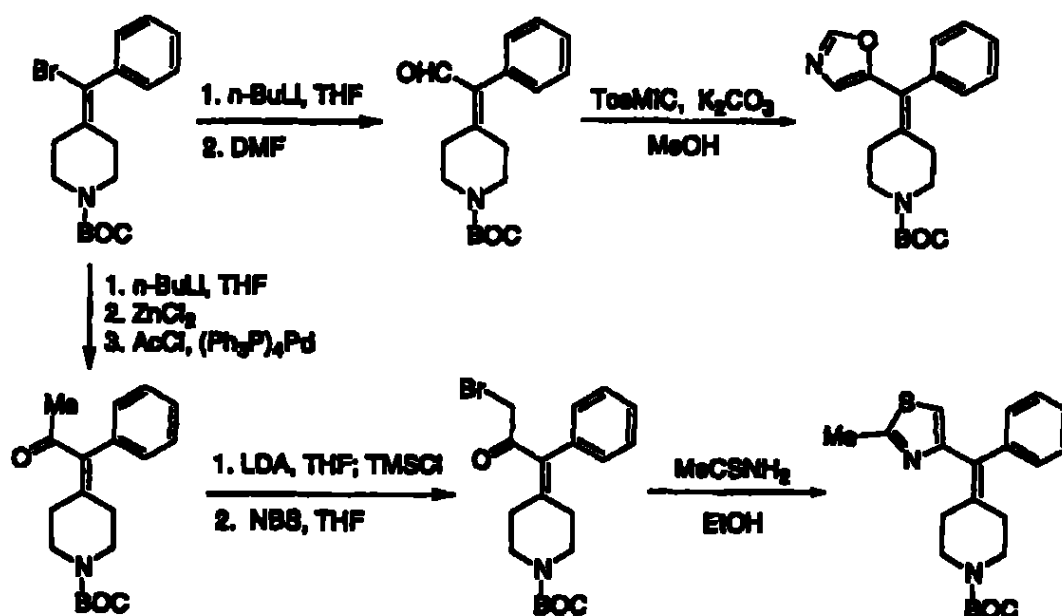
El esquema de reacción V proporciona ejemplos más específicos del esquema de reacción U.

## ESQUEMA DE REACCION V



El esquema de reacción W mostró algunos otros métodos para instalar D (o A).

## ESQUEMA DE REACCION W

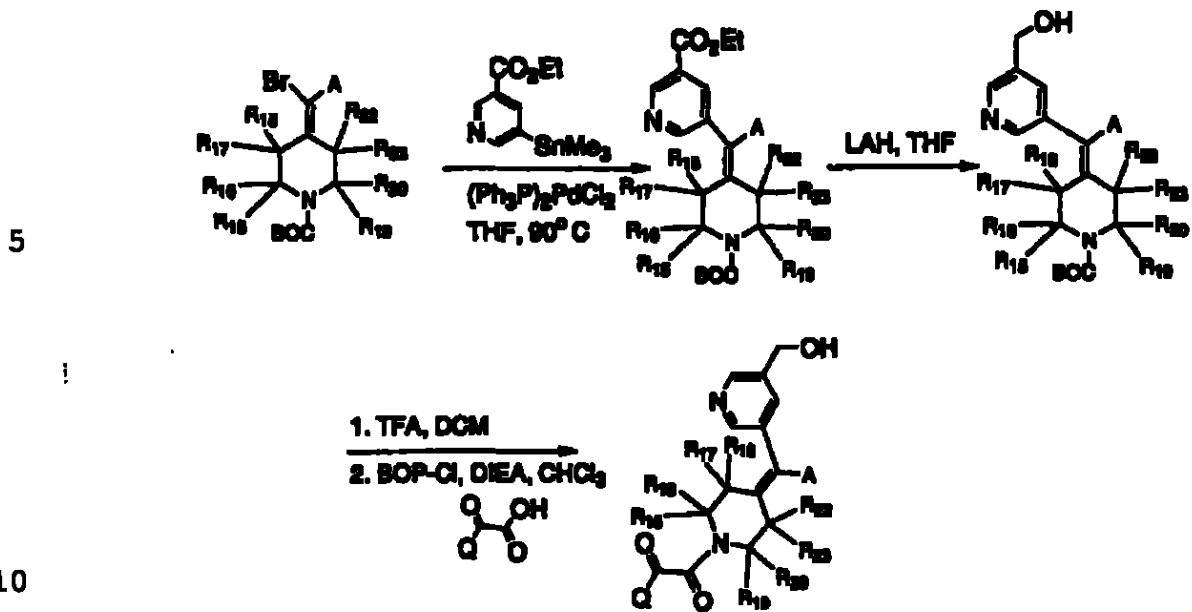


El esquema de reacción X mostró un ejemplo particular en donde un heteroarilo funcionalizado o en este caso arilo se acopló y entonces además la funcionalización puede ocurrir (en este caso la reducción de un éster a un alcohol).



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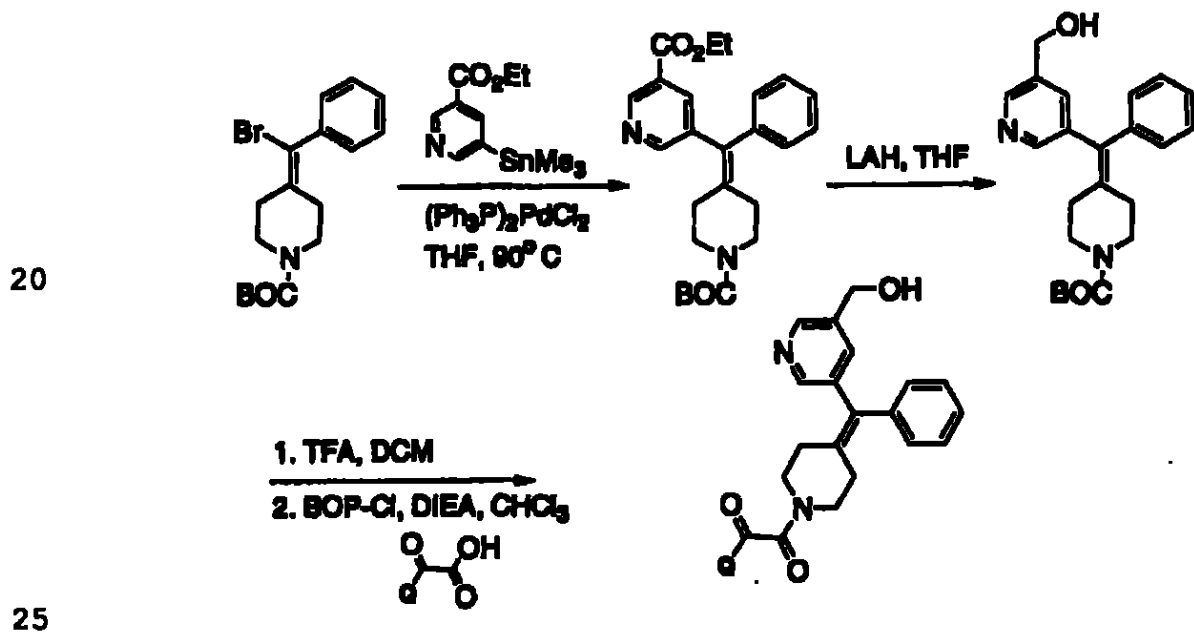
ESQUEMA DE REACCION X



El esquema de reacción Y proporciona ejemplos más específicos del esquema de reacción X.

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ESQUEMA DE REACCION Y

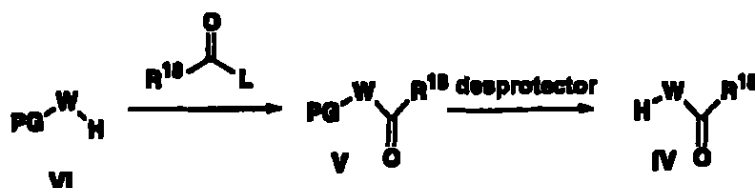


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Los procedimientos para acoplamiento de piperazin  
amidas a derivados de oxoacetilo se describen en las  
referencias Blair, Wang, Wallace, o Wang 93-95 y 106  
respectivamente. Además, estas solicitudes describen  
5 preparaciones de heteroarilos y métodos para sistemas  
heteraromáticos de función en presencia de oxoacetil amidas.  
Las descripciones enteras en la Patente Norteamericana  
6,469,006 otorgada el 22 de Octubre del 2002; Patente  
Norteamericana 6,476,034 otorgada el 5 de noviembre del 2002;  
10 Número de Serie de la Solicitud de Patente Norteamericana  
10/027,612 presentada el 19 de diciembre de 2001, las cuales  
son una continuación en parte del Número de serie de Patente  
Norteamericana 09/888,686 presentada el 25 de junio del 2001  
(correspondiente al documento PCT WO 02/04440, publicado el  
15 17 de Enero del 2002); y el Número de serie de la solicitud  
de Patente Norteamericana 10/214,982 presentada el 7 agosto  
del 2002, la cual es una continuación en parte del Número de  
serie de Patente Norteamericana 10/038,306 presentada el 2 de  
enero del 2002 (correspondiente al documento PCT WO 02/62423  
20 publicado el 15 de agosto del 2002) se incorporaron como  
referencias en la presente. Los procedimientos usados para  
acoplar ácidos oxoacéticos de diazaindol hasta piperazin  
amidas en estas referencias pueden potencialmente usarse  
analógicamente para formar los compuestos de esta invención  
25 excepto que el H-Y se usa en lugar de piperazin benzamidas.

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5 El esquema de reacción 54a detalla un método general apropiado para la síntesis de muchos de los  
 10 compuestos de fórmula I. Como se muestra en estos esquemas de reacción, un derivado de piperazina protegido adecuado, PG-YH, de fórmula VI, (en donde PG es un grupo protector amino apropiado) se aciló con un agente acilante apropiado,  $\text{R}^{18}\text{C}(\text{O})\text{L}$ , (en donde L es un grupo de partida adecuado) para proporcionar el derivado de piperazina acilado protegido de fórmula V. El compuesto V entonces se desprotege usando métodos estándar para proporcionar el derivado de piperazina  
 15 acilado de fórmula IV. Por ejemplo, cuando PG representa el terciario-butoxicarbonilo el compuesto de fórmula V puede desprotegerse para proporcionar un compuesto de fórmula IV por tratamiento con un ácido potente, tal como ácido trifluoroacético frío puro o ácido clorhídrico acuoso, en un  
 20 solvente apropiado tal como diclorometano. Alternativamente, cuando PG representa bencilo la desprotección puede ser efectiva por hidrogenación.

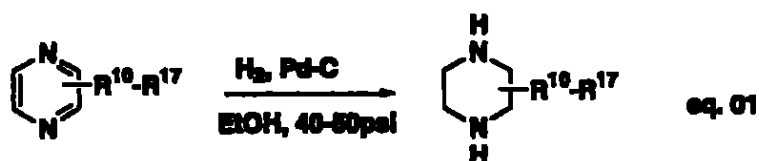
Los ejemplos que contienen piperazinas substituidas se prepararon usando el procedimiento general resumido en los  
 25 esquemas de reacción 55-38. Las piperazinas substituidas son

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ya sea disponibles comercialmente de Aldrich, Co. o se preparan de acuerdo a los procedimientos de la literatura (Behun et al, Ref. 88(a), esquema de reacción 31, eq. 01). La hidrogenación de pirazinas sustituidas de alquilo bajo una presión de 40 hasta 50 psi en EtOH proporciono piperazinas sustituidas. Cuando el sustituyentes es un éster o amida, el sistema de pirazina se puede reducir parcialmente para reducir a tetrahidropirazina (Rossen et al, Ref. 88(b), esquema de reacción 55, eq. 02). Las piperazinas sustituidas con carbonilo pueden obtenerse bajo las mismas condiciones descritas anteriormente usando piperazinas de dibencilo disponibles comercialmente (esquema de reacción 55, eq. 03).

## ESQUEMA DE REACCION 55

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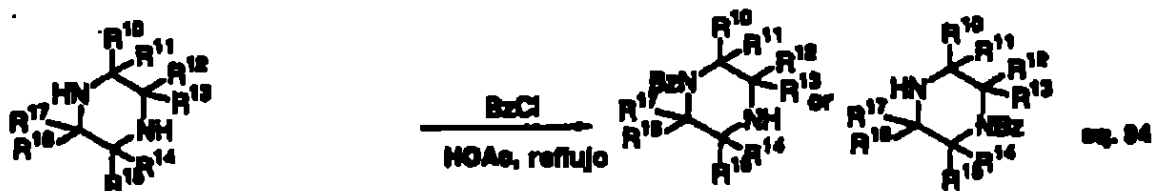
La mono-benzoilación de piperazinas sustituidas simétricamente puede lograrse por usar uno de los siguientes procedimientos (esquema de reacción 57). (a) Tratamiento de una solución de piperazina en ácido acético con cloruro de acetilo dio piperazina mono-benzoilada deseada (Desai et al. Ref. 27, esquema de reacción 57, eq. 04). (b) Las piperazinas simétricas se trataron con 2 equivalentes de n-butillitio, seguido por la adición de cloruro de benzoilo a

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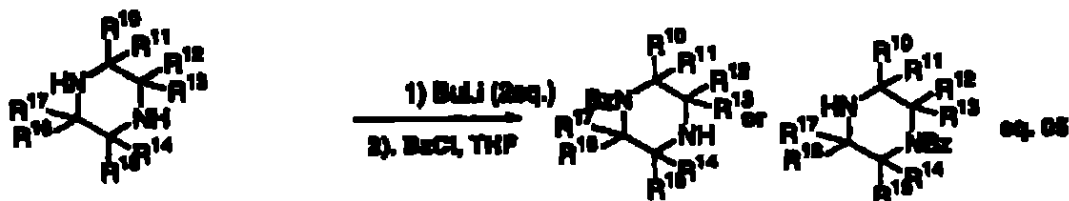
temperatura ambiente (Wang et al, Ref. 89, esquema de reacción 57, eq. 05).

## ESQUEMA DE REACCION 57

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La mono-benzoylación de piperazinas sustituidas no simétricas puede lograrse por usar uno de los siguientes procedimientos (esquema de reacción 57), en el cual todos los métodos se ejemplificaron por piperazinas sustituidas de mono-alquilo. (a) Las piperazinas no simétricas se trataron con 2 equivalentes de n-butilitio, seguidos por la adición de cloruro de benzoilo a temperatura ambiente para dar una mezcla de 2 regioisómeros, los cuales pueden separarse por cromatografía (Wang et al, Ref. 89 y 90(b), esquema de reacción 58 eq. 06); (b) El ácido benzoico se convirtió a su éster de pentafluorofenilo, y entonces reacciono además con 2-alquilpiperazina para proporcionar mono-benzoilpiperazinas con el grupo benzoilo en el nitrógeno menos imposibilitado

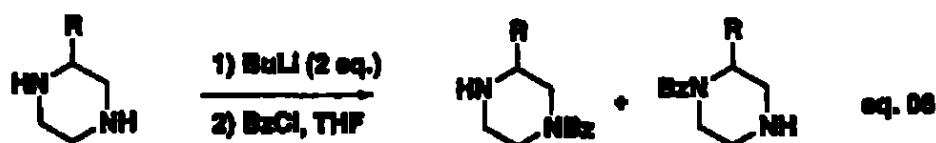
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(Adamczyk et al, Ref. 90(a), esquema de reacción 58, eq. 07);

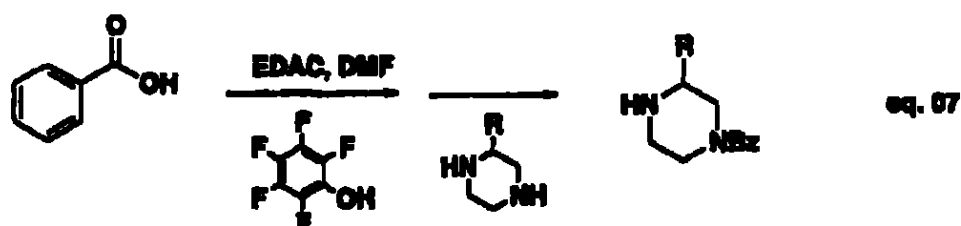
(c) Una mezcla de piperazina y metil benzoato se trató con cloruro de dialquilaluminio en cloruro de metileno durante 2-4 días para proporcionar mono-benzoilpiperazina con el grupo benzoilo en el nitrógeno menos imposibilitado (esquema de reacción 58 eq. 08); (d) Piperazinas no simétricas se trataron con 2 equivalentes de n-butilitio, seguido por la adición subsiguiente de cloruro de trietilsililo y cloruro de benzoilo en THF a temperatura ambiente para dar mono-benzoilpiperazinas con el grupo benzoilo en el nitrógeno más imposibilitado (Wang et al, Ref. 90(b), esquema de reacción 58, eq. 09).

# ESQUEMA DE REACCION 58

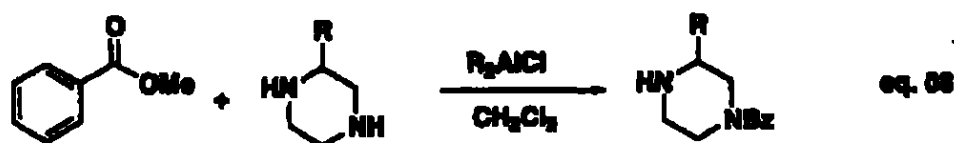
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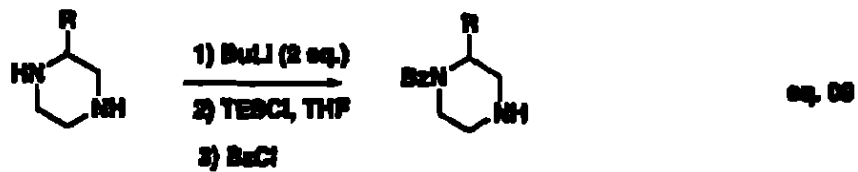


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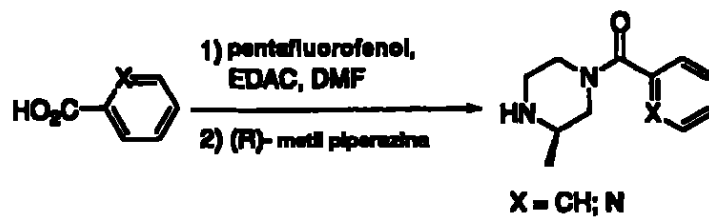
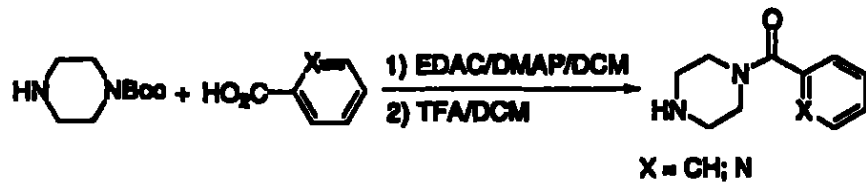
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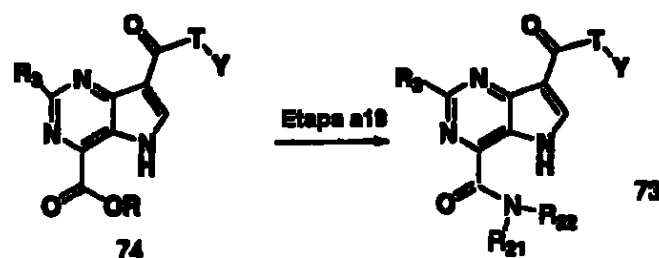
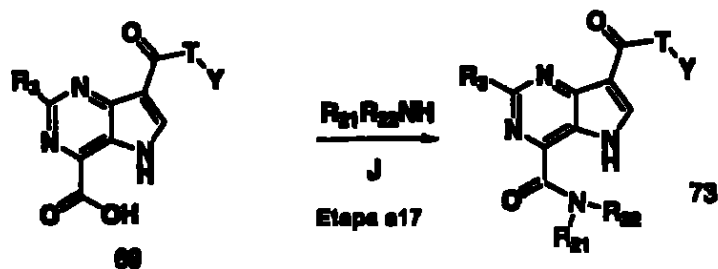


Los intermediarios de piperazinas pueden prepararse usando química estándar como se muestra en el esquema de reacción 64.

## ESQUEMA DE REACCION 64



## ESQUEMA DE REACCION 65



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Las etapas a16, a17, y a18 incluyen reacciones y condiciones para la formación de enlaces amida 1°, 2° y 3° como se muestra en el esquema de reacción 65 el cual proporciona los compuestos tales como aquellos de fórmula 73.

- 5 Los compuestos de fórmula 73 representan intermediarios para la preparación de compuestos I, o compuestos I dependiendo de la identidad de T e Y.

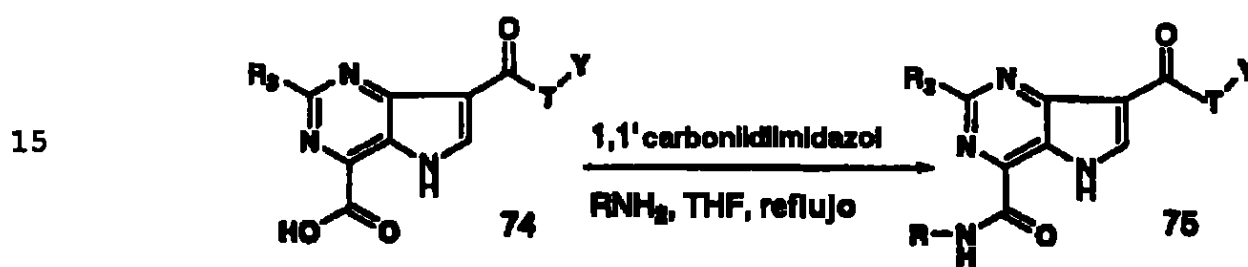
Las condiciones de reacción para la formación de enlaces de amida abarca cualquier reactivo que genera un  
10 intermediario reactivo para la activación de ácido carboxílico para la formación de amida, por ejemplo, (pero no se limitan a), haluro de acilo, de carbodiimida, sal de acil iminio, anhídridos simétricos, anhídridos mezclados (incluyendo anhídridos mezclados fosfinicos/fosfónicos),  
15 ésteres activos (incluyendo éster de silylo, metil éster y tioéster), acil carbonato, acil azida, acil sulfonato y sal de aciloxi N-fosfonio. La reacción de ácidos carboxílicos de diazaíndol con aminas para formar amidas puede ser mediada por condiciones de formación de enlaces de amidas estándar  
20 descritas en la técnica. Algunos ejemplos de la formación de enlace de amida se enlistaron en la referencias 41-53 pero no es limitante. Algún ácido carboxílico para reactivos de acoplamiento de amina que se aplican son EDC, Diisopropilcarbodiimida u otras carbodiimidas, PyBop  
25 (benzotriazoliloxitris(dimetilamino)fosfonio



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hexafluorofosfato), 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametil uronio hexafluorofosfato (HBTU). Un método útil particularmente para ácido 7-carboxílico de azaindol para las reacciones de 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 inferior que en la referencia citada, desde 80°C (o posiblemente inferior) hasta 150°C o superior. Un ejemplo de condiciones más específicas que pueden ser posiblemente exitosas se detallan en el esquema de reacción 66.

## ESQUEMA DE REACCION 66



Los siguientes 4 métodos generales proporcionan una descripción más detallada de los procedimientos potencialmente útiles para la preparación de diazindolindolcarboxamidas y éstos métodos pueden potencialmente ser utilizados para la síntesis de intermediarios 73, útiles para la preparación de compuestos I o para la preparación de compuestos de fórmula I por sí mismos.

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## Método 1:

A una mezcla de un intermediario de ácido, tal como 74, (1 equivalente, 0.48 mmol), amina apropiada (4 equivalentes) y DMAP (58 mg, 0.47 mmol) se disuelve  $\text{CH}_2\text{Cl}_2$  (1 ml), deberá agregarse EDC (90 mg, 0.47 mmol). La mezcla resultante deberá agitarse a temperatura ambiente durante 12h, y entonces se evapora *in vacuo*. El residuo frío se puede disolver en MeOH, y se somete a purificación por CLAR de fase inversa preparativa.

10

## Método 2:

A una mezcla de amina apropiada (4 equivalentes) y HOBT (16 mg, 0.12 mmol) en THF (0.5 mL) frío se puede agregar un intermediario de ácido, tal como 74, (25 mg, 0.06 mmol) y NMM (50  $\mu\text{l}$ , 0.45 mmol), seguido por EDC (23 mg, 0.12 mmol). La mezcla de reacción se puede agitar a temperatura ambiente durante 12 h. Los volátiles pueden evaporarse *in vacuo*; y el residuo se disolvió en MeOH y se somete a purificación por CLAR de fase inversa preparativa.

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## Método 3:

A una mezcla de un intermediario de ácido, tal como 74, (0.047 mmol), amina (4 equivalentes) y DEPBT (preparado de acuerdo a Li, H.; Jiang, X. Ye, Y.; Fan, C.; Todd, R.; Goodman, M. Organic Letters 1999, 1, 91; 21 mg, 0.071 mmol)

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en DMF (0.5 mL) se puede agregar TEA (0.03 ml, 0.22 mmol). La mezcla resultante se puede agitar a temperatura ambiente durante 12 h; y entonces se diluyó con MeOH (2 ml) y purificó por CLAR de fase inversa preparativa.

5

#### Método 4:

Una mezcla de un intermediario de ácido, tal como 74, (0.047mmol) y 8.5 mg (0.052mmol) de 1,1-carbonildiimidazol en THF anhidro (2 ml) podría calentarse hasta reflujo bajo nitrógeno. Después de 2.5 h, 0.052 mmol de amino podría agregarse y calentarse continuamente. Después de un periodo adicional de 3-20 h a reflujo, la mezcla de reacción podría enfriarse y concentrarse *in vacuo*. El residuo podría purificarse por cromatografía en gel de sílice para proporcionar un compuesto de fórmula I.

Además, el ácido carboxílico podría convertirse en cloruro de ácido usando reactivos tal como cloruro de tienilo (puro o en un solvente inerte) o cloruro de oxalilo en un solvente tal como benceno, tolueno, THF, o CH<sub>2</sub>Cl<sub>2</sub>. Las amidas podrían alternativamente, formarse por la reacción de cloruro de ácido con un exceso de amonio, amina primaria o secundaria en un solvente inerte tal como benceno, tolueno, THF, o CH<sub>2</sub>Cl<sub>2</sub> o con cantidades estequiométricas de aminas en la presencia de amina terciaria tal como trietilamina o una base tal como

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piridina o 2,6-lutidina. Alternativamente, el cloruro de ácido podría 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 mezclable tal como dioxano o THF. El esquema de reacción 25B detalla una preparación normal de un cloruro de ácido y la derivación a amida de fórmula I. Adicionalmente, el ácido carboxílico puede convertirse a un éster preferiblemente éster de metilo o etilo y entonces se hace reaccionar con amina. El éster puede formarse por la reacción con diazometano o alternativamente diazometano de trimetilsililo usando condiciones estándar las cuales son bien conocidas en la técnica. Las referencias y procedimientos para el uso de estos u otras reacciones de formación de éster pueden encontrarse en la referencia 52 ó 54.

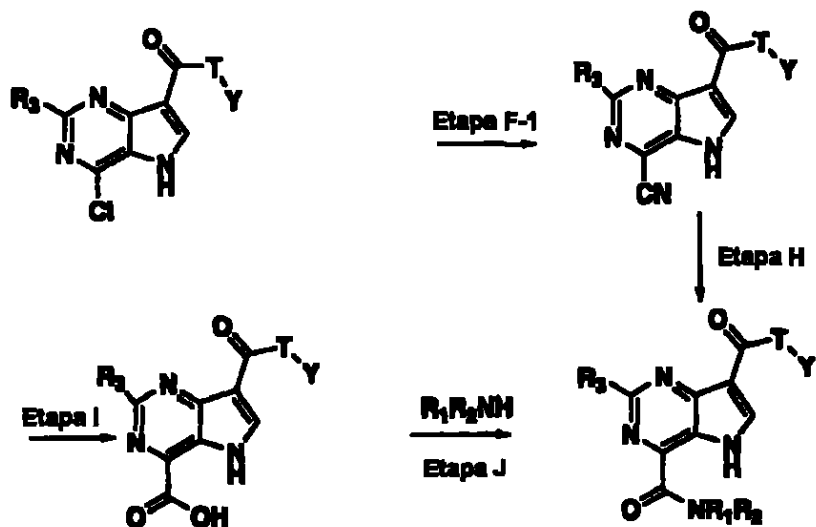
Las referencias adicionales para la formación de amidas a partir de ácido son: Norman, M.H.; Navas, F. III; Thompson, J.B.; Rigdon, G.C.; J. Med. Chem. 1996, 39(24), 4692-4703; Hong, F.; Pang, Y.-P.; Cusack, B.; Richelson, E.; J. Chem. Soc., Perkin Trans 1 1997, 14, 2083-2088; Langry, K.C.; Org. Prep. 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.; 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.

# ESQUEMA DE REACCION 67

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El esquema de reacción 67 muestra transformaciones  
sintéticas posibles en diazazaindol de cloro. La etapa F-1  
del esquema de reacción 31 puede llevarse a cabo de acuerdo a  
los siguientes procedimientos: Yamaguchi, S.; Yoshida, M.;  
Miyajima, I.; Araki, T.; Hirai, Y.; J. Heterocycl. Chem.  
1995, 32(5), 1517-1519 en los cuales se usa 1 eq de Cloruro,  
1.9 eq de Cu(I)CN, en DMF seco y se somete a reflujo durante  
48h. La concentración de cloruro en DMF es preferiblemente  
de 0.094 mmol por ml de solvente. Los tiempos de reacción de  
1-48h pueden ser apropiados dependiendo del sustrato y  
temperaturas de reacción entre 80°C y de reflujo (156°C) que  
pueden utilizarse. Un procedimiento alternativo para llevar

332 329

acabo la etapa F-1 como se describe en la sección experimental del ejemplo 12 ocurre por la reacción del intermediario de cloruro con cianuro de potasio (0.9 hasta 5 eqs, preferiblemente 1.5 eqs) en un solvente tal como DMF en la presencia de sulfonato de 4-tolueno de sodio catalítico a una temperatura elevada tal como 100°C durante 3 h. La temperatura de reacción puede variar entre 50 y 200°C dependiendo del sustrato y tiempo de reacción a partir de 30 min. durante 48 h. Las reacciones pueden conducirse en un tubo sellado para minimizar el escape de volátiles si es necesario.

Etapa de transformación I, la hidrólisis del nitrilo a ácido puede llevarse acabo usando condiciones ácidas tales como MeOH y HCl a temperatura ambiente seguido por el calentamiento del intermediario de imididato en metanol el cual proporciona el intermediario de éster de metilo el cual puede entonces hidrolizarse usando carbonato de potasio, MeOH o LiOH, o KOH en Metanol. Este método se prefiere para producir compuestos intactos I. Alternativamente, KOH/en etanol o metanol pueden utilizarse para lograr esta transformación en la etapa I. Otros métodos para estas transformaciones se conocen bien en la literatura o en las referencias incorporadas en la sección experimental.

La etapa de transformación H puede usarse para producir directamente carboxamidas no sustituidas ( $R^1 = R^2 =$

247 330

hidrógeno) por medio de agitación en ácido sulfúrico concentrado frío o a temperatura ambiente durante 0.5 hasta 15 días. Alternativamente la agitación con MeOH y HCl a temperatura ambiente seguida por una preparación hidrolítica (agua y acetato de etilo o diclorometano), puede producir el mismo producto.

Etapa J, el acoplamiento de amida se lleva acabo como se describe anteriormente en las discusiones para los esquemas de reacción 65 y 66.

#### **Química**

##### **General:**

Las preparaciones adicionales de los materiales de inicio y precursores, particularmente aquellos para añadir heteroarilos o carboxamidas y para la construcción de piperazinas sustituidas y piperidinas de alqueno han sido descritas en un número diferente de PCT y patentes/solicitudes Norteamericanas (Referencia 93-95, 106, 108, 109, 110, 111, 112, 113 y 114) y Solicitud Norteamericana Número de Serie 10/871,931 presentada el 18 de junio del 2004, la cual se incorpora en la presente por referencia.

Todos los datos de Cromatografía Líquida alquilo (CL) se registraron en un cromatógrafo de líquido LC-10AS Shimadzu usando un detector SPD-IOA V UV-Vis con datos de

334 331

Espectrometría de Masas (EM) determinados usando una  
Plataforma de Micromasas para CL en modo de rocío  
electrónico.

5 Método CL/EM (identificación de 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           |
| 10 | 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              |
| 15 | Columna I: | columna YMC ODS-A C18 87 3.0x50 mm        |
|    | Columna J: | columna XTERRA C-18 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 S34.6x33 mm         |
| 20 | Columna N: | columna XTERRA MS C18 7u 3.0x50 mm        |
|    | Columna O: | columna Phenomenex 10u 4.6x50 mm          |
|    | Columna P: | columna Waters Atlantis 4.6x50 mm C18 5um |
|    | Columna Q: | columna Phenomenex 5u 4.6x50 mm C18       |
|    | Columna R: | columna Phenomenex Lina C18 5um 3.0x50 mm |
| 25 | Columna S: | columna Phenomenex C18 10u 3.0x50 mm      |



**Gradiente:** 100% Solvente A/ 0% de Solvente B hasta 0% de Solvente A /100% de Solvente B

**Tiempo de espera** 1 minuto

**10      Detector de longitud de onda: 220 nm**

**Solvente B:** 10% de H<sub>2</sub>O/90% de MeOH/0.1% de ácido trifluoroacético

### Condiciones de Ejecución de CL Alterna B:

**20 Tiempo de Gradiente: 2 minutos**

**índice de flujo:** 5 ml/min

25 Solvante A: 5% de CH<sub>3</sub>CN/95% de H<sub>2</sub>O/10 mM de .

acetato de amonio

Solvente B:

95% de CH<sub>3</sub>CN/55% de H<sub>2</sub>O/10 mM de  
acetato de amonio

5

Los compuestos purificados por CLAR preparativa se diluyen en MeOH y/o DMSO (1.2 ml) y se purifican usando los siguientes métodos en un sistema de CLAR preparativa automatizado Shimadzu LC-10A o en un sistema de CLAR preparativa automatizado Shimadzu LC-8A con el detector (SPD-10A V UV-VIS) de longitud de onda y sistemas de solvente (A y B) iguales a lo anterior.

Método CLAR preparativa (es decir, purificación del compuesto)

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Método de Purificación: Gradiente inicial (10% de B, 90% de A) elevado hasta un gradiente final (100% de B, 0% de A) durante 20 minutos, espera de 3 minutos (100% de B, 0% de A)

20

Solvente A:

10% de MeOH/90% de H<sub>2</sub>O/0.1% de  
ácido Trifluoroacético

Solvente B:

10% de H<sub>2</sub>O/90% de MeOH/0.1% de  
ácido Trifluoroacético

25

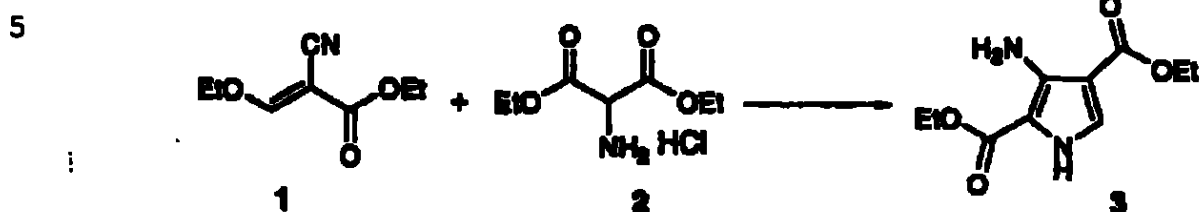
Columna:

columna YMC C18 S5 20x100 mm

33 } 334

Detector de longitud de onda: 220 nm

Los materiales de inicio, pueden obtenerse de fuentes comerciales o prepararse usando procedimientos de la literatura.



A una mezcla de clorohidrato de aminomalonato de dietilo (8.0 g, 47.3 mmol) y etil(etoximetileno)cianoacetato (10.0 g, 47.2 mmol) en etanol (60 ml) a temperatura ambiente, se agrega una solución de 21% en peso de etóxido de sodio en etanol (62 ml, 165.4 mmol). La mezcla de reacción entonces se agita a reflujo durante 20 h. Después se enfriarse a temperatura ambiente, la mezcla se neutraliza con AcOH (6.75 ml, 118 mmol), se concentra, diluye con H<sub>2</sub>O (250 ml) y se extrae con CHCl<sub>3</sub> (3 x 250 ml). Los orgánicos combinados se secaron (MgSO<sub>4</sub>), filtraron, concentraron y purificaron por lavado a través de una almohadilla de gel de sílice (100 g, EtOAc) para producir pirrol de amino 3 (10.2 g, 45.1 mmol, 95%) como un sólido de color amarillo. <sup>1</sup>H RMN: (500 MHz, DMSO-d<sub>6</sub>) δ 11.55 (s amplio, 1H), 7.21 (d, J=4.0, 1H), 5.57 (s, 2H), 4.21 (q, J=7.5 Hz, 2H), 4.18 (q, J=7.8 Hz, 2H), 1.27 (t, J=7.5 Hz, 2H), 1.25 (t, J=7.8 Hz, 2H); CL/EM: (ES+) m/z (M-Oet)<sup>+</sup> = 181; CLAR Tr = 0.96, columna N.

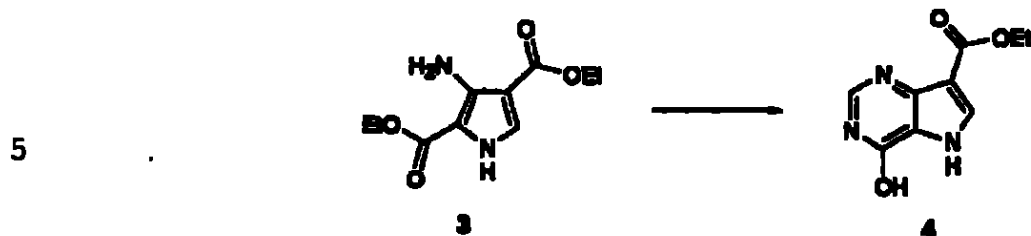
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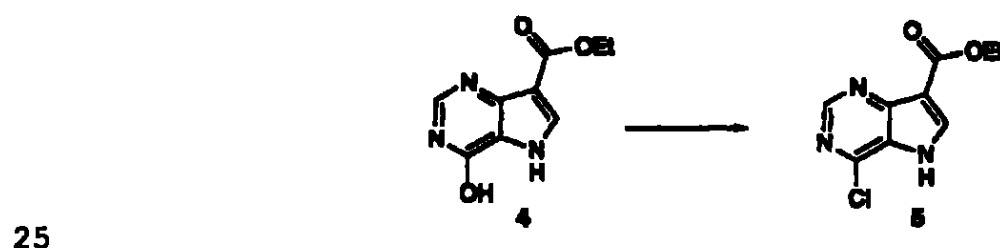
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Preparación del etil éster del ácido 4-hidroxi-5H-pirrolo[3,2-d]pirimidina-7-carboxílico 4



Una mezcla de pirrol de amino 3 (10.0 g, 44.2 mmol) y acetato de formamidina (13.8 g, 133 mmol) en etanol (100 ml) se calienta a 105°C durante 20 h. La mezcla de reacción se filtra mientras todavía esta caliente para colectar los sólidos que se enjuagaron con EtOH. El filtrado se permitirse enfriar a temperatura ambiente, se filtra hasta colectar los sólidos que se lavaron con EtOH. Los sólidos combinados se sometieron a suspensión con Et<sub>2</sub>O, filtraron y secaron bajo vacío para producir 4,6-diazaindol 4 (6.60 g, 31.9 mmol, 72%) como un sólido de color amarillo pálido el cual se uso sin purificación adicional. <sup>1</sup>H RMN: (500 MHz, DMSO-d<sub>6</sub>) δ 7.91 (s, 1H), 7.89 (s, 1H), 4.22 (q, J=7.2 Hz, 2H), 3.17 (s, 2H), 1.27 (t, J=7.2 Hz, 3H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 208; CLAR Tr = 0.55 min., columna N.

20 Preparación de etil éster del ácido 4-cloro-5H-pirrolo[3,2-d]pirimidin-7-carboxílico 5

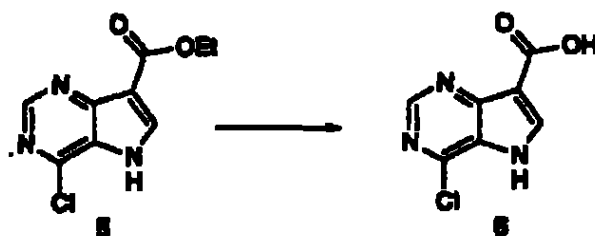


4,6-diazaindol 4 (2.74 g, 13.2 mmol) se sometio  
suspensión en POCl<sub>3</sub> (37 ml, 400 mmol) y se calienta a 105°C  
durante 3.5 h. La mezcla de reacción se enfrió, diluyó con  
Et<sub>2</sub>O (150 ml) y el precipitado resultante se colectó por  
5 filtración, se enjuagó con EtOAc y Et<sub>2</sub>O y se secó bajo vacío  
para producir 7-cloro-4,6-diazaindol 5 (2.48 g, 11.0 mmol,  
83%) como un polvo de color amarillo el cual se uso sin  
purificación adicional. CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 226; CLAR  
Tr = 0.84 min., columna N.

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Preparación del ácido 4-cloro-5H-pirrolo[3,2-d]pirimidina-7-  
carboxílico 6

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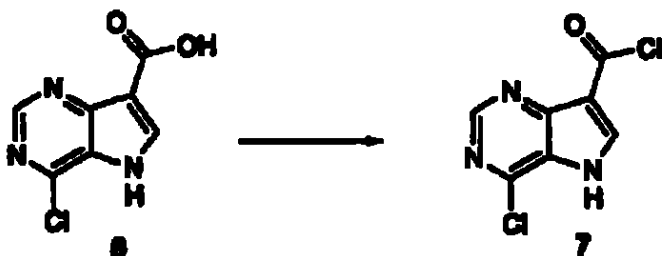
A una solución de 7-cloro-4,6-diazaindol 5 (4.0 g,  
18 mmol) en THF (90 ml) se agrega una solución de LiOH•H<sub>2</sub>O  
(2.5 g, 59 mmol) en H<sub>2</sub>O (60 ml). La mezcla de reacción se  
agita a 100°C durante 1 día, concentra y re-cristaliza de H<sub>2</sub>O  
(20 ml). Los cristales se colectaron por filtración, lavaron  
con H<sub>2</sub>O y secaron bajo alto vacío. El sólido de color blanco  
opaco se muestra que es sal de litio de ácido diazaindol  
carboxílico 6 (cuantitativo), el cual se uso sin purificación

310 337

adicional.  $^1\text{H}$  RMN: (500 MHz, DMSO- $d_6$ )  $\delta$  8.28 (s, 1H), 8.14 (s, 1H), CL/EM: (ES+)  $m/z$   $(M+H)^+ = 198$ ; CLAR Tr = 0.47 min., columna G.

5 Preparación de cloruro de 4-cloro-5H-pirrólo[3,2-d]pirimidina-7-carbonilo 7

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Una solución de la sal de litio del ácido diazaíndol carboxílico 6 (1.3 g, 6.6 mmol) en cloruro de tionilo (22 ml, 300 mmol) y benceno (30 ml) se calentó a 105°C durante 3 h. La reacción se enfrió y concentró bajo vacío. El residuo sólido de color amarillo ligero mostró ser el cloruro de ácido 7 y se usó sin purificación adicional. El cloruro de ácido 7 se identificó por enfriamiento rápido de una pequeña cantidad con metanol para hacer el éster de metilo análogo o con anilina para hacer amida de fenilo, cada uno de los cuales puede verificarse por CLEM. Éster de metilo: CL/EM: (ES+)  $m/z$   $(M+H)^+ = 212$ ; CLAR Tr = 0.90 min., columna G. Amida de fenilo: CL/EM: (ES+)  $m/z$   $(M+H)^+ = 269$ ; CLAR Tr = 01.56 min., columna G.

341

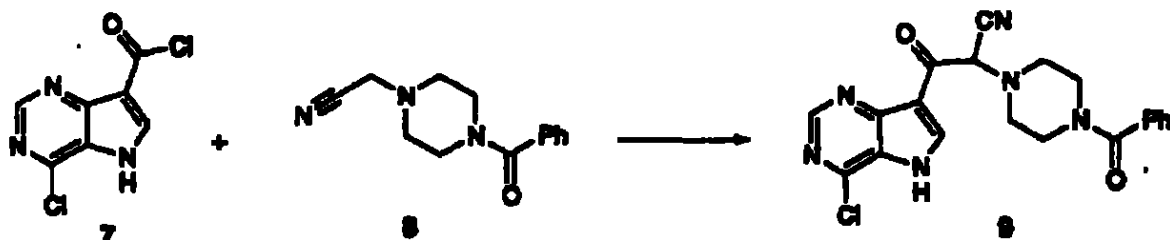
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**Preparación del ejemplo 1:**

2-(4-benzoil-piperazin-1-il)-3-(4-cloro-5H-pirrólo[3,2-d]pirimidin-7-il)-3-oxo-propionitrilo alquilo (Compuesto 9).

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**Ejemplo 1**

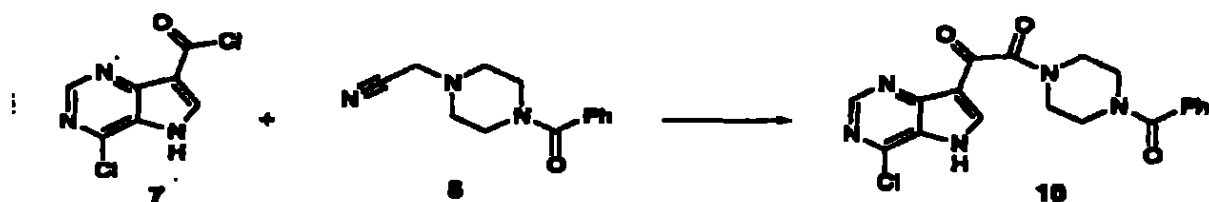
A un solución de cloruro de ácido 7 (0.5 mmol) y cianometilpiperazina 8 (150 mg, 0.66 mmol) en THF (4 ml) se agitó a  $-35^{\circ}\text{C}$ , se agregó lentamente a una solución de 0.5 M de KHMDS en tolueno (3.2 ml, 1.6 mmol). La mezcla de reacción se agitó a  $-35^{\circ}\text{C}$  durante 1h, se enfrió rápidamente con  $\text{NaHCO}_3$  acuoso saturado (50 ml) y se extrajo con EtOAc (2 x 50 ml). Los orgánicos combinados se concentraron y el residuo se purificó por CLAR preparativa para producir intermediario de cetociano 9 (39 mg, 0.96 mmol, 19%) como un sólido de color amarillo.  $^1\text{H}$  RMN: (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.80 (s, 0.5H), 8.80 (s, 0.5H), 8.65 (s, 0.5H), 8.64 (s, 0.5H), 7.50-7.36 (m, 5H), 4.82-4.77 (m, 1H), 3.80-3.25 (m, 4H), 3.02-2.55 (m, 4H); CL/EM: (ES+)  $m/z$   $(\text{M}+\text{H})^+ = 407$ ; CLAR  $R_t =$  0.94 min., columna G, condiciones B.

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# Preparación del ejemplo 2:

1-(4-benzoil-piperazin-1-il)-2-(4-cloro-5H-pirrólo[3,2-d]pirimidin-7-il)-etano-1,2-diona (Compuesto 10).

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Ejemplo 2

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A una solución de cloruro del ácido 7 (6.6 mmol) y cianometilpiperazina 8 (1.96 g, 8.58 mmol) en THF (45 ml) se que se agita a  $-78^{\circ}\text{C}$ , se agregó lentamente a una solución de 0.5 M de KHMDS en tolueno (42 ml, 21 mmol). La mezcla de reacción se agitó a  $-78^{\circ}\text{C}$  durante 2h y entonces una solución de 32% de peso de ácido peracético en AcOH diluido (12 ml, 57 mmol) se agregó y la reacción se agitó a temperatura ambiente durante 1h. La mezcla de reacción se enfrió rápidamente con  $\text{NH}_4\text{Cl}$  acuoso saturado (150 ml) y se agitó con EtOAc (200 ml). El precipitado resultante se colectó por filtración, enjuagó con  $\text{H}_2\text{O}$  y EtOAc, secó bajo vacío y mostró ser el intermediario de dicarbonilo 10 (813 mg, 2.05 mmol, 24%) como un sólido de color opaco.  $^1\text{H}$  RMN: (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.71 (s, 1H), 8.85 (s, 1H), 8.76 (s, 1H), 7.51-7.25 (m, 5H), 3.89-3.20 (m, 8H); CL/EM: (ES+)  $m/z$   $(\text{M}+\text{H})^+ = 398$ ; CLAR  $R_t = 0.80$  min., columna G, condiciones B.

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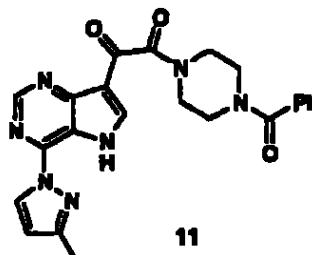
340

### Preparación del ejemplo 3:

1-(4-benzoil-piperazin-1-il)-2-[4-(3-metil-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il]-etano-1,2-diona (Compuesto 11).

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Ejemplo 3



11

En un tubo sellado, intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 3-metilpirazol (31 mg, 0.38 mmol) y etanol (1 ml) se combinaron y calentaron a 140°C con microondas durante 45 min. La reacción se diluyó con MeOH (2 ml), filtró y el filtrado se purificó por CLAR preparativa para producir 11 (36 mg, 0.08 mmol, 65%) como un sólido de color amarillo ligero.  $^1\text{H}$  RMN: (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.83 (s, 1H), 8.83 (d,  $J=2.8$  Hz, 1H), 8.52 (s, 1H), 7.50-7.41 (m, 5H), 6.50 (d,  $J=2.8$  Hz, 1H), 3.95-3.45 (m, 8H), 2.45 (s, 3H); CL/EM: (ES+)  $m/z$   $(\text{M}+\text{H})^+ = 444$ ; CLAR  $R_t = 0.97$  min., columna G, condiciones B.

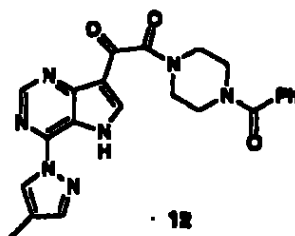
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### Preparación del ejemplo 4:

1-(4-benzoil-piperazin-1-il)-2-[4-(4-metil-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il]-etano-1,2-diona (Compuesto 12).

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Ejemplo 4



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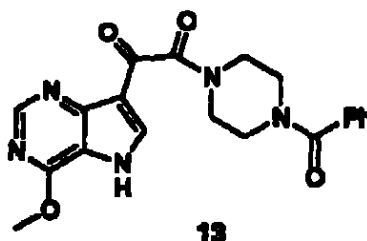
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En un tubo sellado, intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 4-metilpirazol (31 mg, 0.38 mmol) y etanol (1 ml) se combinaron y calentaron a 140°C con microondas durante 30 min. La reacción se diluyó con MeOH (2 ml), se filtró y el filtrado se purificó por CLAR preparativa para producir 12 (34 mg, 0.08 mmol, 61%) como un sólido de color blanco. <sup>1</sup>H RMN: (300 MHz, CDCl<sub>3</sub>) δ 12.13 (br s), 9.17 (s, 1H), 8.74 (s, 1H), 8.40 (s, 1H), 7.85 (s, 1H), 7.46-7.36 (m, 5H), 3.85-3.55 (m, 8H), 2.20 (s, 3H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 444; CLAR R<sub>t</sub> = 0.97 min., columna G, condiciones B.

#### Preparación del ejemplo 5:

1-(4-benzoil-piperazin-1-il)-2-(4-metoxi-5H-pirrólo[3,2-d]pirimidin-7-il)-etano-1,2-diona (Compuesto 13).

Ejemplo 5

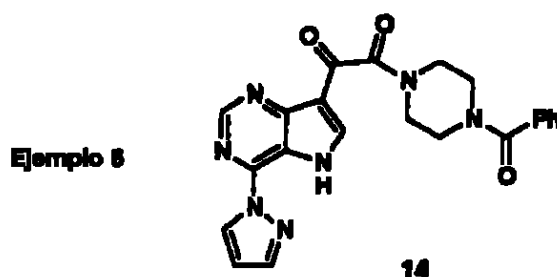


A una solución de intermediario de dicarbonilo 10 (50 mg, 0.13 mmol) en MeOH (1 ml) se agregó KOMe (79 mg, 1.1 mmol). La reacción se calentó a 90°C durante 0.5 h, se enfrió, diluyó con MeOH (2 ml) y H<sub>2</sub>O (1 ml) y se purificó por

CLAR preparativa para producir 13 (24 mg, 0.06 mmol, 48%) como un sólido de color blanco.  $^1\text{H}$  RMN: (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.93 (s, 1H), 8.62 (s, 1H), 7.53-7.40 (m, 5H), 4.39 (s, 3H), 3.98-3.46 (m, 8H); CL/EM: (ES+)  $m/z$   $(\text{M}+\text{H})^+ = 394$ ; CLAR  $R_t =$  0.979 min., columna G, condiciones B.

**Preparación del ejemplo 6:**

1-(4-benzoil-piperazin-1-il)-2-(4-pirazol-1-il-5H-pirrolo[3,2-d]pirimidin-7-il)-etano-1,2-diona (Compuesto 14).



En un tubo sellado, el intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), pirazol (26 mg, 0.38 mmol) y etanol (1 ml) se combinaron y calentaron a 140°C con microondas durante 45 min. La reacción se diluyó con MeOH (3 ml), filtró y el filtrado se purificó por CLAR preparativa para producir 14 (13 mg, 0.03 mmol, 24%) como un sólido de color blanco.  $^1\text{H}$  RMN: (500 MHz,  $\text{CD}_2\text{OD}$ )  $\delta$  8.87 (s, 1H), 8.81 (s, 1H), 8.53 (s, 1H), 8.04 (s, 1H), 7.53-7.39 (m, 5H), 6.69 (s, 1H), 3.98-3.46 (m, 8H); CL/EM: (ES+)  $m/z$   $(\text{M}+\text{H})^+ = 430$ ; CLAR  $R_t = 0.95$  min.;

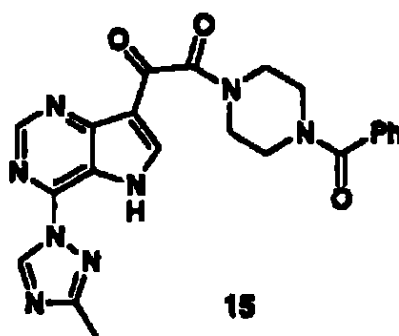
241, 343

columna G., condiciones B.

**Preparación del ejemplo 7:**

5 1-(4-benzoil-piperazin-1-il)-2-[4-(3-metil-[1,2,4]triazol-1-il)-5H-pirrólo[3,2-d]pirimidin-7-il]-etanol-1,2-diona  
 10 (Compuesto 15).

Ejemplo 7



15 En un tubo sellado, el intermediario de dicarbonilo  
 10 (50 mg, 0.13 mmol), 3-metil-1,2,4-triazol (22 mg, 0.38  
 mmol) y etanol (1 ml) se combinaron y calentaron a 140°C con  
 microondas durante 45 min. La reacción se diluyó con  
 MeOH/DMF (1:1, 3 ml), se filtró y el filtrado se purificó por  
 20 CLAR preparativa para producir el 15 (9 mg, 0.02 mmol, 17%)  
 como un sólido de color blanco. <sup>1</sup>H RMN: (500 MHz, DMSO-d<sub>6</sub>) δ  
 12.74 (s amplio, 1H), 9.54 (s, 1H), 8.94 (s, 1H), 8.54 (s,  
 1H), 7.55-7.35 (m, 5H), 3.90-3.22 (m, 8H), 2.53 (s, 3H);  
 CL/ES: (ES+) m/z (M+H)<sup>+</sup> = 445; CLAR R<sub>t</sub> = 0.88 min., columna G,  
 25 condiciones B.

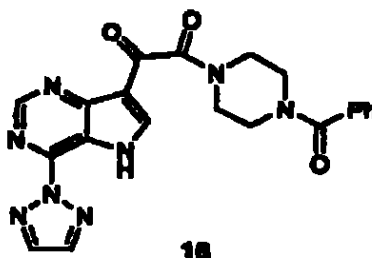
346 344

**Preparación del ejemplo 8:**

1-(4-(2H-1,2,3-triazol-2-il)-5H-pirrolo[3,2-d]pirimidin-7-il)-2-(4-benzoilpiperazin-1-il)-etano-1,2-diona (Compuesto 16).

5

Ejemplo 8



16

10

En un tubo sellado, el intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 3-metil-1,2,4-triazol (52 mg, 0.75 mmol) y polvo de cobre (16 mg, 0.25 mmol) se combinaron y calentaron a 140°C con microondas durante 1h. La reacción se diluyó con MeOH (3 ml), filtró a través de celite y el filtrado se purificó por CLAR preparativa para producir 16 (3 mg, 0.007 mmol, 5%) como un sólido de color amarillo. <sup>1</sup>H RMN: (500 MHz, CD<sub>3</sub>OD) δ 8.97 (s, 1H), 8.61 (s, 1H), 8.28 (s, 1H), 8.27 (s, 1H), 7.52-7.40 (m, 5H), 4.02-3.44 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 431; CLAR R<sub>t</sub> = 0.82 min., columna G, condiciones B.

20

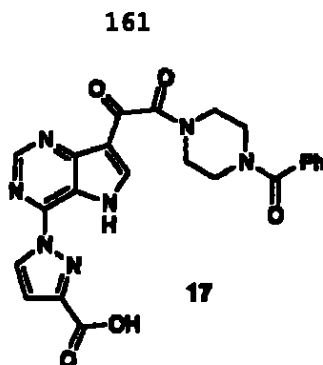
**Preparación del ejemplo 9:**

Ácido 1-(7-[2-(4-benzoil-piperazin-1-il)-2-oxo-acetil]-5H-pirrolo[3,2-d]pimirindin-4-il)-1H-pirazol-3-carboxílico (Compuesto 17).

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341 345

Ejemplo 9



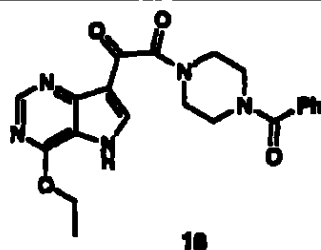
5

En un tubo sellado, el intermediario de dicarbonilo  
 10 (30 mg, 0.076 mmol) y ácido pirazolcarboxílico (26 mg,  
 0.23 mmol), polvo de cobre (10 mg, 0.16 mmol) y  $K_2CO_3$  (52 mg,  
 0.38 mmol) se combinaron y calentaron a  $150^\circ C$  con microondas  
 10 durante 2 h. La reacción se diluyó con MeOH (3 ml), se  
 filtró a través de celite, concentró, disolvió en DMSO y  
 purificó por CLAR preparativa para producir 17 (5 mg, 0.01  
 mmol, 14%) como un sólido de color blanco.  $^1H$  RMN: (500 MHz,  
 DMSO- $d_6$ )  $\delta$  13.32 (s amplio, 1H), 12.55 (s amplio, 1H), 8.98-  
 15 8.96 (m, 2H), 8.71 (s, 1H), 7.51-7.38 (m, 5H), 7.13 (d,  $J=2.4$   
 Hz, 1H), 3.90-3.20 (m, 8H); CL/EM: (ES+)  $m/z$   $(M+H)^+ = 474$ ;  
 CLAR  $R_t = 0.76$  min., columna G, condiciones B.

**Preparación del ejemplo 10:**

20 1-(4-benzoilpiperazin-1-il)-2-(4-etoxi-5H-pirrolo[3,2-  
d]pirimidin-7-il)etano-1,2-diona (Compuesto 18).

Ejemplo 10



25

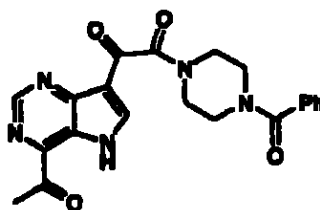
348 346

En un tubo sellado, el intermediario de dicarbonilo 10 (30 mg, 0.076 mmol) y ácido 3-pirazolcaboxílico (26 mg, 0.23 mmol), polvo de cobre (10 mg, 0.16 mmol) y  $K_2CO_3$  (52 mg, 0.38 mmol) en EtOH (1.0 ml) se combinaron y calentaron a 150°C con microondas durante 2 h. La reacción se diluyó con MeOH (3 ml), se filtró a través de celite, concentró, se disolvió en DMSO y purificó por CLAR preparativa para producir 18 (1 mg, 0.002 mmol, 3%) como un sólido de color blanco.  $^1H$  RMN: (500 MHz,  $CD_3OD$ )  $\delta$  8.73 (s, 1H), 8.45 (s, 1H), 7.57-7.40 (m, 5H), 4.77 (q,  $J=7.3$  Hz, 2H), 4.04-3.42 (m, 8H), 1.53 (t,  $J=7.3$  Hz, 3H); CL/EM (ES+)  $m/z$   $(M+H)^+ = 408$ ; CLAR  $R_t = 0.85$  min., columna G, condiciones B.

#### Preparación del ejemplo 11:

1-(4-acetil-5H-pirrólo[3,2-d]pirimidin-7-il)-2-(4-benzopiperazin-1-il)-etan-1,2-diona (Compuesto 19).

Ejemplo 11



19

En un tubo sellado, el intermediario de dicarbonilo 10 (600 mg, 1.5 mmol), tributil(1-etoxivinil)estano (1.5 ml, 4.5 mmol), tetraquis(trifenilfosfina)paladio(0) (350 mg, 0.30 mmol) y 1,4-dioxano (15 ml) se combinaron y calentaron a 120°C con microondas durante 2h. La mezcla de reacción se

344 347

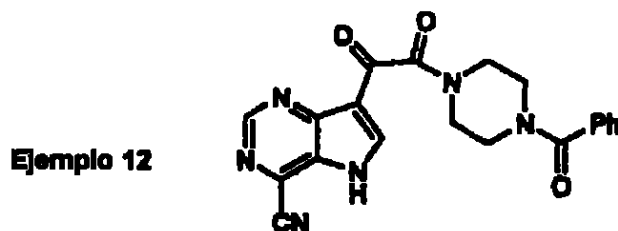
dividió y 25% p/p fue concentrado, diluido con MeOH/CH<sub>2</sub>Cl<sub>2</sub> (2:1, 1.5 ml) y 1N de HCl acuoso (0.5 ml). La reacción se agitó durante la noche, se neutralizó con 1N de NaOH acuoso (0.5 ml) y se concentró. El residuo se disolvió en DMSO, se  
 5 filtró y purificó por CLAR preparativa para producir 19 (79 mg, 0.20 mmol, 53%) como un sólido de color rosa. <sup>1</sup>H RMN: (500 MHz, CD<sub>3</sub>OD) δ 9.19 (s, 1H), 8.62 (s, 1H), 7.52-7.40 (m, 5H), 3.92-3.41 (m, 8H), 2.80 (s, 3H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 406; CLAR R<sub>t</sub> = 0.79 min., columna N.

10

#### Preparación del ejemplo 12:

7-(2-(4-benzoilpiperazin-1-il)-2-oxoacetyl)-5H-pirrólo[3,2-d]pirimidina-4-carbonitrilo (Compuesto 20).

15



20

En un tubo sellado, el intermediario de dicarbonilo  
 20 10 (40 mg, 0.10 mmol), cianuro de potasio (10 mg, 0.15 mmol),  
 4-toluensulfinato de sodio (20 mg, 0.11 mmol) y DMF (0.8 ml)  
 se combinaron y calentaron a 100°C durante 3 h. La mezcla de  
 reacción cruda se dividió entre 5% de Na<sub>2</sub>CO<sub>3</sub> acuoso (0.5 ml) y  
 EtOAc (4 ml). La capa orgánica se lavó con 5% de Na<sub>2</sub>CO<sub>3</sub>  
 25 acuoso (0.7 ml), concentró, disolvió en MeOH/DMSO (3:1, 2 ml)

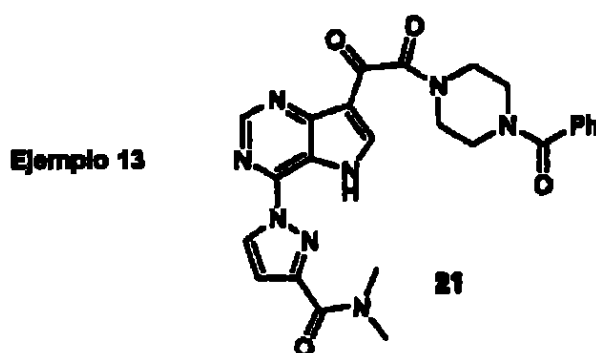


250 348

y purificó por CLAR preparativa para producir 20 (10 mg, 0.03 mmol, 26%) como un sólido de color blanco.  $^1\text{H}$  RMN: (500 MHz, DMSO- $d_6$ )  $\delta$  14.16 (s amplio, 1H), 9.20 (s, 1H), 8.96 (s, 1H), 7.52.-7.36 (m, 5H), 3.90-3.28 (m, 8H), CL/EM: (ES+) m/z (M+H) $^+$  = 389; CLAR  $R_t$  = 0.92 min., columna P, condiciones B.

**Preparación del ejemplo 13:**

1-(7-(2-(4-benzoylpiperazin-1-il)-2-oxoacetil)-5H-pirrolo[3,2-d]pirimidin-4-il)-N,N-dimetil-1H-pirazol-3-carboxamida (Compuesto 21).



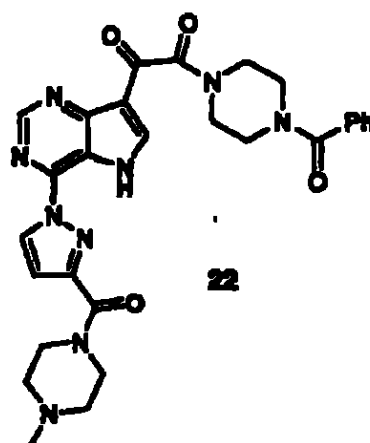
En un tubo sellado, el intermediario de dicarbonilo (50 mg, 0.13 mmol), N,N-dimetil-1H-pirazol-3-carboxamida (53 mg, 0.38 mmol), cobre(0) (10 mg) y 1,4-dioxano (0.8 ml) se combinaron y calentaron a 150°C con microondas durante 2h. La mezcla de reacción se concentró, diluyó con MeOH y DMSO, filtró y purificó por CLAR preparativa para producir 21 (2.3 mg, 0.005 mmol, 4%) como un sólido de color amarillo.  $^1\text{H}$  NMR: (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.94-8.87 (m, 2H), 8.59 (s, 1H), 7.56-7.36 (m, 5H), 6.94 (d, J=2.8 Hz, 1H), 4.07-3.43 (m, 8H), 3.29 (s,

3H), 3.19 (s, 3H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 501; CLAR R<sub>t</sub> = 1.16 min., column N.

**Preparación del Ejemplo 14:**

5 1-(4-benzoilpiperazin-1-il)-2-(4-(3-(1-metilpiperazina-4-carbonil)-1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 22).

Ejemplo 14



15

Se disolvieron ácido carboxílico 17 (34 mg, 0.73 mmol), N-metilpiperazina (15 mg, 0.15 mmol), N,N-diisopropiletilamina (0.13 ml, 94 mg, 0.73 mmol) y cloruro bis(2-oxo-3-oxazolidinil)fosfínico (41 mg, 0.16 mmol) en CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) y se agitaron durante 20h. La mezcla de reacción se concentró, diluyó con MeOH (1.7 ml), filtró y purificó por CLAR preparativa para producir 22 (41 mg, 0.73 mmol, 99%) como un sólido de color blanco. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.93 (d, J=2.8 Hz, 1H), 8.90 (s, 1H), 8.60 (s, 1H), 7.54-7.37 (m, 5H), 6.98 (d, J=2.8 Hz, 1H), 4.06-3.12 (m,

20

25

252 350

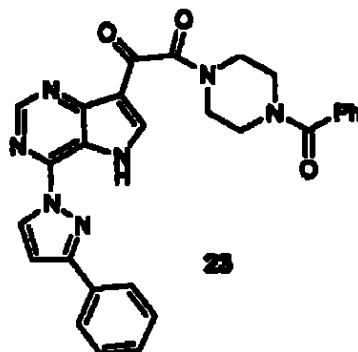
16H), 2.97 (s, 3H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 556; CLAR R<sub>t</sub> = 1.03 min., columna P., condiciones B.

### Preparación del Ejemplo 15:

5 1-(4-benzoilpiperazin-1-il)-2-(4-(3-fenil-1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidina-7-il)etano-1,2-diona (Compuesto 23).

10

Ejemplo 15



23

En un tubo sellado, el intermediario de dicarbonilo  
 15 10 (50 mg, 0.13 mmol), 3-fenil-1H-pirazol (80 mg, 0.56 mmol)  
 y 1,4-dioxano (2.5 ml) se combinaron y calentaron a 170°C con  
 microondas durante 20 min. La reacción se concentró y  
 trituró con MeOH (3 ml). Los sólidos resultantes se lavaron  
 con MeOH y con Et<sub>2</sub>O para producir 23 (33 mg, 0.07 mmol, 50%)  
 20 como un sólido color marrón. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ  
 12.42 (s amplio, 1H), 8.95 (d, J=2.8 Hz, 1H), 8.92 (s, 1H),  
 8.57 (br d, J=3.1 Hz, 1H), 8.27 (d, J=7.3 Hz, 2H), 7.55 (dd,  
 J=7.3, 7.3 Hz, 2H), 7.48 (t, J=7.3 Hz, 1H), 7.51-7.38 (m,  
 5H), 7.30 (d, J=2.8 Hz, 1H), 3.92-3.21 (m, 8H); CL/EM: (ES+)  
 25 m/z (M+H)<sup>+</sup> = 505; CLAR R<sub>t</sub> = 1.40 min., columna Q,

23 351

condiciones B.

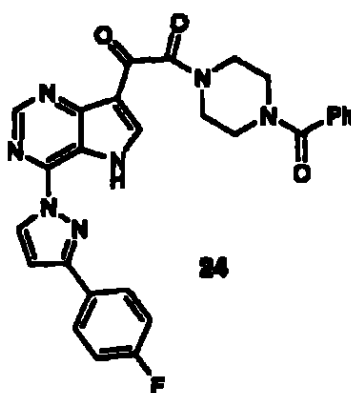
**Preparación del Ejemplo 16:**

1-(4-benzoylpiperazin-1-il)-2-(4-(3-(4-fluorofenil)-1H-

pirazol-1-il)-5H-pirrólo[3,2-d]pirimidin-7-il)etan-1,2-diona

(Compuesto 24).

Ejemplo 16



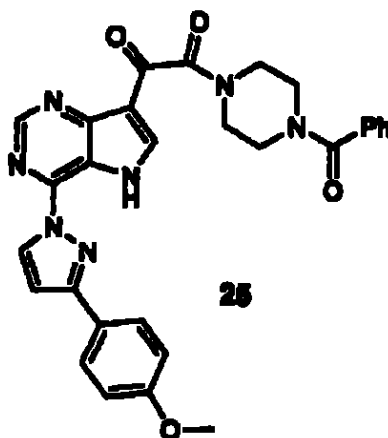
24

En un tubo sellado, el intermediario de dicarbonilo  
 10 (50 mg, 0.13 mmol), 3-(4-fluorofenil)-1H-pirazol (150 mg,  
 0.93 mmol) y 1,4-dioxano (2 ml) se combinaron y calentaron a  
 160°C con microondas durante 20 min. La reacción se  
 concentró, diluyó con MeOH (3 ml), neutralizó con NaHCO<sub>3</sub>  
 acuoso saturado y 24 (15 mg, 0.03 mmol, 22%) se colectaron  
 20 por filtración como un sólido color marrón. <sup>1</sup>H NMR: (500 MHz,  
 DMSO-d<sub>6</sub>) δ 12.48 (s amplio, 1H), 8.96 (d, J=2.8 Hz, 1H), 8.91  
 (s, 1H), 8.58 (s amplio, 1H), 8.34 (dd, J=8.7, 5.6 Hz, 2H),  
 7.50-7.39 (m, 5H), 7.88 (t, J=8.7 Hz, 2H), 7.80 (d, J=2.8 Hz,  
 1H), 3.91-3.23 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 524; CLAR R<sub>t</sub>  
 25 = 1.42 min., columna Q, condiciones B.

734 352

**Preparación del Ejemplo 17:**

1-(4-benzoilpiperazin-1-il)-2-(4-(3-(4-metoxifenil)-1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona  
 5 (Compuesto 25).

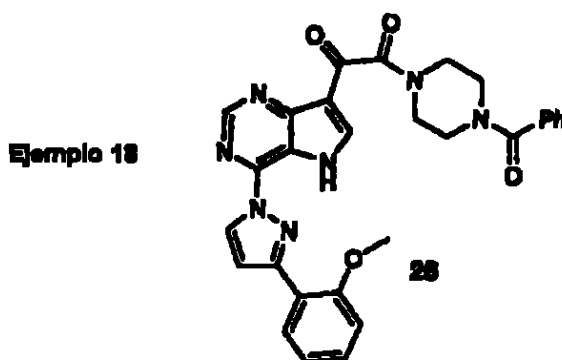
**Ejemplo 17**

En un tubo sellado, el intermediario de dicarbonilo  
 15 10 (50 mg, 0.13 mmol), 3-(4-metoxifenil)-1H-pirazol (105 mg,  
 0.60 mmol) y 1,4-dioxano (2.5 ml) se combinaron y calentaron  
 a 170°C con microondas durante 20 min. La reacción se  
 concentró y trituró con MeOH (3 ml). Los sólidos resultantes  
 se lavaron con MeOH y con Et<sub>2</sub>O para producir el 25 (43 mg,  
 20 0.08 mmol, 61%) como un sólido de color marrón. <sup>1</sup>H NMR: (500  
 MHz, DMSO-d<sub>6</sub>) δ 12.41 (s amplio, 1H), 8.91 (d, J=2.8 Hz, 1H),  
 8.89 (s, 1H), 8.55 (br d, J=3.4 Hz, 1H), 8.20 (d, J=8.7 Hz,  
 2H), 7.51-7.39 (m, 5H), 7.23 (d, J=2.8 Hz, 1H), 7.08 (d,  
 J=8.7 Hz, 2H), 3.85 (s, 3H), 3.92-3.21 (m, 8H); CL/EM: (ES+)  
 25 m/z (M+H)<sup>+</sup> = 535; CLAR R<sub>t</sub> = 1.40 min., columna Q, condiciones B.

313 353

**Preparación del Ejemplo 18:**

1-(4-benzoilpiperazin-1-il)-2-(4-(3-(2-metoxifenil)-1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etano-1,2-diona  
(Compuesto 26)



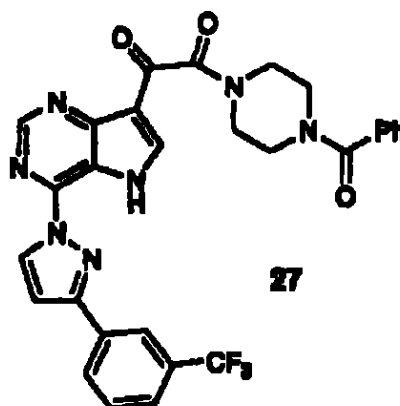
En un tubo sellado, el intermediario de dicarbonilo 10 (51 mg, 0.13 mmol), 3-(2-metoxifenil)-1H-pirazol (109 mg, 0.60 mmol) y 1,4-dioxano (2 ml) se combinaron y calentaron a 170°C con microondas durante 20 min. La reacción se concentró y trituró con MeOH (3 ml). Los sólidos resultantes se lavaron con MeOH y con Et<sub>2</sub>O para producir 26 (32 mg, 0.06 mmol, 47%) como un sólido color marrón. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.34 (s amplio, 1H), 8.91 (s, 1H), 8.90 (d, J=2.8 Hz, 1H), 8.55 (br d, J=3.4 Hz, 1H), 8.37 (dd, J=7.8, 1.5 Hz, 1H), 7.50-7.39 (m, 5H), 7.47 (ddd, J=8.2, 7.0, 1.5 Hz, 1H), 7.21 (d, J=2.8 Hz, 1H), 7.20 (d, J=8.2 Hz, 1H), 7.14 (dd, J=7.8, 7.0 Hz, 1H), 3.94 (s, 3H), 3.91-3.23 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 535; CLAR Tr = 1.42 min., columna Q, condiciones B.

352

354

**Preparación del Ejemplo 19:**

1-(4-benzoylpiperazin-1-il)-2-(4-(3-(3-  
(trifluorometil)fenil)-1H-pirazol-1-il)-5H-pirrolo[3,2-  
 5 d]pirimidin-7-il)etan-1,2-diona (Compuesto 27).

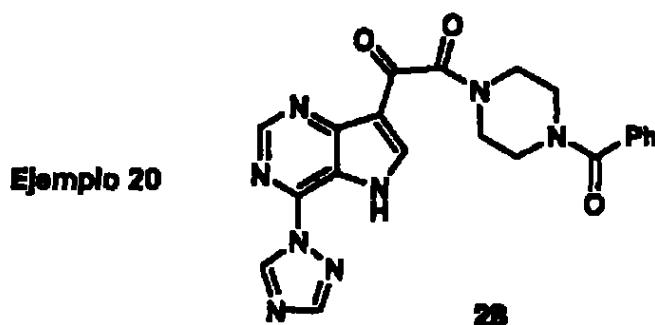
**Ejemplo 19**

En un tubo sellado, el intermediario de dicarbonilo  
 15 10 (50 mg, 0.13 mmol), 3-(3-(trifluorometil)fenil)-1H-pirazol  
 (150 mg, 0.70 mmol) y 1,4-dioxano (2 ml) se combinaron y  
 calentaron a 160°C con microondas durante 20 min. La reacción  
 se concentró, disolvió en MeOH (3 ml) y purificó por CLAR  
 preparativa para producir 27 (34 mg, 0.06 mmol, 46%) como un  
 20 sólido de color blanco. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.63 (s  
 amplio, 1H), 9.00 (d, J=2.8 Hz, 1H), 8.94 (s, 1H), 8.64 (s,  
 1H), 8.62 (d, J=7.9 Hz, 1H), 8.54 (s, 1H), 7.83 (d, J=7.6 Hz,  
 1H), 7.79 (dd, J=7.9, 7.6 Hz, 1H), 7.52-7.36 (m, 5H), 7.47  
 (d, J=2.8 Hz, 1H), 3.90-3.25 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup>  
 25 = 574; CLAR R<sub>t</sub> = 1.77 min., columna Q, condiciones B.

387 355

**Preparación del Ejemplo 20:**

1-(4-(1H-1,2,4-triazol-1-il)-5H-pirrólo[3,2-d]pirimidin-7-il)-2-(4-benzoilpiperazin-1-il)etan-1,2-diona (Compuesto 28).



En un tubo sellado, el intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 1,2,4-triazol (26 mg, 0.44 mmol), cobre(0) (8 mg, 0.13 mmol),  $K_2CO_3$  (23 mg, 0.17 mmol) y 1,4-dioxano (0.8 ml) se combinaron y calentaron a 140°C con microondas durante 6h. La mezcla de reacción se diluyó con MeOH/ $CH_2Cl_2$  (1:1, 2 ml), filtró, concentró, disolvió en MeOH/DMSO (5:4, 1.8 ml) y se purificó por CLAR preparativa. El sólido de color amarillo resultante se trituroó con MeOH para producir 28 (15 mg, 0.03 mmol, 28%) como un sólido de color amarillo ligero.  $^1H$  NMR: (500 MHz, DMSO- $d_6$ )  $\delta$  12.95 (s, 1H), 9.71 (s, 1H), 8.98 (s, 1H), 8.61 (s, 1H), 8.56 (s amplio, 1H), 7.52-7.36 (m, 5H), 3.92-3.23 (m, 8H); CL/EM: (ES+) m/z (M+H) $^+$  = 431; CLAR  $R_t$  = 0.98 min., columna C.



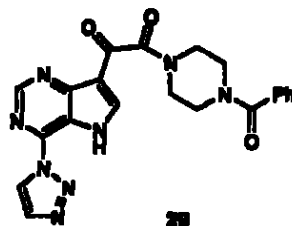
78 356

**Preparación del Ejemplo 21:**

1-(4-(1H-1,2,3-triazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)-2-(4-benzoilpiperazin-1-il)etan-1,2-diona (Compuesto 29).

5

Ejemplo 21



29

En un tubo sellado, el intermediario de dicarbonilo 10 (60 mg, 0.15 mmol) y 1,2,3-triazol (95 mg, 1.4 mmol) en 1,4-dioxano (3 ml) se combinaron y calentaron a 170°C con microondas durante 20 min. La reacción se concentró y el residuo se trituró con MeOH para producir 29 (10 mg, 0.023 mmol, 16%) como un sólido de color amarillo. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.08 (s, 1H), 9.04 (s, 1H), 8.66 (s, 1H), 8.07 (s, 1H), 7.57-7.41 (m, 5H), 4.08-3.43 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 431; CLAR R<sub>t</sub> = 0.95 min., columna O, condiciones B.

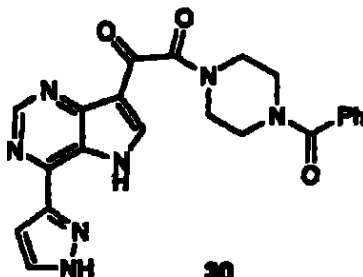
15

**Preparación del Ejemplo 22:**

1-(4-(1H-pirazol-3-il)-5H-pirrolo[3,2-d]pirimidin-7-il)-2-(4-benzoilpiperazin-1-il)etano-1,2-diona (Compuesto 30).

20

Ejemplo 22



30

25

389 357

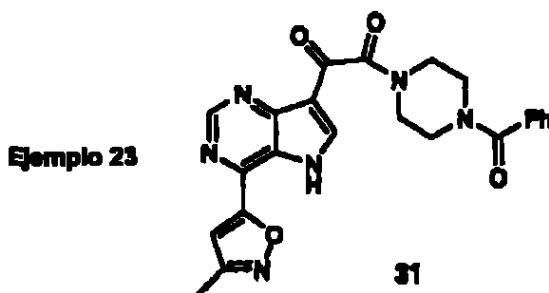
En un tubo sellado, el intermediario de dicarbonilo  
 10 (50 mg, 0.13 mmol), 3-(tributilstannil)pirazol (188 mg,  
 0.52 mmol), tetraquis(trifenilfosfina)-paladio(0) (72 mg,  
 0.06 mmol) y 1,4-dioxano (0.8 ml) se combinaron y calentaron  
 5 a 110°C con microondas durante 1h. La mezcla de reacción se  
 diluyó con MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 2 ml) y se filtró para coleccionar  
 los sólidos. Los sólidos se disolvieron en DMSO y se  
 purificaron por CLAR preparativa para producir 30 (28 mg,  
 0.07 mmol, 52%) como un sólido de color blanco. <sup>1</sup>H NMR: (500  
 10 MHz, DMSO-d<sub>6</sub>) δ 13.63 (s amplio, 1H), 12.41 (s, 1H), 9.03 (s,  
 1H), 8.44 (d, J=2.3 Hz, 1H), 8.03 (d, J=2.3 Hz, 1H), 7.50-  
 7.37 (m, 5H), 7.13 (d, J=1.8 Hz, 1H), 3.90-3.23 (m, 8H);  
 CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 430; CLAR R<sub>t</sub> = 0.87 min., columna R,  
 condiciones B.

15

#### Preparación del Ejemplo 23:

1-(4-benzoilpiperazin-1-il)-2-(4-(3-metilisoxazol-5-il)-5H-  
pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 31).

20



En un tubo sellado, el intermediario de dicarbonilo  
 25 10 (50 mg, 0.13 mmol), 3-metil-5-(tributilstannil)isoxazol

260 358

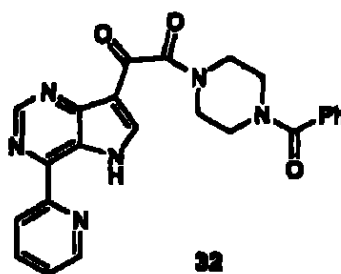
(141 mg, 0.38 mmol), tetraquis(trifenilfosfina)-paladio (0) (30 mg, 0.03 mmol) y 1,4-dióxano (1 ml) se combinaron y calentaron a 110°C con microondas durante 2h, y entonces se calentaron a 120°C durante 2h. La reacción se repitió como se describe anteriormente y la solución de reacción se calentó a 110°C con microondas durante 5h. Las 2 reacciones se combinaron, diluyeron con MeOH/DMSO, filtraron y purificaron por CLAR preparativa. El sólido de color amarillo resultante se trituroó con MeOH para producir 31 (4 mg, 0.008 mmol, 3%) como un sólido de color blanco. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.11 (s, 1H), 8.66 (s, 1H), 7.56-7.42 (m, 5H), 7.27 (s, 1H), 4.06-3.45 (m, 8H), 2.47 (s, 3H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 445; CLAR R<sub>t</sub> = 1.23 min., columna L.

15 **Preparación del Ejemplo 24:**

1-(4-benzoilpiperazin-1-il)-2-(4-(piridin-2-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etano-1,2-diona (Compuesto 32).

20

Ejemplo 24



32

En un tubo sellado, el intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 2-(tributilstannil)piridina (140 mg, 0.38 mmol), tetraquis(trifenilfosfina)-paladio(0) (30 mg;

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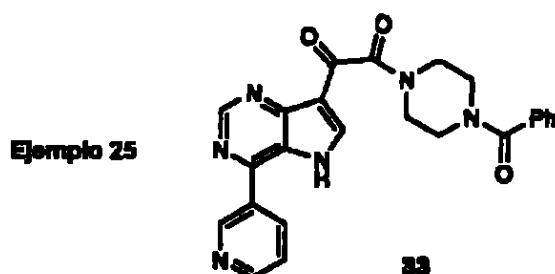
0.03 mmol) y 1,4-dioxano (0.8 ml) se combinaron y calentaron a 110°C con microondas durante 1h. La mezcla de reacción se concentró, se diluyó con MeOH, filtró y purificó por CLAR preparativa para producir 32 (8 mg, 0.02 mmol, 14%) como un sólido de color amarillo ceroso. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.15-9.10 (m, 1H), 8.89 (s amplio, 1H), 8.70 (d, J=7.9 Hz, 1H), 8.62 (s, 1H), 8.09-8.05 (m, 1H), 7.61-7.55 (m, 1H), 7.54-7.37 (m, 5H), 4.05-3.42 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 441; CLAR R<sub>t</sub> = 1.54 min., columna P.

10

**Preparación del Ejemplo 25:**

1-(4-benzoilpiperazin-1-il)-2-(4-(piridin-3-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 33).

15



En un tubo sellado, el intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 3-(tributilstannil)piridina (160 mg, 0.43 mmol), tetraquis(trifenilfosfina)-paladio(0) (40 mg, 0.03 mmol) y 1,4-dioxano (0.8 ml) se combinaron y calentaron a 130°C durante 4h. La mezcla de reacción se concentró hasta sequedad y se dividió entre EtOAc (5 ml) y NaHCO<sub>3</sub> acuoso saturado con fluoruro de cesio. La suspensión bifásica se

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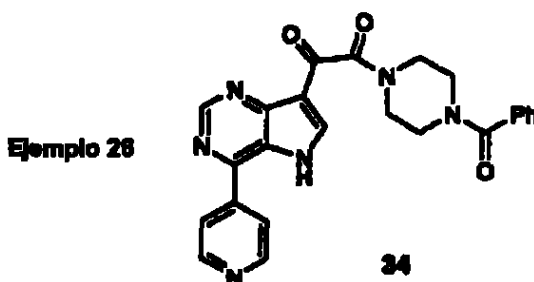
filtró, se separó y la capa acuosa se concentró hasta sequedad. El residuo se diluyó con MeOH (2 ml) y DMSO (0.5 ml), filtró y purificó por CLAR preparativa para producir 33 (7 mg, 0.02 mmol, 12%) como un sólido de color amarillo. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.41 (s, 1H), 9.20 (s, 1H), 8.96 (d, J=5.5 Hz, 1H), 8.91 (d, J=7.6 Hz, 1H), 8.73 (s, 1H), 8.05 (dd, J=7.6, 5.5 Hz, 1H), 7.56-7.42 (m, 5H), 4.10-3.43 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 441; CLAR R<sub>t</sub> = 0.92 min., columna S.

10

#### Preparación del Ejemplo 26:

1-(4-benzoilpiperazin-1-il)-2-(4-(piridin-4-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 34).

15



En un tubo sellado, el intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 4-(tributylestanil)piridina (140 mg, 0.38 mmol), tetraquis(trifenilfosfina)-paladio(0) (30 mg, 0.03 mmol) y 1-4-dioxano (0.8 ml) se combinaron y calentaron a 110°C con microondas durante 2h, y entonces a 120°C durante 2h. La mezcla de reacción se concentró, diluyó con MeOH/DMSO, filtró y se purificó por CLAR preparativa para

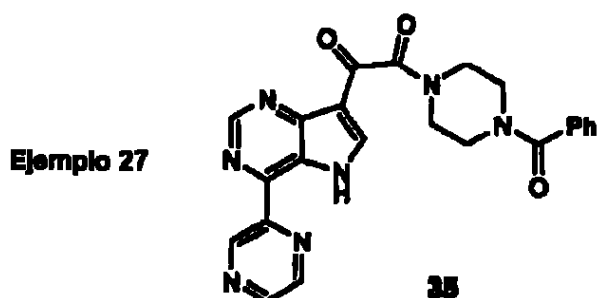
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257 361

producir 34 (22 mg, 0.08 mmol, 38%) como un sólido de color amarillo.  $^1\text{H}$  NMR: (500 MHz;  $\text{CD}_3\text{OD}$ )  $\delta$  9.24 (s, 1H), 9.04 (d,  $J=5.8$  Hz, 2H), 8.75 (s, 1H), 8.52 (d,  $J=5.8$  Hz, 2H), 7.57-7.40 (m, 5H), 4.12-3.44 (m, 8H); CL/EM: (ES+)  $m/z$   $(\text{M}+\text{H})^+$  = 441; CLAR  $R_t$  = 0.78 min., columna L.

**Preparación del Ejemplo 27:**

1-(4-benzoilpiperazin-1-il)-2-(4-(pirazin-2-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 35).



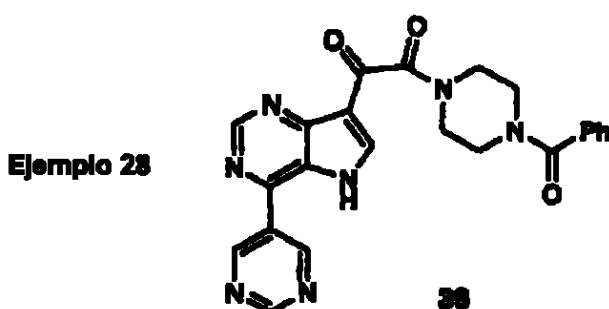
En un tubo sellado, el intermediario de dicarbonilo 10 (50 mg, 0.13 mmol), 2-(tributylestanil)pirazina (160 mg, 0.43 mmol), tetraquis(trifenilfosfina)-paladio(0) (30 mg, 0.03 mmol) y 1-4-dioxano (0.8 ml) se combinaron y calentaron a 120°C con microondas durante 2h, y entonces a 130°C durante 2h. La mezcla de reacción se concentró hasta sequedad, se diluyó con MeOH (2.5 ml) y DMSO (0.5 ml), filtró y purificó por CLAR preparativa. El sólido de color amarillo resultante se trituroó con MeOH para producir 35 (8 mg, 0.02 mmol, 15%) como un sólido de color amarillo ligero.  $^1\text{H}$  NMR: (500 MHz;

361 362

DMSO- $d_6$ )  $\delta$  12.93 (s amplio, 1H), 9.75 (d,  $J=1.2$  Hz, 1H), 9.21 (s, 1H), 8.93 (dd,  $J=2.4, 1.2$  Hz, 1H), 8.90 (d,  $J=2.4$  Hz, 1H), 8.64 (s amplio, 1H), 7.53-7.35 (m, 5H), 3.96-3.21 (m, 8H); CL/EM: (ES+)  $m/z$   $(M+H)^+ = 442$ ; CLAR Tr = 1.15 min.,  
 5 columna S.

**Preparación del Ejemplo 28:**

1-(4-benzoilpiperazin-1-il)-2-(4-(pirimidin-5-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 36).



15 En un tubo sellado, el intermediario de dicarbonilo  
 10 (50 mg, 0.13 mmol), 5-(tributylestanil)pirimidino (160 mg, 0.43 mol), tetraquis(trifenilfosfina)-paladio(0) (30 mg, 0.03 mmol) y 1-4-dioxano (0.8 ml) se combinaron y calentaron a 130°C con microondas durante 2h. La mezcla de reacción se  
 20 concentró, diluyó con MeOH/DMSO, filtró y purificó por CLAR preparativa. El sólido de color naranja resultante se trituró con acetona para producir 36 (36.3 mg, 0.08 mmol, 63%) como un sólido de color amarillo.  $^1H$  NMR: (500 MHz, DMSO- $d_6$ )  $\delta$  13.48 (s amplio, 1H), 9.42 (s, 1H), 9.41 (s, 2H),  
 25 9.18 (s 1H), 7.52-7.39 (m, 5H), 3.91-3.24 (m, 8H); CL/EM:

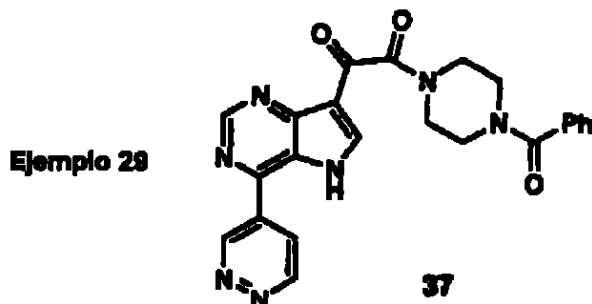
Gesi 363

(ES+)  $m/z$   $(M+H)^+ = 442$ ; CLAR  $R_t = 0.90$  min., columna S.

**Preparación del Ejemplo 29:**

1-(4-benzoylpiperazin-1-il)-2-(4-(piridazin-4-il)-5H-

5 pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 37).



10

En un tubo sellado, el intermediario de dicarbonilo  
10 (50 mg, 0.13 mmol), 4-(tributylestanil)piridazina (160 mg,  
0.43 mmol), tetraquis(trifenilfosfina)-paladio(0) (30 mg,  
0.03 mmol) y 1,4-dioxano (0.8 ml) se combinaron y calentaron  
15 a 130°C con microondas durante 2h. La mezcla de reacción se  
concentró, diluyó con MeOH, filtró y purificó por CLAR  
preparativa. El aceite de color negro resultante se purificó  
por CLAR preparativa y el sólido de color amarillo resultante  
se trituyó con acetona para producir 37 (18.7 mg, 0.04 mmol,  
20 33%) como un sólido de color blanco opaco.  $^1\text{H}$  NMR: (500 MHz,  
DMSO- $d_6$ )  $\delta$  13.48 (s amplio, 1H), 9.82 (s amplio, 1H), 9.54  
(dd,  $J=5.2$ , 1.1 Hz, 1H), 9.22 (s 1H), 8.85 (s amplio, 1H),  
• 8.29 (dd,  $J=5.2$ , 2.0 Hz, 1H), 7.54-7.37 (m, 5H), 3.91-3.25  
(m, 8H); CL/EM: (ES+)  $m/z$   $(M+H)^+ = 442$ ; CLAR  $T_r = 0.89$  min.,  
25 columna S.



740

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Preparación de 2-(4-(isoquinolin-1-il)piperazin-1-il)acetonitrilo 38.

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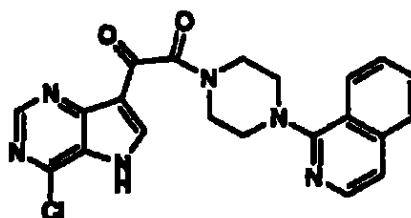
A una solución de 1-(piperazin-1-il)isoquinolina (459 mg, 2.15 mmol) en THF (15 ml) se agregó NEt<sub>3</sub> (3.6 ml, 27 mmol) y cloroacetonitrilo (1.8 ml, 28 mmol) y la reacción se agitó 3h. La mezcla de reacción se filtró, se concentró y el residuo se purificó por cromatografía en gel de sílice (Biotage 25-short, 25% de EtOAc/hexanos hasta 100% de EtOAc/hex) para producir 38 (188 mg, 0.75 mmol, 35%) como un sólido de color blanco. CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 253; CLAR R<sub>t</sub> = 1.23 min., columna Q, condiciones B.

#### Preparación del Ejemplo 30:

20

1-(4-cloro-5H-pirrólo[3,2-d]pirimidin-7-il)-2-(4-(isoquinolin-1-il)piperazin-1-il)etan-1,2-diona (Compuesto 39).

Ejemplo 30



39

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72 365

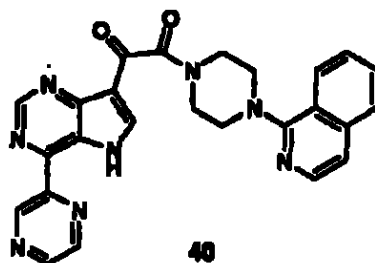
A una suspensión de intermediario de cloruro de ácido 7 (115 mg, 0.53 mmol) y 2-(4-(isoquinolin-1-il)piperazin-1-il)acetonitrilo 38 (188 mg, 0.75 mmol) en THF (5 ml), a -78°C, se agregó 0.5 M de KHMDS en tolueno (3.4 ml, 1.7 mmol). La reacción se agitó 2h, y la presencia del intermediario de cianocetona deseado se verificó por CLEM. Una solución de 32% de ácido peracético se agregó en ácido acético acuoso diluido (0.5 ml, 2.4 mmol) y la mezcla de reacción se permitió calentar a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con EtOAc (10 ml) y NH<sub>4</sub>Cl acuoso saturado (10 ml) y se filtró. Las capas se separaron y la capa acuosa se extrajo con EtOAc (25 ml). Las capas orgánicas combinadas se concentraron y se purificaron por CLAR preparativa para producir el 39 (102 mg, 0.24 mmol, 45%) como un sólido de color amarillo brillante. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.84 (s, 1H), 8.70 (s, 1H), 8.38 (d, J=7.9 Hz, 1H), 8.06 (d, J=7.2 Hz, 1H), 7.99 (dd, J=7.9, 7.6 Hz, 1H), 7.89 (d, J=6.7 Hz, 1H), 7.83 (dd, J=7.6, 7.2 Hz, 1H), 7.62 (d, J=6.7 Hz, 1H), 4.20-3.79 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 421; CLAR R<sub>t</sub> = 0.83 min., columna S.

#### Preparación del Ejemplo 31:

1-(4-(isoquinolin-1-il)piperazin-1-il)-2-(4-(pirazen-2-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etano-1,2-diona (Compuesto 40).

38 360

Ejemplo 31



5

En un tubo sellado, el intermediario de dicarbonilo  
 39 (40 mg, 0.10 mmol), 2-(tributylestanil)pirazina (105 mg,  
 0.28 mmol), tetraquis(trifenilfosfina)-paladio(0) (30 mg,  
 0.03 mmol) y 1,4-dioxano (0.8 ml) se combinaron y calentaron  
 a 130°C con microondas durante 2h. La mezcla de reacción se  
 diluyó con MeOH (1 ml) y DMSO (1 ml), filtró a través de  
 celite y purificó por CLAR preparativa para producir 40 (12  
 mg, 0.03 mmol, 27%) como un sólido de color amarillo. <sup>1</sup>H NMR:  
 (500 MHz, CD<sub>3</sub>OD) δ 9.85 (s, 1H), 9.21 (s, 1H), 8.93 (s amplio,  
 1H), 8.83 (d, J=2.4 Hz, 1H), 8.72 (s, 1H), 8.42 (d, J=8.9 Hz,  
 1H), 8.09 (d, J=7.9 Hz, 1H), 8.05 (dd, J=8.0, 7.0 Hz, 1H),  
 7.87 (dd, J=8.9, 8.0 Hz, 1H), 7.85 (d, J=7.0 Hz, 1H), 7.66  
 (d, J=6.7 Hz, 1H), 4.24-4.20 (m, 2H), 4.14-4.04 (m, 2H),  
 3.99-3.91 (m, 4H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 465; CLAR R<sub>t</sub> =  
 0.92 min., columna S.

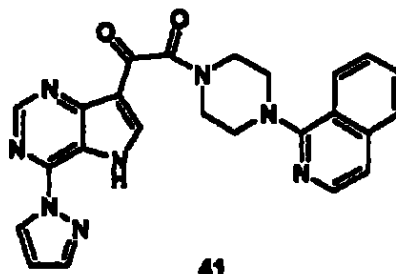
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#### Preparación del Ejemplo 32:

1-(4-(1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)-2-(4-  
(isoquinolin-1-il)piperazin-1-il)etan-1,2-diona (Compuesto  
41).

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Ejemplo 32



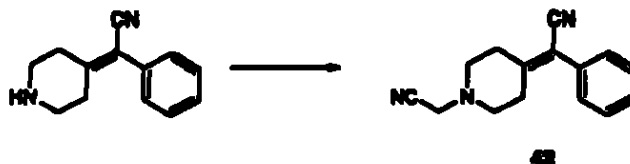
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En un tubo sellado, el intermediario de dicarbonilo 39 (41 mg, 0.10 mmol), pirazol (26 mg, 0.38 mmol), cobre(0) (10 mg) y 1,4-dioxano (0.8 ml) se combinaron y calentaron a 140°C con microondas durante 50 min. La mezcla de reacción se diluyó con MeOH (1 ml) y DMSO (1 ml), se filtró a través de celite y se purificó por CLAR preparativa para producir 41 (11 mg, 0.02 mmol, 23%) como un sólido de color amarillo ligero. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.90 (s amplio, 1H), 8.85 (d, J=2.5 Hz, 1H), 8.61 (s, 1H), 8.42 (d, J=8.5 Hz, 1H), 8.09 (d, J=7.9 Hz, 1H), 8.08 (s, 1H), 8.04 (dd, J=7.6, 7.3 Hz, 1H), 7.89-7.85 (m, 1H), 7.85 (d, J=6.7 Hz, 1H), 7.66 (d, J=7.0 Hz, 1H), 6.72 (dd, J=2.5, 1.6 Hz, 1H), 4.22-4.18 (m, 2H), 4.12-4.07 (m, 2H), 3.97-3.89 (m, 4H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 453; CLAR R<sub>t</sub> = 0.97 min., columna S.

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**Preparación de 2-(1-(cianometil)piperidin-4-ilideno)-2-fenilacetonitrilo 42**



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320

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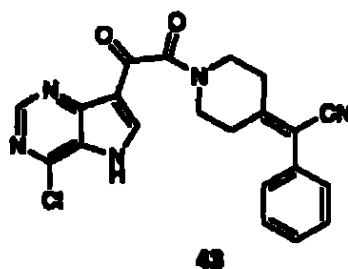
A una solución de 2-fenil-2-(piperidin-4-ilideno)acetonitrilo (6.8 g, 34 mmol) en THF (150 ml) se agregó NEt<sub>3</sub> (40 ml, 300 mmol) y cloroacetonitrilo (20 ml, 315 mmol) y la reacción se agitó 16h. Los precipitados se  
5 filtraron y el filtrado se concentró hasta sequedad. Los residuos se purificaron por cromatografía de gel de sílice (Biotage 40-short, 20% EtOAc/Hex hasta 50% EtOAc/Hex) para producir 42 (1.7 g, 7.2 mmol, 21 %) como un sólido ceroso de color amarillo. <sup>1</sup>H NMR: (500 MHz, CDCl<sub>3</sub>) δ 7.44-7.34 (m, 3H),  
10 7.30-7.27 (m, 2H), 3.65 (s, 2H), 2.96 (t, J=5.3 Hz, 2H), 2.90 (t, J=5.3 Hz, 2H), 2.70 (t, J=5.6 Hz, 2H), 2.62 (t, J=5.6 Hz, 2H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 238; CLAR R<sub>t</sub> = 1.33 min., columna O, condiciones B.

15 **Preparación del Ejemplo 33:**

2-(1-(2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-7-il)-2-oxoacetil)piperidin-4-ilideno)-2-fenilacetonitrilo (Compuesto 43).

20

Ejemplo 33



A una suspensión del intermediario de cloruro de ácido 7 (100 mg, 0.46 mmol) y el intermediario de  
25 fenilcianoalqueno 42 (143 mg, 0.60 mmol) en THF (4 ml) a

3f)

369

-78°C se agregó una solución de 0.5M de KHMDS en tolueno (3.0 ml, 1.5 mmol). La reacción se agitó 2h y la presencia del intermediario de cianocetona deseado se verificó por CLEM. Una solución de 32% de ácido peracético en ácido acético

5 acuoso diluido (0.44 ml, 2.1 mmol) se agregó a la mezcla de reacción y entonces se permitió tibiaar a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con EtOAc (15 ml) y NH<sub>4</sub>Cl acuoso saturado (10 ml). Las capas se separaron y la capa acuosa se extrajo con EtOAc (2 x 20 ml).

10 Las capas orgánicas combinadas se concentraron, el residuo se purificó por CLAR preparativa y el sólido de color amarillo resultante se trituroó con MeOH para producir 43 (18.6 mg, 0.04 mmol, 10%) como un sólido de color blanco. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 13.73 (s, 1H), 8.85 (s, 0.5H), 8.84 (s, 0.5H),

15 8.79 (s, 0.5H), 8.76 (s, 0.5H), 7.54-7.30 (m, 5H), 3.86 (t, J=5.8 Hz, 1H), 3.70 (t, J=5.8 Hz, 1H), 3.56 (t, J=5.8 Hz, 1H), 3.38 (t, J=5.8 Hz, 1H), 2.93 (t, J=5.8 Hz, 1H), 2.65 (t, J=5.8 Hz, 1H), 2.63 (dd, J=5.8 Hz, 1H), 2.36 (t, J=5.8 Hz, 1H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 406; CLAR R<sub>t</sub> = 1.28 min.,

20 columna S.

**Preparación del Ejemplo 34:**

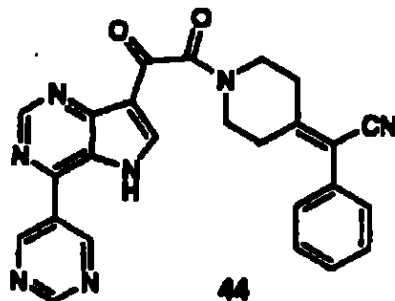
2-(1-(2-oxo-2-(4-(pirimidin-5-il)-5H-pirrolo[3,2-d]pirimidin-  
7-il)acetil)piperidin-4-ilideno)-2-fenilacetonitrilo

25 (Compuesto 44).

33 ✓

370

Ejemplo 34

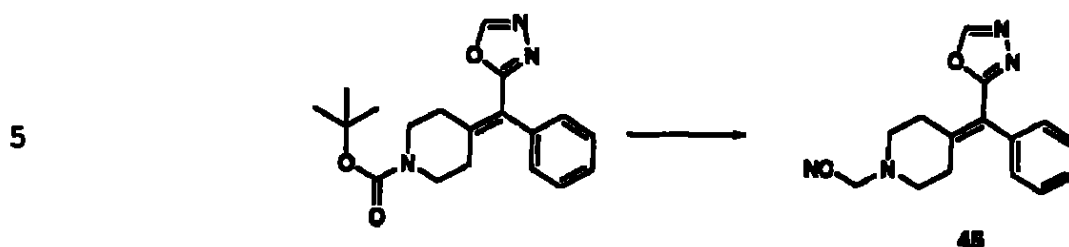


5

En un tubo sellado, intermediario de dicarbonilo 33 (30 mg, 0.074 mmol), 5-(tributilestanil)pirimidina (82 mg, 0.22 mmol), tetraquis(trifenilfosfina)-paladio(0) (20 mg, 0.02 mmol) y 1-4-dioxano (0.8 ml) se combinaron y calentaron a 130°C con microondas durante 2h. La mezcla de reacción se diluyó con MeOH/DMSO, filtró y purificó por CLAR preparativa para producir 44 (8 mg, 0.02 mmol, 30%) como un sólido de color amarillo. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 9.47 (s, 1H), 9.45 (s, 1H), 9.40 (s, 0.5H), 9.39 (s, 0.5H), 9.19 (s, 0.5H), 9.18 (s, 0.5H), 8.72 (s, 0.5H), 8.69 (s, 0.5H), 7.53-7.31 (m, 5H), 4.02 (dd, J=6.1, 5.8 Hz, 1H), 3.84 (dd, J=6.1, 5.8 Hz, 1H), 3.75 (dd, J=5.8, 5.8 Hz, 1H), 3.57 (dd, J=6.1, 5.8 Hz, 1H), 3.07 (dd, J=6.1, 5.8 Hz, 1H), 2.86 (dd, J=5.8, 5.8 Hz, 1H), 2.74 (dd, J=6.1, 5.8 Hz, 1H), 2.54 (dd, J=6.1, 5.8 Hz, 1H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 450; CLAR R<sub>t</sub> = 1.48 min., columna O.

233 371

Preparación de 2-(4-((1,3,4-oxadiazol-2-il)(fenil)metileno)piperidin-1-il)acetonitrilo 45.



4-((1,3,4-oxadiazol-2-il)(fenil)metilen)piperidin-1-carboxilato terc-butilo (100 mg, 0.29 mmol) se diluyó con 4M de HCl en 1-4-dioxano (1.2 ml, 4.8 mmol) y se agitó 1h. La reacción se concentró y el residuo se diluyó con THF (1.5 ml), trietilamino (0.5 ml, 3.8 mmol) y cloroacetonitrilo (0.25 ml, 3.9 mmol). La reacción se agitó 3 d, se concentró, diluyó con MeOH, filtró y purificó por CLAR preparativa para producir 45 (43 mg, 0.15 mmol, 53%) como un sólido de color blanco. <sup>1</sup>H NMR: (500 MHz, CDCl<sub>3</sub>) δ 8.27 (s, 1H), 7.41-7.31 (m, 3H), 7.20-7.16 (m, 2H), 3.55 (s, 2H), 3.02 (t, J=5.8 Hz, 2H), 2.75 (t, J=5.8 Hz, 2H), 2.61 (t, J=5.8 Hz, 2H), 2.39 (t, J=5.8 Hz, 2H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 281; CLAR R<sub>t</sub> = 0.97 min., columna G, condiciones B.

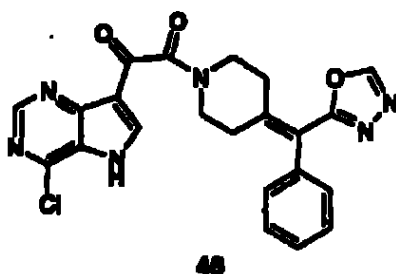
#### Preparación del Ejemplo 35:

1-(4-((1,3,4-oxadiazol-2-il)(fenil)metilin)piperidin-1-il)-2-(4-(1H-1,2,4-triazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona (Compuesto 46).



371 372

Ejemplo 35



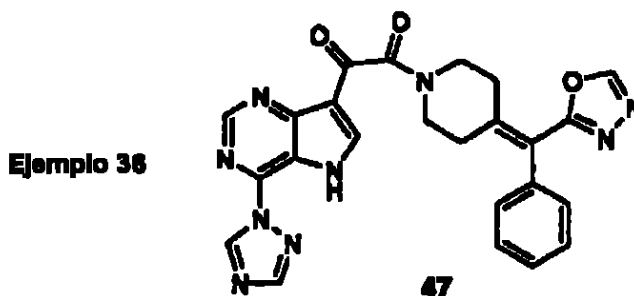
A una suspensión de intermediario de cloruro de ácido 7 (600 mg, 2.8 mmol) y 2-(4((1,3,4-oxadiazol-2-il)(fenil)metilen)piperidin-1-il)acetonitrilo 45 (800 mg, 2.9 mmol) en THF (5 ml), a  $-78^{\circ}\text{C}$  se agregó una solución de 0.5M de KHMDS en tolueno (17.2 ml, 8.6 mmol). La reacción se agitó 2h. Una solución de 32% de ácido peracético se agregó en ácido acético acuoso diluido (2.8 ml, 13 mmol) y la mezcla de reacción se permitió calentar a temperatura ambiente durante 1h. La mezcla de reacción se diluyó con EtOAc (30 ml) y salmuera (25 ml) y se filtró. Las capas se separaron y la capa orgánica se concentró. El residuo se trituró con  $\text{Et}_2\text{O}$  para producir 46 (340 mg, 0.76 mmol, 27%) como un sólido de naranja/amarillo.  $^1\text{H}$  NMR: (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.73 (s, 1H), 9.17 (s, 0.5H), 9.10 (s, 0.5H), 8.83 (s, 0.5H), 8.82 (s, 0.5H), 8.76 (s, 0.5H), 8.74 (s, 0.5H), 7.49-7.15 (m, 5H), 3.80 (t,  $J=5.8$  Hz, 1H), 3.71 (t,  $J=5.8$  Hz, 1H), 3.49 (t,  $J=5.8$  Hz, 1H), 3.40 (t,  $J=5.8$  Hz, 1H), 3.02 (t,  $J=5.8$  Hz, 1H), 2.75 (t,  $J=5.8$  Hz, 1H), 2.52 (t,  $J=5.8$  Hz, 1H), 2.25 (t,  $J=5.8$  Hz, 1H); CL/EM: (ES+)  $m/z$   $(M+H)^+ = 449$ ; CLAR  $R_f = 1.10$

251 373

min., columna P, condiciones B.

**Preparación del Ejemplo 36:**

1-(4-((1,3,4-oxadiazol-2-il)(fenil)metileno)piperidin-1-il)-  
 2-(4-(1H-1,2,4-triazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-  
 11)etan-1,2-diona (Compuesto 47).



En un tubo sellado, el intermediario de dicarbonilo  
 46 (30 mg, 0.07 mmol), 1,2,4-triazol (28 mg, 0.41 mmol),  
 cobre(0) (8 mg, 0.13 mmol),  $K_2CO_3$  (20 mg, 0.14 mmol) y 1,4-  
 dioxano (1 ml) se combinaron y calentaron a 140°C con  
 microondas durante 2h. La mezcla de reacción se diluyó con  
 MeOH/DMSO (2:3, 1 ml) y se purificó por CLAR preparativa para  
 producir 47 (4 mg, 0.008 mmol, 12%) como un sólido de color  
 amarillo.  $^1H$  NMR: (500 MHz,  $CD_3OD$ )  $\delta$  9.62 (s, 0.5H), 9.62 (s,  
 0.5H), 8.87 (s, 0.5H), 8.79 (s, 0.5H), 8.60 (s, 0.5H), 8.58  
 (s, 0.5H), 8.44 (s, 0.5H), 8.43 (s, 0.5H), 7.48-7.14 (m, 6H),  
 3.95 (dd,  $J=6.1$ , 5.8 Hz, 1H), 3.83 (dd,  $J=6.1$ , 5.8 Hz, 1H),  
 3.68 (dd,  $J=6.1$ , 5.5 Hz, 1H), 3.58 (dd,  $J=5.8$ , 5.8 Hz, 1H),  
 3.10 (dd,  $J=6.1$ , 5.8 Hz, 1H), 2.90 (dd,  $J=6.1$ , 5.5 Hz, 1H),  
 2.61 (dd,  $J=6.1$ , 5.8 Hz, 1H), 2.42 (dd,  $J=6.1$ , 5.5 Hz, 1H);

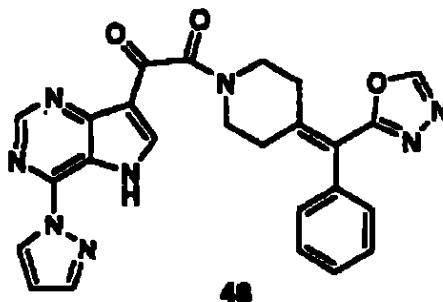
CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 482; CLAR R<sub>t</sub> = 1.13 min., columna P, condiciones B.

**Preparación del Ejemplo 37:**

5 1-(4-((1,3,4-oxadiazol-2-il)(fenil)metilen)piperidin-1-il)-2-(4-(1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-  
1,2-diona (Compuesto 48).

10

Ejemplo 37



48

En un tubo sellado, el intermediario de dicarbonilo  
 46 (30 mg, 0.07 mmol), pirazol (34 mg, 0.5 mmol) y  
 15 1,4-dioxano (0.7 ml) se combinaron y calentaron a 140°C con  
 microondas durante 50 min. La mezcla de reacción se diluyó  
 con MeOH/DMSO (1:1, 1.2 ml) y se purificó por CLAR  
 preparativa para producir 48 (10 mg, 0.02 mmol, 32%) como un  
 sólido de color amarillo. <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.86 (s,  
 20 1H), 8.85 (s, 0.5H), 8.82 (d, J=2.8 Hz, 0.5H), 8.81 (d, J=2.8  
 Hz, 0.5H), 8.79 (s, 0.5H), 8.53 (s, 0.5H), 8.51 (s, 0.5H),  
 8.04 (d, J=1.5 Hz, 0.5H), 8.03 (d, J=1.5 Hz, 0.5H), 7.46-7.16  
 (m, 5H), 6.71-6.67 (m, 1H), 3.94 (dd, J=6.1, 5.8 Hz, 1), 3.81  
 (dd, J=6.1, 5.8 Hz, 1H), 3.69 (dd, J=6.1, 5.8 Hz, 1H), 3.57

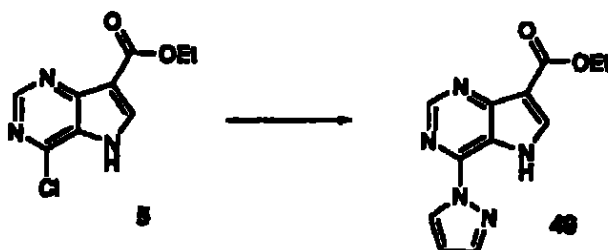
~~277~~ 375

(dd, J=5.8, 5.8 Hz, 1H), 3.08 (dd, J=5.8, 5.8 Hz, 1H), 2.91 (dd, J=6.1, 5.8 Hz, 1H), 2.59 (dd, J=6.1, 5.8 Hz, 1H), 2.43 (dd, J=6.1, 5.8 Hz, 1H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 481; CLAR R<sub>t</sub> = 1.27 min., columna P, condiciones B.

5

Preparación de 4-(1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidina-7-carboxilato de etilo 49.

10



15

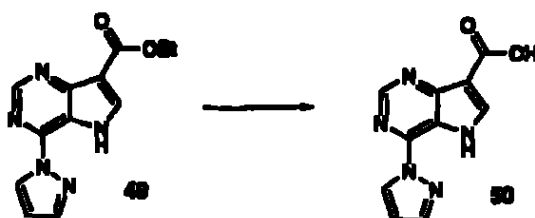
20

En un tubo sellado de cloruro de 4-cloro-5H-pirrolo[3,2-d]pirimidina-7-carbonilo 5 (2.0 g, 8.9 mmol), pirazol (1.8 g, 26.5 mmol) y 1,4 dioxano (10 ml) se calentaron a 138°C durante 2h. Durante el enfriamiento a temperatura ambiente un precipitado se formó el cual se colectó y se lavó con NaHCO<sub>3</sub> acuoso saturado y éter de dietilo para producir 49 (340 mg, 1.3 mmol) como un sólido de color blanco. El filtrado se trató con NaHCO<sub>3</sub> acuoso saturado (20 ml) y el precipitado resultante se lavó con NaHCO<sub>3</sub> acuoso saturado y éter de dietilo para producir el 49 adicional (2.0 g, 7.8 mmol, 99% de producción total). <sup>1</sup>H NMR: (500 MHz, CD<sub>3</sub>OD) δ 8.99 (s amplio, 1H), 8.78 (s amplio, 1H), 8.29 (s, 1H), 8.06 (s amplio, 1H), 6.72 (s amplio, 1H), 4.30 (q, J=7.0 Hz, 2H), 1.33 (t,

378 376

$J=7.0$  Hz, 3H); CL/EM: (ES+)  $m/z$   $(M+H)^+ = 258$ ; CLAR  $R_t = 1.20$  min., column L.

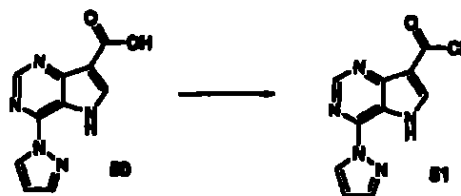
Preparación de ácido 4-(1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidina-7-carboxílico 50.



A una solución de 4-(1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidina-7-carboxilato 49 (2.0 g, 7.8 mmol) en THF (45 ml) se agregó a una solución de  $\text{LiOH}\cdot\text{H}_2\text{O}$  (1.3 g, 31 mmol) en  $\text{H}_2\text{O}$  (30 ml) y la reacción se agitó a  $100^\circ\text{C}$  durante 16h. se agregó  $\text{LiOH}\cdot\text{H}_2\text{O}$  adicional (2.0 g, 48 mmol), el calentamiento continuo durante 2h, se agregó MeOH (10 ml) y se calentó continuamente a  $100^\circ\text{C}$  durante 1d. La mezcla de reacción se enfrió, filtró, concentró a ~20% de volumen y se neutralizó con hielo y HCl concentrado. El precipitado de color blanco que se formó se colectó por filtración y se lavó con salmuera,  $\text{H}_2\text{O}$ , EtOAc, y  $\text{Et}_2\text{O}$  para producir 50 (cuantitativo), el cual se usó sin purificación adicional.  $^1\text{H}$  NMR: (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  12.07 (s amplio, 1H), 8.89 (s amplio, 1H), 8.75 (s, 1H), 8.14 (s, 1H), 8.09 (s amplio, 1H), 6.76-6.73 (m, 1H); CL/EM: (ES+)  $m/z$   $(M+H)^+ = 230$ ; CLAR Tr = 0.75 min., column S.

377 377

**Preparación de cloruro 4-(1H-pirazol-1-il)-5H-pirrol [3,2-d]pirimidina-7-carbonilo 51.**



5

Se agregó cloruro de oxalilo (405 ml, 51 mmol) a una solución de ácido diazaíndol carboxílico 50 (1.08 g, 4.7 mmol) en  $\text{CH}_2\text{Cl}_2$  (8 ml) y la mezcla de reacción se agitó 14h. se agregó DMF catalítico (3 gotas) a la mezcla de reacción y después de 3h la reacción se enfrió rápidamente con MeOH. La mezcla de reacción cruda se concentró hasta sequedad para producir 51 (1.21 g, 49 mmol, 96%) como un sólido color marrón que se uso sin purificación adicional.  $^1\text{H}$  NMR: (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  12.45 (s amplio, 1H), 8.87 (s, 1H), 8.87 (d,  $J=2.6$  Hz, 1H), 8.32 (d,  $J=3.3$  Hz, 1H), 8.14 (d,  $J=1.5$  Hz, 1H), 6.77 (dd,  $J=2.6, 1.5$  Hz, 1H); éster de metilo (se obtuvo por agitación de 51 en MeOH): CL/EM: (ES+)  $m/z$   $(M+H)^+ = 244$ ; CLAR  $R_t = 0.95$  min., columna O, condiciones B.

**20 Preparación de 2-(1-(cianometil)piperidin-4-ilideno)-2-(piriden-2-il)acetonitrilo 52.**



25

200 378

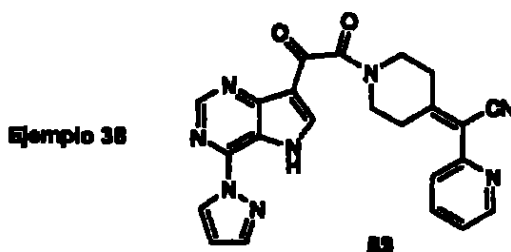
A una solución de 2-(piperidín-4-ilideno)-2-(piridín-2-il)acetonitrilo (560 mg, 2.8 mmol) en THF (20 ml) se agregó NEt<sub>3</sub> (5 ml, 38 mmol) y cloroacetonitrilo (3 ml, 47 mmol) y la reacción se agitó 16h. Los precipitados resultantes se filtraron y el filtrado se concentró hasta sequedad. Los residuos se purificaron por cromatografía en gel de sílice (Biotage 40-short, 50% EtOAc/hexanos hasta 100% EtOAc/hexanos) para producir 52 (470 mg, 2.0 mmol, 71 %) como un sólido de color amarillo. <sup>1</sup>H NMR: (500 MHz, CDCl<sub>3</sub>) δ 8.64 (br d, J=4.9 Hz, 1H), 7.77 (ddd, J=7.9, 7.6, 1.9 Hz, 1H), 7.50 (d, J=7.9 Hz, 1H), 7.27 (dd, J=7.6, 4.9 Hz, 1H), 3.58 (s, 2H), 2.94 (t, J=5.8 Hz, 2H), 2.91 (t, J=5.8 Hz, 2H), 2.83 (t, J=5.8 Hz, 2H), 2.67 (t, J=5.8 Hz, 2H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 239; CLAR Tr = 0.99 min., columna O, condiciones B.

15

#### Preparación del Ejemplo 38:

2-(1-(2-(4-(1H-pirazol-1-il)-5H-pirrólo[3,2-d]pirimidin-7-il)-2-oxoacetil)piperidín-4-ilideno)-2-(piridín-2-il)acetonitrilo (Compuesto 53).

20



A una suspensión de intermediario de pirazol de cloruro de ácido 51 (100 mg, 0.40 mmol) e intermediario

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379

3-piridinilcianoalqueno 52 (100 mg, 0.42 mmol) en THF (4 ml) a  $-78^{\circ}\text{C}$  se agregó a una solución de 0.5M de KHMDS en tolueno (3.0 ml, 1.5 mmol). La mezcla de reacción se agitó a  $-78^{\circ}\text{C}$  durante 3h y la presencia del intermediario de cianocetona deseada se verificó por CLEM. Una solución de 32% de ácido peracético en ácido acético acuoso diluido (0.44 ml, 2.1 mmol) se agregó a la mezcla de reacción y entonces se permitió tibiaar a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con  $\text{H}_2\text{O}$  (5 ml) y  $\text{NH}_4\text{Cl}$  acuoso saturado (5 ml) y se extrajo con EtOAc (3 x 20ml). Las capas se separaron y la capa acuosa se extrajo con EtOAc (2 x 20 ml). Las capas orgánicas combinadas se concentraron, el residuo se purificó por CLAR preparativa para producir 53 (7.3 mg, 0.02 mmol, 4%) como un sólido de color amarillo.  $^1\text{H}$  NMR: (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.95 (s, 0.5H), 8.93 (s, 0.5H), 8.88 (d,  $J=2.8$  Hz, 0.5H), 8.86 (d,  $J=3.1$  Hz, 0.5H), 8.71 (br d,  $J=4.9$  Hz, 0.5H), 8.64-8.61 (m, 1H), 8.60 (s, 0.5H), 8.11 (s amplio, 0.5H), 8.10 (s amplio, 0.5H), 8.03 (ddd,  $J=7.9$ , 7.6, 1.5 Hz, 0.5H), 7.97 (ddd,  $J=7.9$ , 7.6, 1.5 Hz, 0.5H), 7.65 (d,  $J=7.9$  Hz, 0.5H), 7.60 (d,  $J=7.9$  Hz, 0.5H), 7.52 (dd,  $J=7.9$ , 4.9 Hz, 0.5H), 7.46 (dd,  $J=7.9$ , 4.9 Hz, 0.5H), 6.76-6.72 (m, 1H), 4.03 (dd,  $J=6.1$ , 6.1 Hz, 1H), 3.86 (dd,  $J=6.1$ , 5.8 Hz, 1H), 3.81 (dd,  $J=6.1$ , 5.5 Hz, 1H), 3.64 (dd,  $J=5.8$ , 5.8 Hz, 1H), 3.10 (dd,  $J=6.1$ , 5.8 Hz, 1H), 2.94 (dd,  $J=6.1$ , 5.5 Hz, 1H), 2.90 (dd,  $J=6.1$ , 5.8 Hz, 1H), 2.75 (dd,  $J=5.8$ , 5.8 Hz,



380

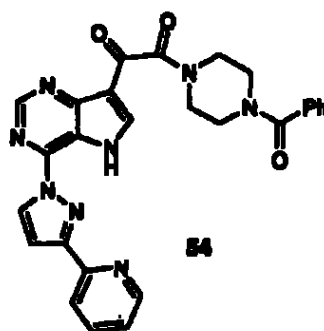
1H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 439; CLAR R<sub>t</sub> = 1.37 min., columna O.

**Preparación del Ejemplo 39:**

5 1-(4-benzoilpiperazin-1-il)-2-(4-(3-(piridin-2-il)-1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)etan-1,2-diona  
(Compuesto 54).

10

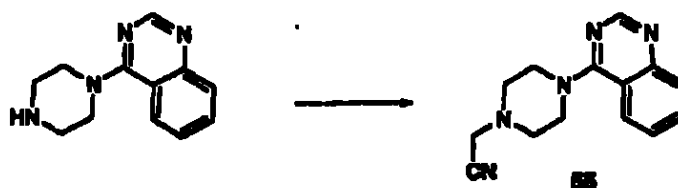
Ejemplo 39



En un tubo sellado, el intermediario de dicarbonilo  
15 10 (52 mg, 0.13 mmol), 2-(1H-pirazol-3-il)piridina (104 mg, 0.71 mmol) y 1,4-dioxano (2.0 ml) se combinaron y calentaron a 150°C con microondas durante 1h. La mezcla de reacción se concentró, diluyó con MeOH, filtró y purificó por CLAR preparativa para producir 54 (31 mg, 0.06 mmol, 47%) como un  
20 sólido de color blanco opaco. <sup>1</sup>H NMR: (500 MHz, DMSO-d<sub>6</sub>) δ 12.60 (s amplio, 1H), 8.97 (d, J=1.8 Hz, 1H), 8.94 (s, 1H), 8.73-8.66 (m, 2H), 8.61 (s amplio, 1H), 8.02 (t, J=7.0 Hz, 1H), 7.54-7.38 (m, 6H), 7.31 (d, J=1.8 Hz, 1H), 3.92-3.13 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 507; CLAR R<sub>t</sub> = 1.19 min.,  
25 columna N.

24 381

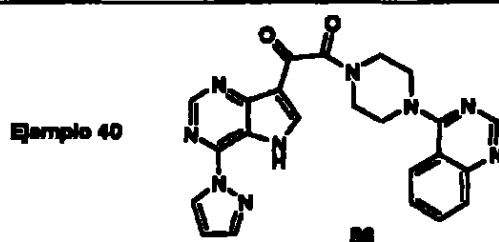
Preparación de 2-(4-(quinazolina-4-il)piperazin-1-il)acetonitrilo 55.



5 A una solución de 4-(piperazin-1-il)quinazolina (1.8 g, 8.3 mmol) en THF (50 ml) se agregó NEt<sub>3</sub> (20 ml, 150 mmol) y cloroacetonitrilo (12 ml, 190 mmol) y la reacción se agitó 16h. La mezcla de reacción se enfrió rápidamente con 50% de NaHCO<sub>3</sub> acuoso saturado y se extrajo con EtOAc (3 x 200 ml). Los orgánicos combinados se purificaron por cromatografía en gel de sílice (50% de EtOAc/hexanos hasta 80% EtOAc/hexanos) para producir 55 (1.6 g, 6.1 mmol, 73%) como un aceite de color amarillo viscoso. <sup>1</sup>H NMR: (500 MHz, CDCl<sub>3</sub>) δ 8.74 (s, 1H), 8.06 (d, J=8.6 Hz, 1H), 7.90 (d, J=8.5 Hz, 1H), 7.82-7.55 (m, 1H), 7.54-7.50 (m, 1H), 3.94-3.88 (m, 4H), 3.63 (s, 2H), 2.86-2.81 (m, 4H); CL/EM: (ES<sup>+</sup>) m/z (M+H)<sup>+</sup> = 254; CLAR R<sub>t</sub> = 0.71 min., columna<sup>1</sup> O.

#### Preparación del Ejemplo 40:

20 1-(4-1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)-2-(4-(quinazolin-4-il)piperazin-1-il)-etan-1,2-diona (Compuesto 56).



A una suspensión de intermediario de pirazol de cloruro de ácido 51 (100 mg, 0.04 mmol) y 2-(4-(quinazolin-4-il)-piperazin-1-il)-acetonitrilo 55 (98 mg, 0.39 mmol) en THF (4 ml) a -78°C se agregó una solución de 0.5M de KHMDS en tolueno (3.0 ml, 1.5 mmol). La mezcla de reacción se agitó 3h y la presencia del intermediario de cianocetona deseado se verificó por CLEM. La reacción se trató con una solución de 32% de ácido peracético en ácido acético acuoso diluido (0.40 ml, 1.9 mmol) y entonces se permitió tibiair a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con NH<sub>4</sub>Cl acuoso saturado (5 ml) y se extrajo con EtOAc (3 x 20 ml). Las capas orgánicas combinadas se concentraron, el residuo se purificó por CLAR preparativa para producir 56 (33 mg, 0.07 mmol, 18%) como un sólido de color amarillo. <sup>1</sup>H RMN: 500 MHz, CD<sub>3</sub>OD) δ 8.86 (s, 1H), 8.5 (d, J=2.7 Hz, 1H), 8.75 (s, 1H), 8.61 (s, 1H), 8.30 (d, J=8.2 Hz, 1H), 8.09-8.05 (m, 2H), 7.84 (d, J=8.5 Hz, 1H), 7.79 (dd, J=8.2, 7.6 Hz, 1H), 6.72 (s amplio, 1H), 4.62-4.56 (m, 2H), 4.43-4.38 (m, 2H), 4.12-4.07 (m, 2H), 3.91-3.86 (m, 2H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 439; CLAR R<sub>t</sub> = 1.06 min., columna O.

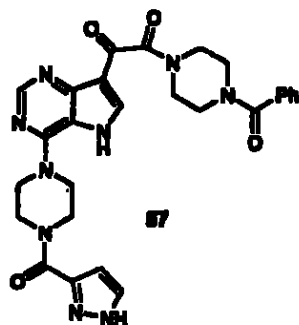
**Preparación del Ejemplo 41:**

1-(4-(4-(1H-pirazol-3-carbonil)piperazin-1-il)-5H-pirrolo[3,2-d]pirimidin-7-il)-2-(4-benzoilpiperazin-1-il)etan-1,2-diona (Compuesto 57).

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Ejemplo 41



57

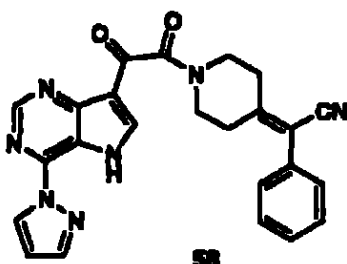
5

En un tubo sellado, el intermediario de dicarbonilo  
 10 (50 mg, 0.13 mmol), alcoxi(4-metilpiperazin-1-il)(1H-  
 pirazol-3-il)metanona (75 mg, 0.39 mmol) y polvo de cobre (10  
 mg, 0.16 mmol) se combinaron y calentaron a 150°C con  
 10 microondas por 2 horas. La reacción se purificó por CLAR  
 preparativa para producir 57 (65 mg, 0.12 mmol, 92%) como un  
 sólido de color blanco. <sup>1</sup>H RMN: (500 MHz, CD<sub>3</sub>COCD<sub>3</sub>) δ 10.31  
 (s amplio, 2H), 8.82 (s, 1H), 8.85 (s, 1H), 7.80 (s, 1H),  
 7.50-7.40 (m, 5H), 6.74 (s, 1H), 4.50-4.37 (m, 6H), 4.09-3.96  
 15 (m, 2H), 3.86-3.60 (m, 8H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 542;  
 CLAR R<sub>t</sub> = 0.85 min., columna G, condiciones B.

#### Preparación del Ejemplo 42:

20 2-(1-(2-(4-(1H-pirazol-1-il)-5H-pirrolo[3,2-d]pirimidin-7-  
 il)-2-oxoacetil)piperidin-4-ilideno)-2-fenilacetonitrilo  
 (Compuesto 58).

Ejemplo 42



58

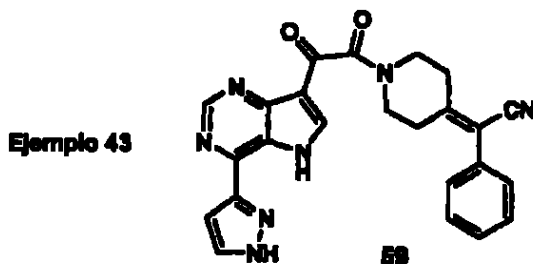
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En un tubo sellado, el intermediario de dicarbonilo  
33 (31 mg, 0.077 mmol), pirazol (20 mg, 0.29 mmol) y  
1,4-dioxano (0.8 ml) se combinaron y calentaron a 140°C con  
microondas por 50 min. La mezcla de reacción se diluyó con  
5 MeOH/DMSO (2:1, 1.5 ml), filtró y purificó por CLAR  
preparativa para producir 58 (10 mg, 0.024 mmol, 31 %) como  
un sólido de color naranja. <sup>1</sup>H RMN: (500 MHz, CD<sub>3</sub>OD) δ 8.90  
(s, 0.5H), 8.88 (s, 0.5H), 8.86 (d, J = 2.8 Hz, 0.5H), 8.84  
(d, J = 2.8 Hz, 0.5H), 8.57 (s, 0.5H), 8.54 (s, 0.5H), 8.08  
10 (s amplio, 0.5H), 8.06 (s amplio, 0.5H), 7.53-7.31 (m, 5H),  
6.74-6.70 (m, 1H), 4.00 (t, J = 5.8 Hz, 1H), 3.82 (t, J = 5.8  
Hz, 1H), 3.75 (t, J = 5.8 Hz, 1H), 3.56 (t, J = 5.8 Hz, 1H),  
3.05 (t, J = 5.8 Hz, 1H), 2.87 (t, J = 5.8 Hz, 1H), 2.72 (t,  
J = 5.8 Hz, 1H), 2.55 (t, J = 5.8 Hz, 1H); CL/EM: (ES<sup>+</sup>) m/z  
15 (M+H)<sup>+</sup> = 438; CLAR R<sub>t</sub> = 1.73 min., columna O.

**Preparación del Ejemplo 43:**

2-(1-(2-(4-(1H-pirazol-3-il)-5H-pirrolo[3,2-d]pirimidin-7-  
il)-2)oxoacetil)piperidin-4-ilideno)-2-fenilacetonitrilo  
20 (Compuesto 59).



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En un tubo sellado, el intermediario de dicarbonilo  
33 (33 mg, 0.081 mmol), 3-(tributylestannil)-1H-pirazol (73  
mg, 0.20 mmol), tetraquis(trifenilofosfina)-paladio(0) (20  
mg, 0.02 mmol) y 1,4-dioxano (0.8 ml) se combinaron y  
5 calentaron a 130°C con microondas por 2h. La mezcla de  
reacción se diluyó con MeOH/DMSO (2:1, 1.5 ml), se filtró y  
purificó por CLAR preparativa para producir 59 (3.4 mg, 0.008  
mmol, 10%) como un sólido de color amarillo. <sup>1</sup>H RMN: (500  
MHz, CD<sub>3</sub>COCD<sub>3</sub>) δ 11.84 (s amplio, 1H), 9.06 (s, 0.5H), 9.05  
10 (s, 0.5H), 8.58 (s, 0.5H), 8.55 (s, 0.5H), 8.01 (d, J = 2.7  
Hz, 0.5H), 8.01 (d, J = 2.7 Hz, 0.5H), 7.55-7.32 (m, 5H),  
7.24 (d, J = 2.7 Hz, 0.5H), 7.23 (d, J = 2.7 Hz, 0.5H), 4.01  
(t, J = 5.8 Hz, 1H), 3.84 (t, J = 5.8 Hz, 1H), 3.74 (t, J =  
5.8 Hz, 1H), 3.56 (t, J = 5.8 Hz, 1H), 3.07 (t, J = 5.8 Hz,  
15 1H), 2.84 (t, J = 5.8 Hz, 1H), 2.78 (t, J = 5.8 Hz, 1H), 2.54  
(t, J = 5.8 Hz, 1H); CL/EM: (ES+) m/z (M+H)<sup>+</sup> = 438; CLAR R<sub>t</sub> =  
1.29 min., columna L.

### Biología

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- "μM" significa micromolar;
- "ml" significa mililitro;
- "μl" significa microlitro;
- "mg" significa miligramo;

25

Los materiales y los procedimientos experimentales

usados para obtener los resultados reportados en las Tablas 1-3 se describen a continuación.

Células:

5                   • *Producción de Virus* - línea celular de riñón  
embriónico humano, 293, propagado en Modified Eagle Medium de  
Dulbecco (Life Technologies, Gaithersburg, MD) que contiene  
suero de bovino fetal al 10% (FBS, Sigma, St. Louis, MO).

10                   • *Infección del Virus* - línea celular epitelial  
humana, HeLa, que expresa los receptores de VIH-1 CD4 y CCR5  
se propagó en Modified Eagle Medium de Dulbecco (Life  
Technologies, Gaithersburg, MD) que contiene suero de bovino  
fetal al 10% (FBS, Sigma, St. Louis, MO) y complementado con  
0.2 mg/mL de Geneticina (Life Technologies, Gaithersburg, MD)  
15 y 0.4 mg/mL de Zeocina (Invitrogen, Carlsbad, CA).

Virus - Se produjo un virus reportero infecciosos  
de ronda sencilla por células 293 de riñón embriónico humano  
de co-transfección con un vector de expresión de ADN  
20 envoltente de VIH-1, y un ADNc proviral que contiene una  
mutación de eliminación envoltente y un gen reportero de  
luciferasa insertado en lugar de secuencias nef de VIH-1  
(Chen et al, Ref. 41). Las transfecciones se realizan  
usando reactivo de lipofectAMINA PLUS como se describe por el  
25 fabricante (Life Technologies, Gaithersburg, MD).

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Experimento

1. El compuesto se agregó a las células HeLa CD4 CCR5 formadas en placas de 96 pozos a una densidad celular de  $1 \times 10^4$  células por pozo en 100  $\mu$ l de Modified Eagle Medium de Dulbecco que contiene suero de bovino fetal al 10% a una concentración de  $<20 \mu$ M.  
5
2. 100  $\mu$ l de virus reportero infeccioso de ronda sencilla en Modified Eagle Medium de Dulbecco, entonces se agregó a las células formadas en placas y el compuesto a una multiplicidad de infección aproximada (MOI) de 0.01, resultando en un volumen final de 200  $\mu$ l por pozo y una concentración final de compuesto de  $<10 \mu$ M.  
10
3. Se cosecharon muestras 72 h después de la infección.  
15
4. La infección viral se observó al medir la expresión de luciferasa del ADN viral en las células infectadas usando un equipo de ensayo de gen reportero de luciferasa (Roche Molecular Biochemicals, Indianapolis. IN). Los sobrenadantes de células infectadas se retiraron y se agregaron por pozo, 50  $\mu$ l de Modified Eagle Medium de Dulbecco (sin rojo de fenol) y 50  $\mu$ l de reactivo de ensayo de luciferasa reconstituido como se describe por el fabricante (Roche Molecular Biochemicals, Indianapolis. IN). La actividad de luciferasa se cuantificó entonces al medir la luminiscencia usando un contador de centelleo microbeta  
20  
25



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Wallac.

5. El porcentaje de inhibición para cada compuesto se calculó al cuantificar el nivel de expresión de luciferasa en las células infectadas en presencia de cada compuesto, como un porcentaje del observado para las células infectadas en ausencia del compuesto y restando tal valor determinado de 100.

6.  $EC_{50}$  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 curva 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  $EC_{50}$  para los compuestos se muestran en las Tablas 2-4. La Tabla 1 es la clave para los datos en las Tablas 2-4.

Los ensayos de citotoxicidad se conducen con la misma HeLa usando la metodología bien conocida en la técnica. Este método se ha descrito en la literatura (S Weislow, R Kiser, DL Fine, J Bader, RH Shoemaker y 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.

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Las células se incubaron en presencia de fármaco durante seis días, después de lo cual la viabilidad celular se mide usando el ensayo de reducción de pigmento (MTT) y se determina como CC50. Este ensayo mide la actividad reductora intracelular presente en las células activamente respirantes).

Células fueron incubadas en la presencia de de fármaco por seis días, después de los cuales la viabilidad de las células fue medida usando un ensayo de reducción colorante (MMT) y se determino como CC50. Este ensayo midió la actividad de reducción intrarcelular presente en células de respiración activa.

Resultados

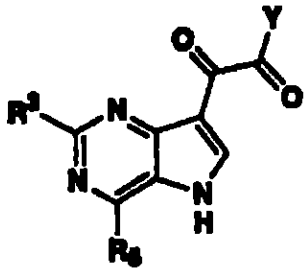
Tabla 1. Clave de Datos Biológicos para CE50s

|                               |                                            |                                                                                           |                              |
|-------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------|
| Compuestos<br>*con CE50s >5µM | Compuestos con<br>CE50s >1 µM pero<br><5µM | Compuestos con<br>CE50 >50 nM pero<br>todavía probados<br>a concentraciones<br>superiores | Compuestos<br>con CE50 >1 µM |
| Grupo C                       | Grupo B                                    | Grupo A'                                                                                  | Grupo A                      |

\*Algunos de estos compuestos pudieron haberse probado a una concentración inferior que su CE50, pero mostraron cierta capacidad para provocar inhibición y así se deben evaluar a una concentración superior, para determinar el CE50 exacto.

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Tabla 2



Ejemplos

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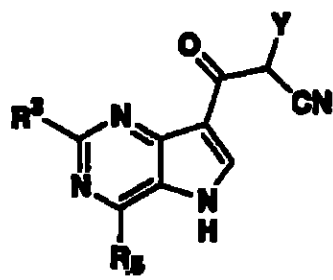
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| Número de Ejemplo | Número de Compuesto | R3 | R5 | Y | Grupo BC de la Tabla 1 |
|-------------------|---------------------|----|----|---|------------------------|
| Ejemplo 2         | 10                  | H  | Cl |   | A                      |
| Ejemplo 3         | 11                  | H  |    |   | A                      |
| Ejemplo 4         | 12                  | H  |    |   | A                      |
| Ejemplo 5         | 13                  | H  |    |   | A                      |
| Ejemplo 6         | 14                  | H  |    |   | A                      |
| Ejemplo 7         | 15                  | H  |    |   | A                      |
| Ejemplo 8         | 16                  | H  |    |   | A                      |
| Ejemplo 9         | 17                  | H  |    |   | A                      |
|                   |                     |    |    |   |                        |

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Tabla 3



Ejemplos

| Número de Ejemplo | Número de Compuesto | R3 | R5 | Y | Grupo BC <sub>20</sub> de la Tabla 1 |
|-------------------|---------------------|----|----|---|--------------------------------------|
| Ejemplo 1         | 9                   | H  | Cl |   | A                                    |
| Ejemplo 10        | 18                  | H  |    |   | A                                    |
| Ejemplo 11        | 19                  | H  |    |   | A                                    |
| Ejemplo 12        | 20                  | H  |    |   | A                                    |
| Ejemplo 13        | 21                  | H  |    |   | A                                    |
| Ejemplo 14        | 22                  | H  |    |   | A                                    |
| Ejemplo 15        | 23                  | H  |    |   | A                                    |
| Ejemplo 16        | 24                  | H  |    |   | A                                    |
| Ejemplo 17        | 25                  | H  |    |   | A                                    |

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|            |    |   |    |  |   |
|------------|----|---|----|--|---|
| Ejemplo 18 | 26 | H |    |  | A |
| Ejemplo 19 | 27 | H |    |  | A |
| Ejemplo 20 | 28 | H |    |  | A |
| Ejemplo 21 | 29 | H |    |  | A |
| Ejemplo 22 | 30 | H |    |  | A |
| Ejemplo 22 | 30 | H |    |  | A |
| Ejemplo 24 | 32 | H |    |  | A |
| Ejemplo 25 | 33 | H |    |  | A |
| Ejemplo 26 | 34 | H |    |  | A |
| Ejemplo 27 | 35 | H |    |  | A |
| Ejemplo 28 | 36 | H |    |  | A |
| Ejemplo 29 | 37 | H |    |  | A |
| Ejemplo 30 | 39 | H | Cl |  | A |

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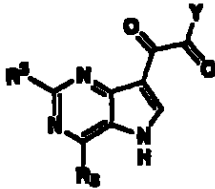
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|            |    |   |    |  |   |
|------------|----|---|----|--|---|
| Ejemplo 31 | 40 | H |    |  | A |
| Ejemplo 32 | 41 | H |    |  | A |
| Ejemplo 33 | 43 | H | Cl |  | A |
| Ejemplo 34 | 44 | H |    |  | A |
| Ejemplo 35 | 46 | H | Cl |  | A |
| Ejemplo 36 | 47 | H |    |  | A |
| Ejemplo 37 | 48 | H |    |  | A |
| Ejemplo 38 | 53 | H |    |  | A |
| Ejemplo 39 | 54 | H |    |  | A |
| Ejemplo 40 | 56 | H |    |  | A |

|            |    |   |  |  |   |
|------------|----|---|--|--|---|
| Ejemplo 41 | 57 | H |  |  | A |
| Ejemplo 42 | 58 | H |  |  | A |
| Ejemplo 43 | 59 | H |  |  | A |

La Tabla 4 muestra otros compuestos de la invención que podrán preparao por la metodología descrita en la presente y se espera que tengan actividad antiviral.

Tabla 4



| Número de Ejemplo | Número de Compuesto | R3 | R5 | Y | Grupo BC <sub>20</sub> de la Tabla 1 |
|-------------------|---------------------|----|----|---|--------------------------------------|
| Ejemplo #         | #                   | H  |    |   |                                      |
|                   |                     | H  |    |   |                                      |

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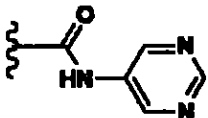
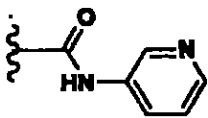
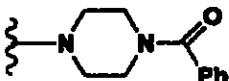
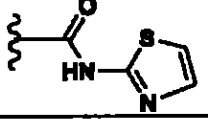
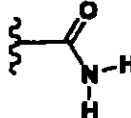
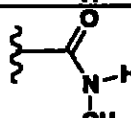
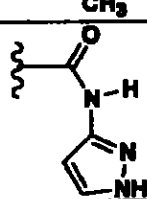
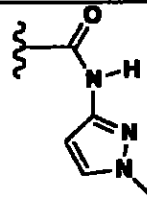
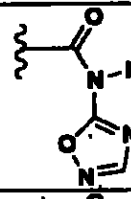
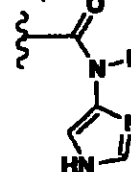
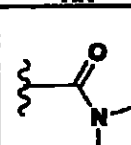
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|  |  |   |                                                                                     |                                                                                      |  |
|--|--|---|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--|
|  |  | H |    |    |  |
|  |  | H |    |    |  |
|  |  | H |    |    |  |
|  |  | H |    |    |  |
|  |  | H |    |    |  |
|  |  | H |   |   |  |
|  |  |   |  |  |  |
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|  |  | H |  |  |  |
|  |  | H |  |  |  |



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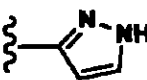
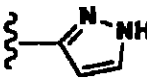
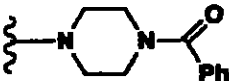
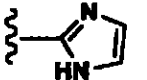
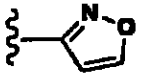
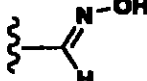
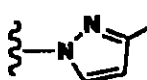
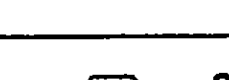
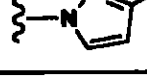
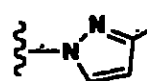
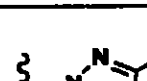
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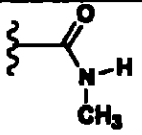
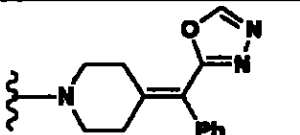
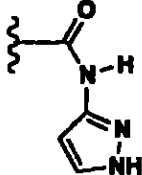
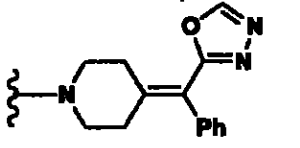
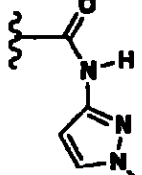
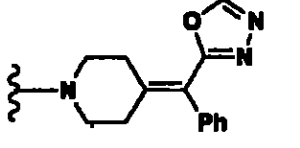
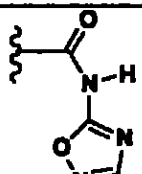
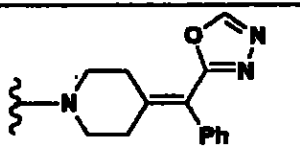
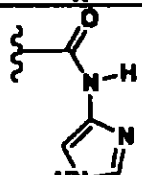
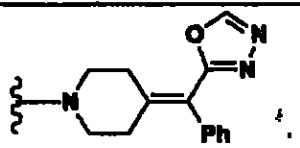
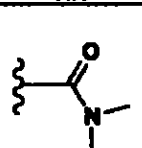
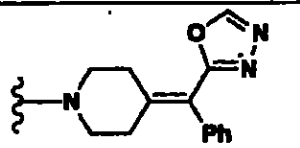
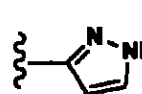
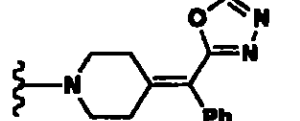
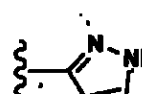
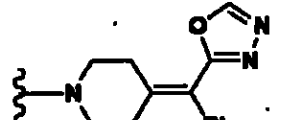
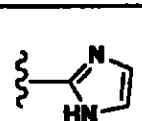
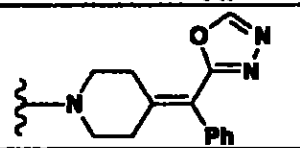
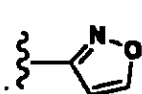
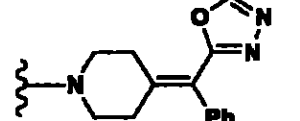
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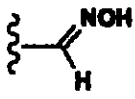
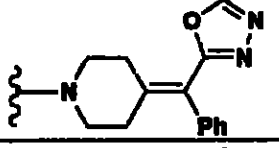
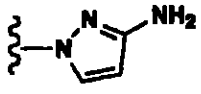
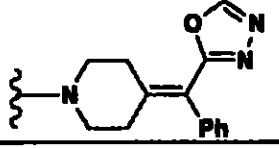
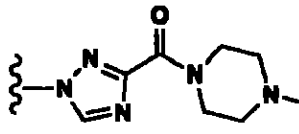
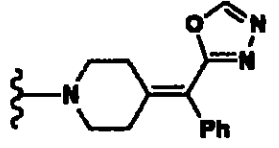
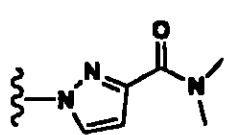
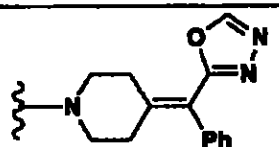
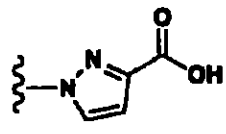
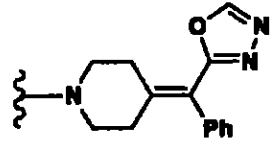
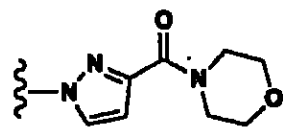
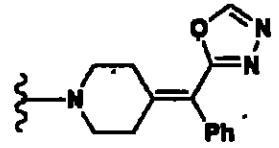
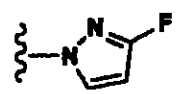
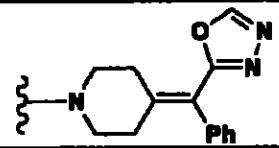
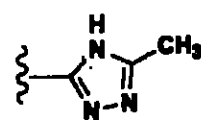
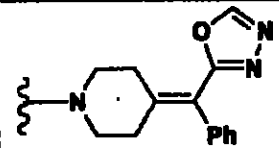
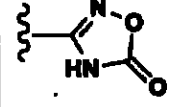
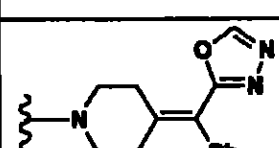
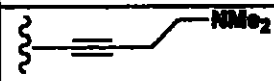
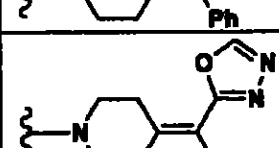
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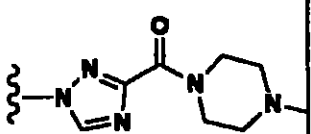
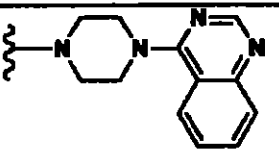
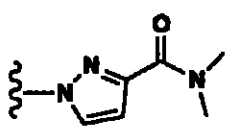
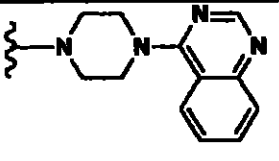
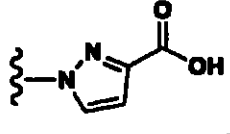
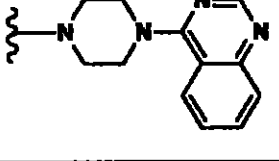
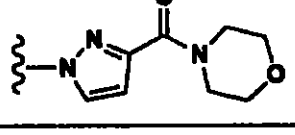
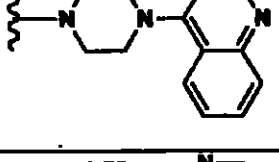
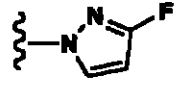
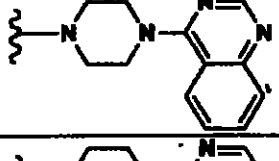
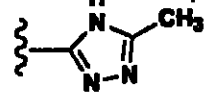
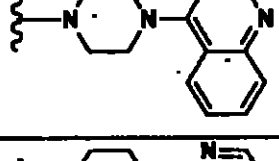
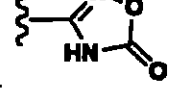
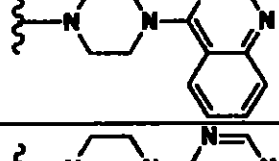
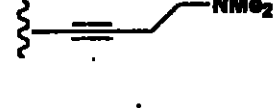
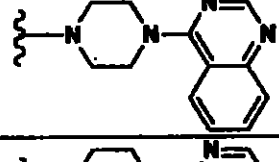
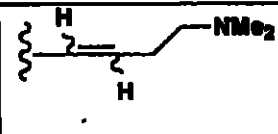
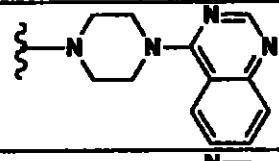
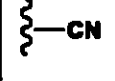
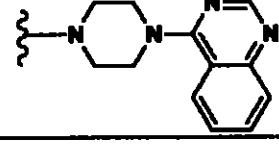
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Los compuestos de la presente invención pueden administrarse oralmente, parenteralmente (incluyendo inyecciones subcutáneas, intravenosas, intramusculares, inyección intrasternal o técnicas de infusión), por rocío de inhalación, o rectalmente, en formulaciones de dosis unitaria que contienen portadores, adyuvantes y vehículos farmacéuticamente aceptable no tóxicos convencionales.

Así, de acuerdo 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, tal como suspensiones o supositorios acuosos u oleaginosos.

Cuando se administran oralmente como una suspensión, estas composiciones se preparan de acuerdo con las técnicas bien conocidas en la técnica de la formulación farmacéutica, y pueden contener celulosa microcristalina para impartir volumen, ácido alginico o alginato de sodio como agente de suspensión, metilcelulosa como mejorador de



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viscosidad, y agentes endulzantes/saborizantes conocidos en la técnica. Como tabletas de liberación inmediata, estas composiciones pueden contener celulosa microcristalina, fosfato dicálcico, almidón, estearato de magnesio y lactosa y/u otros excipientes, aglutinantes, extendedores, desintegrantes, diluyentes y lubricantes conocidos en la técnica.

Las soluciones o suspensiones inyectables pueden formular de acuerdo con la técnica conocida, usando diluyentes o solventes parenteralmente aceptables, no tóxicos, apropiados, tal 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 oleico.

Los compuestos de esta invención pueden administrarse oralmente a los humanos en un intervalo de dosis de 1 hasta 100 mg/kg de peso corporal en dosis divididas. Un intervalo de dosis preferido es de 1 hasta 10 mg/kg de peso corporal oralmente en dosis divididas. Otro intervalo 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

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5 dependerá de una variedad de factores que incluyen la actividad del compuesto específico utilizado, la estabilidad metabólica y longitud de acción de tal compuesto, edad, peso corporal, salud general, sexo, dieta, modo y tiempo de administración, velocidad de excreción, combinación de fármaco, severidad de la condición particular, y la terapia  
que experimenta el huésped.

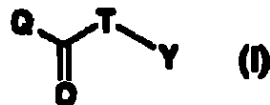
10 Se hace constar que con relación a esta fecha, el mejor método conocido por la solicitante para llevar a la práctica la citada invención, es el que resulta claro de la presente descripción de la invención.

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REIVINDICACIONES

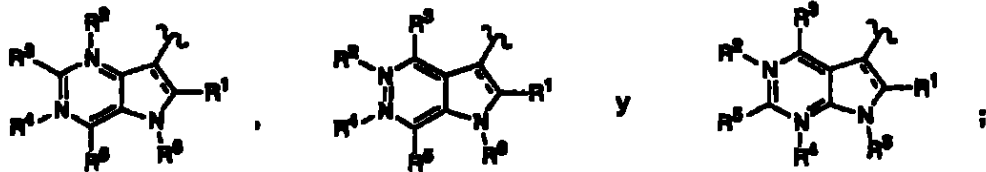
Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones:

1. Compuesto de fórmula I, que incluye sales farmacéuticamente aceptables del mismo,



caracterizado porque:

Q se selecciona del grupo que consiste de



T es  $-\text{C}(\text{O})-$  o  $-\text{CH}(\text{CN})-$ ;

$\text{R}^1$  es hidrógeno o metilo;

$\text{R}^3$  y  $\text{R}^5$  son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, ciano, nitro,  $\text{COOR}^8$ ,  $\text{XR}^9$  y B;

$\text{R}^2$  y  $\text{R}^4$  son independientemente 0 ó no existen con la condición de que solamente uno de  $\text{R}^2$  y  $\text{R}^4$  son 0;

$\text{R}^6$  es  $(\text{CH}_2)_n\text{H}$ , en donde n es 0-1;

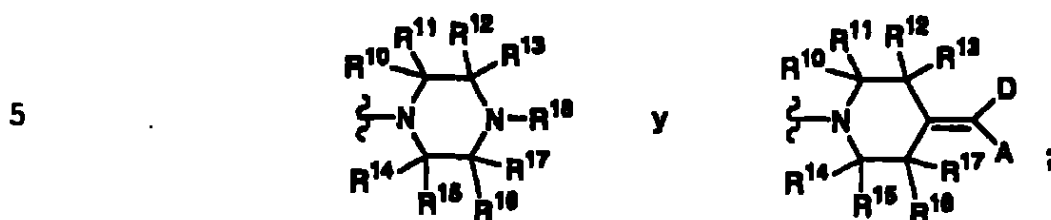
-- representa un enlace carbono-carbono o no

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existe;

- Y - se selecciona del grupo que consiste de



$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o alquilo( $C_{1-6}$ ); en donde alquilo( $C_{1-6}$ ) puede opcionalmente sustituirse con uno hasta tres halógenos iguales o diferentes, OH o CN;

$R^{18}$  es un miembro seleccionado del grupo que consiste de C(O)-fenilo, C(O)-heteroarilo, piridinilo, pirimidinilo, quinolilo, isoquinolilo, quinazolilo, quinoxalinilo, naftiridinilo, ftalazinilo, azabenzofurilo y azaindolilo; en donde el miembro es opcionalmente sustituido con desde uno hasta dos sustituyentes seleccionados del grupo que consiste de metilo, -amino, -NHMe, -NMe<sub>2</sub>, metoxi, hidroximetilo y halógeno;

D se selecciona del grupo que consiste de hidrógeno, ciano,  $S(O)_2R^{24}$ , halógeno,  $COOR^{20}$ ,  $C(O)NR^{21}R^{22}$ , fenilo y heteroarilo; en donde fenilo o heteroarilo es sustituido independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres sustituyentes iguales o diferentes seleccionados de F (como

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se definió anteriormente);

A se selecciona del grupo que consiste de fenilo, piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde fenilo, piridinilo, furanilo, tienilo, isoxazol o oxazol es  
5 sustituido independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F;

B se selecciona del grupo que consiste de alquilo(C<sub>1-6</sub>), C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)CH<sub>3</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NC(O)pirazolilo, fenilo y heteroarilo; en donde alquilo(C<sub>1-6</sub>), fenilo y  
10 heteroarilo son sustituidos independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes, o desde uno hasta tres sustituyentes iguales o diferentes seleccionados de F;

15 Heteroarilo se selecciona del grupo que consiste de piridinilo, pirazinilo, piridazinilo, pirimidinilo, furanilo, tienilo, benzotienilo, tiazolilo, oxazolilo, isoxazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, pirazolilo, tetrazolilo y triazolilo;

20 F se selecciona del grupo que consiste de alquilo(C<sub>1-6</sub>), alqueno(C<sub>1-6</sub>), fenilo, piridinilo, hidroxilo, alcoxi(C<sub>1-6</sub>), halógeno, bencilo, -NR<sup>23</sup>C(O)-alquilo(C<sub>1-6</sub>), -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, y -CONR<sup>24</sup>R<sup>25</sup>; en donde alquilo(C<sub>1-6</sub>) o fenilo son cada uno opcionalmente sustituidos  
25 con hidroxilo, alcoxi(C<sub>1-6</sub>), alquilo(C<sub>1-6</sub>), CF<sub>3</sub>, dimetilamino o

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desde uno hasta tres halógenos iguales o diferentes;

$R^8$ ,  $R^9$  y  $R^{26}$  son cada uno independientemente seleccionados del grupo que consiste de hidrógeno y alquilo( $C_{1-6}$ );

5 X se selecciona del grupo que consiste de  $NR^{26}$ , O y S;

10  $R^{20}$ ,  $R^{21}$ ,  $R^{22}$ ,  $R^{23}$ ,  $R^{24}$  y  $R^{25}$  son independientemente seleccionados del grupo que consiste de hidrógeno, alquilo( $C_{1-6}$ ), fenilo y heteroarilo; en donde fenilo y heteroarilo son cada uno sustituidos independientemente de forma opcional con uno hasta tres de halógeno o metilo iguales o diferentes; y

$R^{27}$  es piperazinilo, piperazinilo de N-metilo, o 3-pirazolilo.

15 2. Compuesto de conformidad con la reivindicación 1, caracterizado porque T es  $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$ .

3. Compuesto de conformidad con la reivindicación 2, caracterizado porque:

$R^1$  es hidrógeno;

20 -- representa un enlace carbono-carbono; y

$R^2$  y  $R^4$  no existen.

25 D se selecciona del grupo que consiste de hidrógeno, ciano,  $S(O)_2R^{24}$ , halógeno,  $COOR^{20}$ ,  $C(O)NH_2$ , fenilo y heteroarilo; en donde fenilo o heteroarilo es sustituido independientemente de forma opcional con uno hasta tres

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halógenos iguales o diferentes o un miembro seleccionado del grupo que consiste de alquilo(C<sub>1-6</sub>), alquenilo(C<sub>1-6</sub>), hidroxil, alcoxi(C<sub>1-6</sub>), halógeno, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup> y -CONR<sup>24</sup>R<sup>25</sup>; en donde alquilo(C<sub>1-6</sub>) es opcionalmente sustituido con uno hasta tres de halógeno iguales o diferentes o un hidroxil; y

A se selecciona del grupo que consiste de fenilo, piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde fenilo, piridinilo, furanilo, tienilo, isoxazol o oxazol son sustituidos independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o un miembro seleccionado del grupo que consiste de alquilo(C<sub>1-4</sub>), alquenilo(C<sub>1-4</sub>), alcoxi(C<sub>1-3</sub>), halógeno y -NH<sub>2</sub>; en donde alquilo(C<sub>1-4</sub>) es opcionalmente sustituido con uno hasta tres halógenos iguales o diferentes.

4. Compuesto de conformidad con la reivindicación 3, caracterizado porque:

R<sup>6</sup> es hidrógeno; y

R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> son cada uno independientemente H o metilo con la condición de que un máximo de dos de R<sup>10</sup> -R<sup>17</sup> es un metilo.

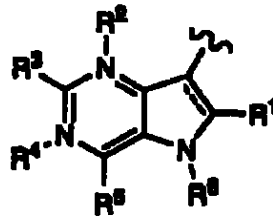
5. Compuesto de conformidad con la reivindicación 4, caracterizado porque:

Q es un miembro seleccionado de grupos (A), (B), y alquilo(C), que consiste de

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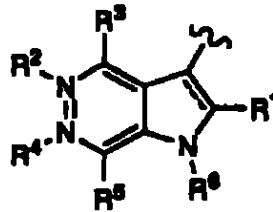
(A)



5

en donde R<sup>3</sup> es hidrógeno, alcoxi C<sub>1</sub>-C<sub>3</sub>, -NR<sup>26</sup>R<sup>9</sup> o halógeno;

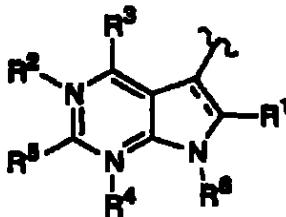
(B)



10

en donde R<sup>3</sup> es hidrógeno, metoxi o halógeno; y

(C)



15

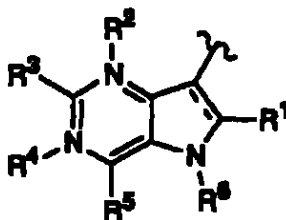
en donde R<sup>3</sup> es hidrógeno, metoxi o halógeno.

6. Compuesto de conformidad con la reivindicación

5, caracterizado porque:

Grupo (A) de Q es:

(A)

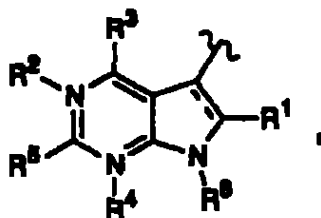


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en donde  $R^3$  es hidrógeno; y  
grupo (C) de Q es:



en donde:

$R^5$  es hidrógeno.

7. Compuesto de conformidad con la reivindicación  
5, caracterizado porque:

Q se selecciona del grupo (A) o (B), y

$R^5$  se selecciona del grupo que consiste de  
hidrógeno, halógeno, heteroarilo, fenilo, ciano, metoxi,  
 $\text{COOR}^6$ ,  $\text{C(O)NH}_2$ ,  $\text{C(O)Nhheteroarilo}$ , y  $\text{C(O)NHCH}_3$ ; en donde  
15  $\text{C(O)Nhheteroarilo}$ , fenilo, y heteroarilo son sustituidos  
independientemente de forma opcional con uno hasta tres  
halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F.

8. Compuesto de conformidad con la reivindicación 7,  
20 caracterizado porque:

$R^5$  se selecciona del grupo que consiste de  $\text{C(O)NH}_2$ ,  
 $\text{C(O)NHCH}_3$  y  $\text{C(O)Nhheteroarilo}$ ; en donde  $\text{C(O)Nhheteroarilo}$  es  
opcionalmente sustituido con uno hasta tres halógenos iguales  
o diferentes o de uno hasta tres sustituyentes iguales o  
25 diferentes seleccionados de F.

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9. Compuesto de conformidad con la reivindicación 7, caracterizado porque:

5  $R^5$  se selecciona del grupo que consiste de fenilo y heteroarilo; en donde fenilo y el heteroarilo son sustituidos independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o de uno hasta tres  
10 sustituyentes iguales o diferentes seleccionados de F.

10. Compuesto de conformidad con la reivindicación 9, caracterizado porque:

10 heteroarilo se selecciona del grupo que consiste de piridinilo, pirazinilo, piridazinilo, pirimidinilo, furanilo, tienilo, tiazolilo, oxazolilo, isoxazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, pirazolilo, tetrazolilo y triazolilo; en donde heteroarilo es sustituido  
15 independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres sustituyentes iguales o diferentes seleccionados de F;

11. Compuesto de conformidad con la reivindicación 5, caracterizado porque:

20  $R^{18}$  es  $-C(O)$ fenilo o  $-C(O)$ heteroarilo; en donde heteroarilo es piridinilo, furanilo o tienilo; en donde heteroarilo es sustituido independientemente de forma opcional con un miembro seleccionado del grupo que consiste de halógeno, metilo, -amino, -NHMe, NMe<sub>2</sub> y hidroximetilo;

25 12. Compuesto de conformidad con la reivindicación

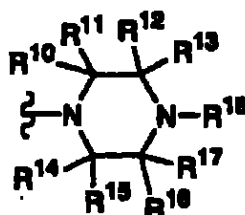
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5, caracterizado porque:

-W- es

5



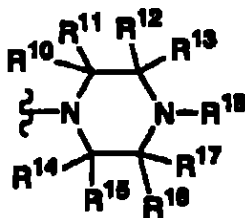
10  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o metilo con la condición de que no más de uno es metilo; y

15  $R^{18}$  se selecciona del grupo que consiste de C(O)-fenilo y C(O)-heteroarilo en donde cada de C(O)-fenilo o -C(O)-heteroarilo puede opcionalmente sustituirse con desde uno hasta dos de metilo, -amino, -NHMe, -NMe<sub>2</sub>, metoxi, hidroximetilo o halógeno.

13. Compuesto de conformidad con la reivindicación 5, caracterizado porque:

-W- es

20



25  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o metilo con la condición de que no más

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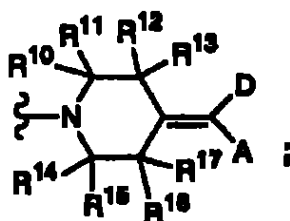
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de uno es metilo; y

$R^{18}$  se selecciona del grupo que consiste de piridinilo, pirimidinilo, quinolilo, isoquinolilo, quinazolilo, quinoxalinilo, naftiridinilo, ftalazinilo, azabenzofurilo y azaindolilo, cada uno de los cuales puede ser opcionalmente sustituido con desde uno hasta dos sustituyentes seleccionados del grupo que consiste de metilo, amino, -NHMe, -NMe<sub>2</sub>, metoxi, hidroximetilo y halógeno.

14. Compuesto de conformidad con la reivindicación 5, caracterizado porque:

-W- es



$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o metilo, con la condición que uno es metilo;

D se selecciona del grupo que consiste de hidrógeno, ciano, S(O)<sub>2</sub>R<sup>24</sup>, halógeno, COOR<sup>20</sup>, C(O)NH<sub>2</sub>, fenilo, y heteroarilo; en donde fenilo o heteroarilo es sustituido independientemente de forma opcional con uno hasta tres halógenos iguales o diferentes o desde uno hasta tres sustituyentes iguales o diferentes seleccionados del grupo

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que consiste de alquilo(C<sub>1-6</sub>), alquenilo(C<sub>1-6</sub>), hidroxil, alcoxil(C<sub>1-6</sub>), halógeno, -NR<sup>24</sup>R<sup>25</sup>, -S(O)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup> y -CONR<sup>24</sup>R<sup>25</sup>; en donde alquilo(C<sub>1-6</sub>) es opcionalmente sustituido con uno hasta tres halógenos iguales o diferentes o un

5 hidroxil; y

A se selecciona del grupo que consiste de fenilo, piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde fenilo, piridinilo, furanilo, tienilo, isoxazol o oxazol es sustituido independientemente de forma opcional con uno hasta

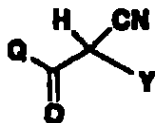
10 tres halógenos iguales o diferentes o desde uno hasta tres sustituyentes iguales o diferentes seleccionados del grupo que consiste de alquilo(C<sub>1-4</sub>), alquenilo(C<sub>1-4</sub>), alcoxil(C<sub>1-3</sub>), halógeno y -NH<sub>2</sub>; en donde alquilo(C<sub>1-4</sub>) es opcionalmente sustituido con uno hasta tres halógenos iguales o diferentes.

15 15. Compuesto de conformidad con la reivindicación 7, caracterizado porque:

Q se selecciona del grupo (A).

16. Compuesto de conformidad con la reivindicación 1, caracterizado porque incluye sales farmacéuticamente

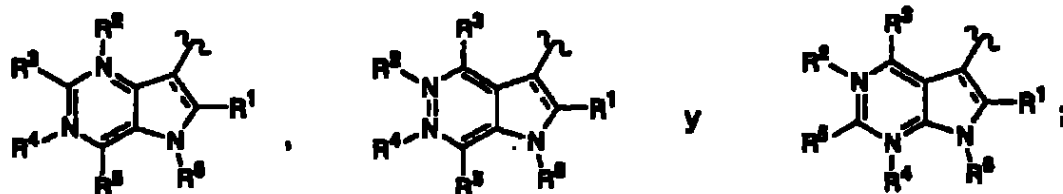
20 aceptables del mismo,



en donde:

25 Q se selecciona del grupo que consiste de

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5  $R^1$  es hidrógeno o metilo;

$R^3$  y  $R^5$  son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, ciano, nitro,  $\text{COOR}^8$ ,  $\text{XR}^9$  y B;

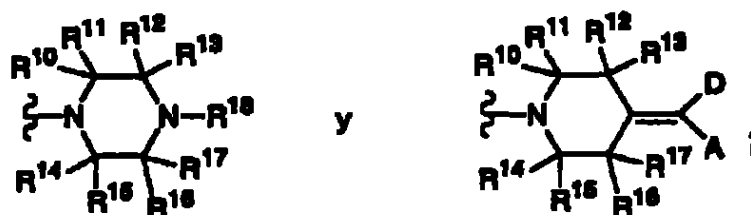
10  $R^2$  y  $R^4$  son independientemente 0 ó no existen, con la condición de que solamente uno de  $R^2$  y  $R^4$  son 0;

$R^6$  es  $(\text{CH}_2)_n\text{H}$  en donde n es 0-1;

-- representa un enlace carbono-carbono o no existe;

-Y- se selecciona del grupo que consiste de

15



20  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno independientemente H o alquilo( $\text{C}_{1-6}$ ); en donde alquilo( $\text{C}_{1-6}$ ) puede estar opcionalmente sustituido con uno hasta tres halógenos iguales o diferentes, OH o CN;

25  $R^{18}$  es un miembro seleccionado del grupo que consiste de C(O)-fenilo, C(O)-heteroarilo, piridinilo, pirimidinilo, quinolilo, isoquinolilo, quinazolilo;

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quinoxalínilo, naftiridinilo, ptalazínilo, azabenzofurilo y  
azaíndolilo; en donde el miembro es opcionalmente sustituido  
con desde uno hasta dos sustituyentes seleccionados del grupo  
que consiste de metilo, -amino, -NHMe, -NMe<sub>2</sub>, metoxi,  
5 hidroximetilo y halógeno;

D se selecciona del grupo que consiste de  
hidrógeno, ciano, S(O)<sub>2</sub>R<sup>24</sup>, halógeno, COOR<sup>20</sup>, C(O)NR<sup>21</sup>R<sup>22</sup>,  
fenilo y heteroarilo; en donde fenilo o heteroarilo es  
sustituido independientemente de forma opcional con uno hasta  
10 tres halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F;

A se selecciona del grupo que consiste de fenilo,  
piridinilo, furanilo, tienilo, isoxazol y oxazol; en donde  
fenilo, piridinilo, furanilo, tienilo, isoxazol o oxazol es  
15 sustituido independientemente de forma opcional con uno hasta  
tres halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F;

B se selecciona del grupo que consiste de  
alquilo(C<sub>1-6</sub>), C(O)NR<sup>21</sup>R<sup>22</sup>, fenilo y heteroarilo; en donde  
20 alquilo(C<sub>1-6</sub>), fenilo y heteroarilo son sustituidos  
independientemente de forma opcional con uno hasta tres  
halógenos iguales o diferentes o desde uno hasta tres  
sustituyentes iguales o diferentes seleccionados de F;

heteroarilo se selecciona del grupo que consiste de  
25 piridinilo, pirazinilo, piridazinilo, pirimidinilo, furanilo,

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tienilo, tiazolilo, oxazolilo, isoxazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, pirazolilo, tetrazolilo y triazolilo;

F se selecciona del grupo que consiste de  
5 alquilo(C<sub>1-6</sub>), alquenilo(C<sub>1-6</sub>), fenilo, piridinilo, hidroxilo, alcoxilo(C<sub>1-6</sub>), halógeno, bencil, -NR<sup>23</sup>C(O)-alquilo(C<sub>1-6</sub>),  
10 -NR<sup>24</sup>R<sup>25</sup>, -S(O)NR<sup>24</sup>R<sup>25</sup>, COOR<sup>26</sup>, -COR<sup>27</sup>, y -CONR<sup>24</sup>R<sup>25</sup>; en donde alquilo(C<sub>1-6</sub>) o fenilo son cada uno opcionalmente sustituidos con hidroxilo, alcoxilo(C<sub>1-6</sub>), dimetilamino o desde uno hasta tres  
10 halógenos iguales o diferentes;

R<sup>8</sup>, R<sup>9</sup> y R<sup>26</sup> son cada uno independientemente seleccionados del grupo que consiste de hidrógeno y alquilo(C<sub>1-6</sub>);

X se selecciona del grupo que consiste de NR<sup>26</sup>, O y  
15 S;

R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup> y R<sup>25</sup> son independientemente seleccionados del grupo que consiste de hidrógeno, alquilo(C<sub>1-6</sub>), fenilo y heteroarilo; en donde fenilo y heteroarilo son cada uno sustituidos independientemente de  
20 forma opcional con uno hasta tres de halógeno o metilo iguales o diferentes; y

R<sup>27</sup> es piperazinilo, N-metilpiperazinilo o 3-pirazolilo.

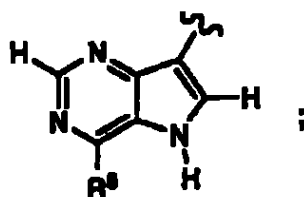
17. Compuesto de conformidad con la reivindicación  
25 6, caracterizado porque:



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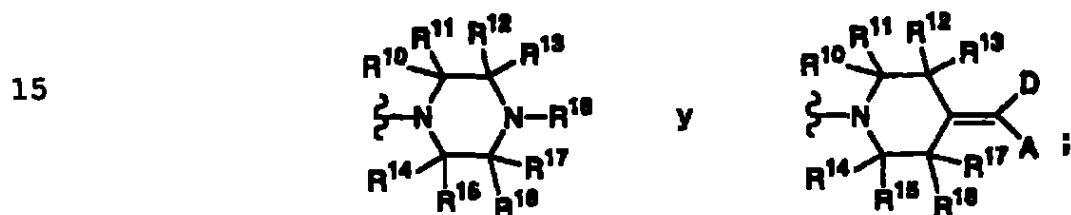
Q es



5  $R^5$  se selecciona del grupo que consiste de hidrógeno, halógeno, ciano,  $XR^9$ , heteroarilo,  $-N(CH_2CH_2)_2NC(O)$ pirazolilo, y  $-C(O)CH_3$ , en donde heteroarilo es opcionalmente sustituido con un sustituyente seleccionado de F;

10 heteroarilo se selecciona del grupo que consiste de piridinilo, pirazinilo, piridazinilo, pirimidinilo, isoxazolilo, isoxazolilo, pirazolilo, y triazolilo;

$-Y-$  se selecciona del grupo que consiste de



$R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  y  $R^{17}$  son cada uno hidrógeno;

20 A es fenilo o piridinilo;

$R^{18}$  es  $C(O)$ -fenilo, isoquinolilo o quinazolilo;

D es ciano o oxadiazolilo;

F se selecciona del grupo que consiste de alquilo( $C_{1-6}$ ), fenilo, piridinilo, alcoxi( $C_{1-2}$ ),  $-COOR^{26}$   $-COR^{27}$  y  $-CONR^{24}R^{25}$ ; en donde fenilo es opcionalmente sustituido con un

25

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grupo seleccionado de metilo, metoxi, fluoro, o trifluorometilo;

X se selecciona del grupo que consiste de O;

R<sup>9</sup> es alquilo(C<sub>1-2</sub>);

5 R<sup>26</sup> es hidrógeno, metilo, o etilo;

R<sup>24</sup> y R<sup>25</sup> son independientemente seleccionados del grupo que consiste de hidrógeno y metilo; y

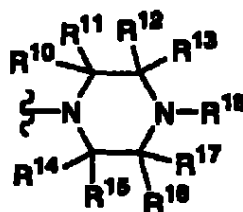
R<sup>27</sup> es piperazinilo, piperazinilo de N-metil, o 3-pirazolilo.

10 18. Compuesto de conformidad con la reivindicación 17, caracterizado porque:

R<sup>5</sup> es heteroarilo opcionalmente sustituido con uno de halógeno o un sustituyente seleccionado de F;

-Y- es

15



R<sup>18</sup> es C(O)-fenilo, isoquinolilo o quinazolilo, y

20 F es alquilo(C<sub>1-6</sub>).

19. Compuesto de conformidad con la reivindicación 18, caracterizado porque R<sup>18</sup> es C(O)-fenilo.

20. Compuesto de conformidad con la reivindicación 18, caracterizado porque R<sup>18</sup> es isoquinolilo o quinazolilo.

25 21. Compuesto de conformidad con la reivindicación

426

422

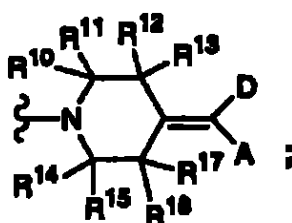
17, caracterizado porque:

$R^5$  es heteroarilo opcionalmente sustituido con un sustituyente seleccionado de F;

heteroarilo se selecciona del grupo que consiste de piridinilo, pirazinilo, piridazinilo, pirimidinilo, isoxazolilo, pirazolilo y triazolilo; y

-Y- es

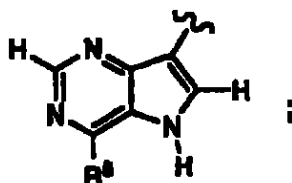
10



22. Compuesto de conformidad con la reivindicación 17, caracterizado porque:

Q es

15



$R^5$  es heteroarilo opcionalmente sustituido con un sustituyente seleccionado de F; y

heteroarilo se selecciona del grupo que consiste de pirazolilo y triazolilo.

23. Compuesto de conformidad con la reivindicación 22, caracterizado porque:

F se selecciona del grupo que consiste de metilo y

422

423

-CONR<sup>24</sup>R<sup>25</sup>; y

R<sup>24</sup> y R<sup>25</sup> son independientemente seleccionados del grupo que consiste de hidrógeno y metilo.

24. Compuesto de conformidad con la reivindicación 23, caracterizado porque:

F es metilo.

25. Composición farmacéutica, caracterizada porque comprende una cantidad efectiva antiviral de un compuesto de fórmula I, que incluye sales farmacéuticamente aceptables del mismo, de conformidad con la reivindicación 1, y uno o más portadores, excipientes o diluyentes farmacéuticamente aceptables.

26. Composición farmacéutica de conformidad con la reivindicación 25, caracterizada porque adicionalmente comprende una cantidad efectiva antiviral de un agente de tratamiento de SIDA seleccionado del grupo que consiste de:

- (a) un agente antiviral de SIDA;
- (b) un agente anti-infeccioso;
- (c) un inmunomodulador; y
- (d) inhibidores de entrada de VIH.

27. Método para el tratamiento de un mamífero infectado con el virus de VIH, caracterizado porque comprende administrar al mamífero una cantidad efectiva antiviral de un compuesto de fórmula I, que incluye sales farmacéuticamente aceptables del mismo, de conformidad con la reivindicación 1,

448

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y uno o más portadores, excipientes o diluyentes farmacéuticamente aceptables.

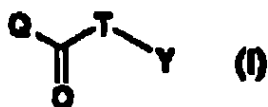
28. Método de conformidad con la reivindicación 27, caracterizado porque administrar al mamífero una cantidad efectiva antiviral de un compuesto de fórmula I, que incluye sales farmacéuticamente aceptables del mismo, de conformidad con la reivindicación 1, en combinación con una cantidad efectiva antiviral de un agente de tratamiento de SIDA seleccionado del grupo que consiste de un agente antiviral de SIDA; un agente anti-infeccioso; inmunomodulador; y un inhibidor de entrada de VIH.

427

425

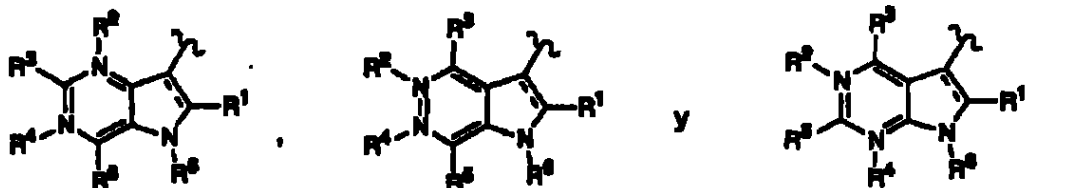
RESUMEN DE LA INVENCION

Se describe la invención que comprende derivados de diazaíndol-dicarbonil-piperazinilo sustituidos de fórmula general I,



en donde:

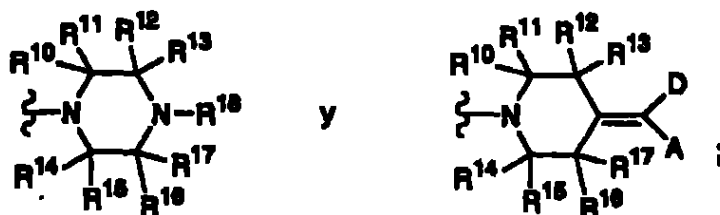
Q se selecciona del grupo que consiste de



-- puede representar un enlace;

T es -C(O)- o -CH(CN)-; y

- Y - se selecciona del grupo que consiste de



composiciones de los mismos y su uso para tratar la infección por VIH.

# PATENT COOPERATION TREATY

10080-WO-PCT

496  
PCT

426

From the INTERNATIONAL SEARCHING AUTHORITY

|                                                                                                                                                                                                                                                                                     |  |                                                                                                                                                                                                                                             |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <b>RECEIVED</b><br><b>BMS PATENT LAW</b><br>To: BRISTOL-MYERS SQUIBB COMPANY<br>Attn: Duboff, Samuel<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>UNITED STATES OF AMERICA<br>APR 15 2005<br>Docketed Item <u>Claims</u><br>Due Date <u>14/04/2005</u><br>Attorney <u>Duboff</u> |  | NOTIFICATION OF TRANSMITTAL OF<br>THE INTERNATIONAL SEARCH REPORT AND<br>WRITTEN OPINION OF THE INTERNATIONAL<br>SEARCHING AUTHORITY, OR THE DECLARATION<br>U.S. SIDS (10080) (HP) 7/14/05<br>done 4/29/05<br>(PCT Rule 44.1)<br>14/04/2005 |  |
| Applicant's or agent's file reference<br>10080PCT                                                                                                                                                                                                                                   |  | APR 28 2005<br>FOR FURTHER ACTION See paragraphs 1 and 4 below                                                                                                                                                                              |  |
| International application No.<br>PCT/US2004/037213                                                                                                                                                                                                                                  |  | International filing date<br>(day/month/year) 04/11/2004                                                                                                                                                                                    |  |
| Applicant<br>BRISTOL-MYERS SQUIBB COMPANY                                                                                                                                                                                                                                           |  |                                                                                                                                                                                                                                             |  |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are 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 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.  
 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 and the written opinion of the International Searching Authority are 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 the expiration of 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 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 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 30 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 18 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 International Searching Authority<br><br>European Patent Office, P.B. 5818 Paternlaan 2<br>NL-2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fac (+31-70) 340-3016 | Authorized officer<br>Josef Ullrich |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|

## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                           |                                                                                                  |                                                                |
|-----------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Applicant's or agent's file reference<br><b>10080PCT</b>  | <b>FOR FURTHER ACTION</b><br>see Form PCT/ISA/220<br>as well as, where applicable, Item 5 below. |                                                                |
| International application No.<br><b>PCT/US2004/037213</b> | International filing date (day/month/year)<br><b>04/11/2004</b>                                  | (Earliest) Priority Date (day/month/year)<br><b>26/11/2003</b> |
| Applicant<br><b>BRISTOL-MYERS SQUIBB COMPANY</b>          |                                                                                                  |                                                                |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

☐

as suggested by the applicant.

☐

as selected by this Authority, because the applicant failed to suggest a figure.

☐

as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.



## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/037213

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/5025 A61K31/519 A61P31/12 A61P31/18

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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)

IPC 7 C07D A61K A61P

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

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                     | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | US 2003/069266 A1 (WANG TAO ET AL)<br>10 April 2003 (2003-04-10)<br>cited in the application<br>examples                                                                                                                                                                                                                                               | 1-28                  |
| A          | FONT M ET AL: "Indoles and<br>pyridazino(4,5-b)indoles as nonnucleoside<br>analog inhibitors of HIV-1 reverse<br>transcriptase"<br>EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY,<br>EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR,<br>vol. 30, no. 12, 1995, pages 963-971,<br>XP002210360<br>ISSN: 0223-5234<br>cited in the application<br>the whole document | 1-28                  |

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the International search

7 April 2005

Date of mailing of the International search report

14/04/2005

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentplan 2  
NL - 2580 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 661 epo nl,  
Fax: (+31-70) 340-3010

Authorized officer

Fazzi, R

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/037213 429

## Box I Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

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

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 27-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/037213

430

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| US 2003069266 A1                          | 10-04-2003          | US 2003207910 A1           | 06-11-2003          |
|                                           |                     | US 2004110785 A1           | 10-06-2004          |
|                                           |                     | BG 108021 A                | 30-04-2004          |
|                                           |                     | BR 0206636 A               | 25-02-2004          |
|                                           |                     | CA 2437524 A1              | 15-08-2002          |
|                                           |                     | CZ 20032316 A3             | 14-01-2004          |
|                                           |                     | EE 200300359 A             | 15-12-2003          |
|                                           |                     | EP 1363705 A1              | 26-11-2003          |
|                                           |                     | HU 0304062 A2              | 28-04-2004          |
|                                           |                     | JP 2004522755 T            | 29-07-2004          |
|                                           |                     | MX PA03006939 A            | 18-11-2003          |
|                                           |                     | NO 20033436 A              | 01-10-2003          |
|                                           |                     | NZ 527193 A                | 28-05-2004          |
|                                           |                     | SK 9592003 A3              | 03-08-2004          |
|                                           |                     | WO 02062423 A1             | 15-08-2002          |

## PCT

## REPORTE DE BUSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

437 431

|                                                            |                                                                 |                                                                             |
|------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------|
| Referencia presentada del solicitante o agente<br>10080PCT | PARA ACCION<br>ADICIONAL                                        | Véase la Forma PCT/ISA/220<br>también, donde es aplicable, artículo 5 abajo |
| Solicitud internacional No.<br>PCT/US2004/037213           | Fecha de presentación internacional (día/mes/año)<br>04/11/2004 | Fecha de prioridad (día/mes/año)<br>26/11/2003                              |
| Solicitante<br>BRISTOL-MYERS SQUIBB COMPANY                |                                                                 |                                                                             |

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y se transmite al solicitante de acuerdo al Artículo 18. Una copia se transmite a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 4 hojas.

☒ También está acompañado de una copia de cada documento de la técnica previa citado en este reporte.

## 1. Base del reporte

a. Con respecto al idioma, la búsqueda Internacional se realizó en base de la solicitud Internacional en el idioma en el cual fue presentada, al menos que por lo contrario se indique bajo este artículo.

☐ La búsqueda internacional se realizó en base de la traducción de la solicitud internacional proporcionada a esta

Autoridad (Regla 23.1 (b))

b. ☐ Con respecto a cualquier secuencia de nucleótido y/o aminoácido descrito en la solicitud internacional, ver cuadro No. I.

2. ☐ Ciertas reivindicaciones fueron imposibles de buscar (ver Cuadro II).

3. ☐ la unidad de la invención es carente (ver Cuadro III)

## 4. Con respecto al título

☒ El texto está aprobado como se presentó por el solicitante.

☐ El texto ha sido establecido por esta Autoridad para leerse como sigue:

## 5. Con respecto al extracto,

☒ El texto está aprobado como se presentó por el solicitante.

☐ El texto ha sido establecido, de acuerdo a la Regla 38.2(b), por esta Autoridad como aparece En el Cuadro IV. El solicitante puede, en el término de un mes a partir de la fecha de envío de este reporte de búsqueda internacional, presentar comentarios a esta Autoridad.

## 6. con respecto a los dibujos,

a. La figura de los dibujos a ser publicada con el extracto es

Figura No. \_\_\_\_

☐ como es sugerida por el solicitante

☐ como es seleccionada por esta Autoridad, debido a que el solicitante no sugiere una figura.

☐ Como es seleccionada por esta Autoridad, debido a que esta figura, caracteriza mejor la invención.

b. ☐ ningunas figuras fueron publicadas con este resume

# REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud internacional No. 432  
PCT/US2004/037213

## A. CLASIFICACION DE LA MATERIA OBJETO

IPC 7: C07D 487/04 A61K 31/5025 A61K 31/519 A61P 31/12 A61P 31/18

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

## B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación)

IPC 7 C07D A61K A61P

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data,

## C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

| Categoría* | Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes                                                                                                                                                                                                                                                                                       | Relevante para la Reiv. No. |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| X          | US 2003/069266 A1(WANG TAO ET AL)<br>10 de abril de 2003 (10-04-2003)<br>citado en la solicitud<br>ejemplos                                                                                                                                                                                                                                                                 | 1-28                        |
| A          | -----<br>FONT M ET AL: "Indoles and<br>Pyridazino(4,5-b)indoles as nonnucleoside<br>analog inhibitors of HIV-1 reverse<br>transcriptase"<br>EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY,<br>EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR,<br>vol. 30, no. 12, 1995, páginas 963-971,<br>XP00220360<br>ISSN : 0223-5234<br>citado en la solicitud<br>el documento completo<br>----- | 1-28                        |

☐ Documentos adicionales se enlistan en la continuación del cuadro C. ☒ Véase familia de patentes anexa.

\* Categorías especiales de los documentos citados

"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.

"E" documento anterior publicado en o después de la fecha de presentación internacional.

"L" documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

"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 fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.

"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.

"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.

"&" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional  
7 de abril de 2005

Fecha de envío del reporte de búsqueda internacional  
14/04/2005

Nombre y dirección Postal de la ISA/  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Oficial autorizado  
Fazzi, R.

Forma PCT/ISA/210 (segunda hoja) (enero 2004)

**REPORTE DE BUSQUEDA INTERNACIONAL**

Solicitud Internacional No.  
PCT/US2004/037213

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**Cuadro II Observaciones en donde ciertas reivindicaciones se encontraron inescrutables (Continuación del artículo 2 de la primera hoja)**

Este Reporte Internacional no ha sido establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2)(a) del PCT por las siguientes razones:

1. ☒ Reivindicaciones Nos.:  
debido a que se relacionan con la materia objeto no se requiere ser investigadas por esta Autoridad, es decir:  
Aunque las reivindicaciones 27-28 se dirigen a un método de tratamiento del cuerpo humano/animal, la búsqueda se ha llevado a cabo y se basa en los efectos alegados del compuesto/composición.
2. ☐ Reivindicaciones Nos.:  
debido a que se relacionan con partes de la solicitud internacional que no cumplen con los requerimientos prescritos a tal extensión que ninguna búsqueda internacional significativa se puede llevar a cabo, específicamente:
3. ☐ Reivindicaciones Nos.:  
Debido a que son reivindicaciones dependientes y no están redactadas de acuerdo con las segundas y terceras oraciones de la Regla 6.4(a).

**Cuadro III Observaciones en donde se carece de unidad de la invención (Continuación del artículo 3 de la primera hoja)**

La Autoridad de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

1. ☐ Ya que todas las cuotas de búsqueda adicionales fueron pagadas a tiempo por la solicitante, este reporte de búsqueda cubre todas las reivindicaciones escrutables.
2. ☐ Ya que todas las reivindicaciones escrutables pudieron ser buscadas sin esfuerzo que justifique una cuota adicional, esta Autoridad no invita al pago de ninguna cuota adicional.
3. ☐ Ya que solamente algunas de las cuotas de búsqueda adicionales requeridas fueron pagadas oportunamente por la Solicitante, este Reporte de Búsqueda Internacional cubre solamente aquellas reivindicaciones para las cuales se pagaron cuotas, específicamente las reivindicaciones Nos.:
4. ☐ Ninguna cuota de búsqueda adicional requerida fue pagada oportunamente por la solicitante. Consecuentemente, este reporte de búsqueda internacional está restringido a la invención primero mencionada en las reivindicaciones; está cubierto por las reivindicaciones Nos.:

Observación en protesta

- ☐ Las cuotas de búsqueda adicionales estuvieron acompañadas por la protesta de la solicitante.
- ☐ Ninguna protesta acompañó el pago de las cuotas de búsqueda adicional.

**REPORTE DE BÚSQUEDA INTERNACIONAL**  
 Información de los miembros de la familia de patentes

Solicitud internacional No. **434**  
 PCT/US2004/057213

| Documento de patente citado en el<br>Reporte de Búsqueda | Fecha de publicación | Miembro(s) de la familia de<br>patente(s) | Fecha de publicación |
|----------------------------------------------------------|----------------------|-------------------------------------------|----------------------|
| US 2003069266 A1                                         | 10-04-2003           | US 2003207910 A1                          | 06-11-2003           |
|                                                          |                      | US 2004110785 A1                          | 10-06-2004           |
|                                                          |                      | BG 108021 A                               | 30-04-2004           |
|                                                          |                      | BR 0206636 A                              | 25-02-2004           |
|                                                          |                      | CA 2437524 A1                             | 15-08-2002           |
|                                                          |                      | CZ 20032316 A3                            | 14-01-2004           |
|                                                          |                      | EE 200300359 A                            | 15-12-2003           |
|                                                          |                      | EP 1363705 A1                             | 26-11-2003           |
|                                                          |                      | HU 0304062 A2                             | 28-04-2004           |
|                                                          |                      | JP 2004522755 T                           | 29-07-2004           |
|                                                          |                      | MX PA03006939 A                           | 18-11-2003           |
|                                                          |                      | NO 20033436 A                             | 01-10-2003           |
|                                                          |                      | NZ 527193 A                               | 28-05-2004           |
|                                                          |                      | SK 9592003 A3                             | 03-08-2004           |
|                                                          |                      | WO 02062423 A1                            | 15-08-2002           |

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

*435*  
*PCT*

To:

see form PCT/ISA220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43b/s.1)

Date of mailing  
(day/month/year) see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/US2004/037213

International filing date (day/month/year)  
04.11.2004

Priority date (day/month/year)  
28.11.2003

International Patent Classification (IPC) or both national classification and IPC  
C07D487/04, A81K31/5025, A81K31/519, A81P31/12, A81P31/18

Applicant  
BRISTOL-MYERS SQUIBB COMPANY

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

### 3. For further details, see notes to Form PCT/ISA220.

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2369 - 0 Tx: 523695 spru d  
Fax: +49 89 2369 - 4465

Authorized Officer

Fazzi, R  
Telephone No. +49 89 2369-8510





**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

436  
International application No. .  
PCT/US2004/037213

**Box No. I Basis of the opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:  
☐ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material:  
☐ in written format  
☐ in computer readable form
  - c. time of filing/furnishing:  
☐ contained in the international application as filed.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27-28

because:

☒ the said international application, or the said claims Nos. 27-28 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

*L4412* 438  
International application No.  
PCT/US2004/037213

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or  
Industrial applicability; citations and explanations supporting such statement**

**1. Statement**

|                               |             |      |
|-------------------------------|-------------|------|
| Novelty (N)                   | Yes: Claims | 1-28 |
|                               | No: Claims  |      |
| Inventive step (IS)           | Yes: Claims |      |
|                               | No: Claims  | 1-28 |
| Industrial applicability (IA) | Yes: Claims | 1-28 |
|                               | No: Claims  |      |

**2. Citations and explanations**

**see separate sheet**

replacement of a carbon atom with a nitrogen atom.

Said substitution is however well known in the state of the art, so that the skilled person would consider the present solution obvious (i.e. for structural similar compounds, a similar biological activity can be expected).

However, if the Applicant could show that current derivatives of formula (I) present a better activity in relation to the compounds disclosed in D1, this unexpected effect could be considered as an indication of non-obviousness.

In the present case, no such effects or properties are indicated in the application.

Moreover, no experimental data showing that also compounds of formula (I) -wherein Q is selected from the pyridazine moiety (second definition, also defined as solution (B) in claim 5)- are a solution to the above-mentioned technical problem, have been found in the present application.

Accordingly, the subject-matter of present claims 1-28 does not fulfil the criteria of Article 33(3) PCT.

#### **5) Industrial applicability (Reference to section V)**

For the assessment of the present claims 27-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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1) Reference is made to the following documents:

D1: US 2003/069266 A1

D2: FONT M ET AL: "Indoles and pyridazino(4,5-b)indoles as nonnucleoside analog inhibitors of HIV-1 reverse transcriptase" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 30, no. 12, 1995, pages 963-971, XP002210360 ISSN: 0223-5234

2) Reference to section III

Claims 27-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3) Novelty (Reference to section V)

D1 discloses substituted azaindoleoxoacetic piperazine derivatives; similar compounds are disclosed in the present application, but they are, however, diazaindole-dicarbonyl-piperaziny derivatives.

Diazaindole derivatives are also not disclosed in document D2.

Thus, the subject-matter of present claims 1-28 seems to meet the requirements of Article 33(2) PCT.

4) Inventive step (Reference to section V)

D1, which may be considered to represent the closest state of the art, describes substituted azaindole derivatives, which possess an antiviral activity and are thus useful in the treatment of HIV and AIDS.

The problem to be solved by the present application may therefore be regarded as the provision of further compounds with the same therapeutical activity.

Having regard to the examples of D1 (cf. pages 120-212), the difference between the teaching of D1 and that of the present application seems to reside merely in the biisosteric

# TRATADO DE COOPERACION EN MATERIA DE PATENTES

441

De la  
AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

|                                                                            |                                                                 |                                                                                                                               |  |
|----------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--|
| Para:<br><br>Ver forma PCT/ISA/220                                         |                                                                 | <b>PCT</b><br><b>OPINIÓN ESCRITA DE LA</b><br><b>AUTORIDAD DE BÚSQUEDA</b><br><b>INTERNACIONAL</b><br><br>(Regla 43bis.1 PCT) |  |
|                                                                            |                                                                 | Fecha de envío<br>(día/mes/año) Ver forma PCT/ISA/210(segunda hoja)                                                           |  |
| Referencia de archivo del solicitante o agente<br>Ver la forma PCT/ISA/220 |                                                                 | PARA ACCION ADICIONAL<br>Ver párrafo 2 abajo                                                                                  |  |
| Solicitud internacional No.<br>PCT/US2004/037213                           | Fecha de presentación internacional (día/mes/año)<br>04.11.2004 | Fecha de prioridad (día/mes/año)<br>26.11.2003                                                                                |  |

Clasificación de Patente Internacional (IPC) o ambas clasificación nacional e IPC  
C07D 487/04, A61K 31/5025, A61K 31/519, A61P 31/12, A61P 31/18

Solicitante  
BRISTOL-MYERS SQUIBB COMPANY

- Esta opinión contiene las indicaciones relacionadas a los siguientes incisos:
  - ☒ Cuadro No. I Bases de la Opinión
  - ☐ Cuadro No. II Prioridad
  - ☒ Cuadro No. III Sin establecimiento de la opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial
  - ☐ Cuadro No. IV Carente de unidad de la invención
  - ☒ Cuadro No. V Declaración razonada bajo la Regla 43bis.1(a)(i) con respecto a la novedad, etapa inventiva y aplicabilidad industrial; citas y explicaciones que soportan esta declaración.
  - ☐ Cuadro No. VI Ciertos documentos citados
  - ☐ Cuadro No. VII Ciertos defectos en la solicitud internacional
  - ☐ Cuadro No. VIII Ciertas observaciones en la solicitud internacional

## 2. ACCIÓN ADICIONAL

Si se hace una demanda para el examen preliminar internacional, esta opinión será considerada ser una opinión escrita de la Autoridad de Examen Preliminar Internacional ("IPEA"). Sin embargo, ese esto no aplica donde el aspirante elige una Autoridad de otra manera que uno sea la IPEA y que la IPEA elegida haya notificado a la Oficina Internacional bajo la Regla 66.1 bis(b) donde las opiniones escritas de esta Autoridad de Búsqueda Internacional no serán así consideraba.

Si esta opinión es, como la provista anteriormente, considerada para ser una opinión escrita de la IPEA, se invita al solicitante a presentar a la IPEA una reaspueta escrita a la vez, cuando sea apropiado, con enmiendas, antes de la expiración de 3 meses a partir de la fecha del envío por correo de la forma PCT/ISA/220 o antes de la expiración de 22 meses a partir de la fecha de prioridad, el que expira más adelante.

Para otras opciones, ver Forma PCT/ISA/220.

3. Para otros detalles, ver notas para la Formar PCT/ISA/220.

|                                                                                                                                                                                    |                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Nombre y dirección de correspondencia de la ISA:<br>(logotipo) Oficina de Patentes Europea<br>D-80298 Munich<br>Tel. (+49-89) 2399-0, Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Oficial autorizado<br><br>Fazzi, R<br><br>Teléfono No. +49 89 2399-8510<br>(logotipo) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|

Forma PCT/ISA/237 (carátula) (enero de 2004)

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**Cuadro No. I Bases de la opinión.**

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1. Con respecto al idioma, esta opinión está basado en la solicitud internacional en el idioma en el que fue presentado, a menos que por otra parte se indique bajo en este artículo.  
  
☐ Esta opinión se ha establecido en las bases de una traducción del lenguaje original en el siguiente idioma , que es el idioma de una traducción proporcionada para los propósitos del reporte internacional (bajo las Reglas 12.3 y 23.1 (b)).
2. Con respecto a cualquier secuencia de nucleótido y/o aminoácido descrita en solicitud internacional y necesariamente a la invención reivindicada, esta opinión está establecida en bases de:
  - a. tipo de material
    - ☐ un listado de secuencias
    - ☐ tabla(s) relacionada al listado de secuencias
  - b. formato del material:
    - ☐ en formato escrito
    - ☐ en forma legible en computadora
  - c. tiempo de presentación/proporción:
    - ☐ contenida en la solicitud internacional como se presentó.
    - ☐ presentado junto con la solicitud internacional en forma legible en computadora.
    - ☐ proporcionado subsiguientemente a esta Autoridad para los propósitos de búsqueda.
3. ☐ Además, en el caso que más de una versión o copia de un listado de secuencias y/o tabla que se relaciona al mismo, se haya presentado o proporcionado, las declaraciones requeridas que la información en las copias subsecuentes o adicionales es idéntica a ésta en la solicitud como se presentó o no va más allá de la solicitud como se presentó, como apropiadamente, fue proporcionada.
4. Comentarios adicionales:

**Cuadro No. III Sin establecimiento de la opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial**

Las cuestiones de la invención reivindicada parece ser de novedad, involucra una etapa inventiva (puede ser no obvio), o sea aplicable industrialmente, no se ha examinado con respecto de:

- ☐ solicitud internacional completa  
☒ reivindicaciones Nos. 27-28

porque:

☒ la solicitud internacional, o las reivindicaciones Nos. 27-28 con respecto a la siguiente materia objeto la cual no requiere un examen preliminar internacional (*especificar*):

ver hoja separada

☐ descripción, reivindicaciones o dibujos (*Indique los elementos particulares abajo*) o dichas reivindicaciones Nos. son muy confusas por lo que no puede formarse una opinión significativa (*especifique*):

☐ las reivindicaciones, o reivindicaciones Nos. son apoyadas de manera muy inadecuada por la descripción por lo que no puede formar una opinión significativa:

☐ ningún reporte internacional de búsqueda ha sido establecido para la solicitud completa o dicha reivindicaciones Nos.

☐ el listado de secuencia del nucleótido y/o aminoácido no cumple con los estándares proporcionados en el anexo C de las Instrucciones Administrativas en donde:

la forma escrita

☐ no ha sido proporcionada

☐ no cumple con los estándares

la forma legible en computadora

☐ no ha sido proporcionada

☐ no cumple con los estándares

☐ las tablas relacionadas con el listado de secuencia del nucleótido y/o aminoácido, si solamente están en forma legible en computadora no cumple con los requisitos técnicos proporcionados en el Anexo C-bis de las Instrucciones administrativas.

☐ Ver hoja separada para los detalles adicionales



**Cuadro No. V Declaración razonada bajo la Regla 43b/a. 1(a)(I) con respecto a la novedad, etapa inventiva o aplicabilidad Industrial; citas y explicaciones que soportan esta declaración.**

**1. DECLARACIÓN**

**Novedad (N)**                      **Si: Reivindicaciones 1-28**  
                                         **No: Reivindicaciones**

**Etapas Inventiva (EI)**           **Si: Reivindicaciones**  
                                         **No: Reivindicaciones 1-28**           :

**Aplicabilidad**                      **Si: Reivindicaciones 1-26**  
**Industrial (AI)**                      **No: Reivindicaciones**

**2. Citas y Explicaciones**  
**ver hoja separada**

**OPINIÓN ESCRITA DE LA  
AUTORIDAD DE BÚSQUEDA  
INTERNACIONAL (HOJA SEPARADA)**

---

~~444~~ 445  
No. de Solicitud Internacional  
PCT/US2004/037213

1) Se hace referencia a los siguientes documentos:

D1: US2003/069266 A1

D2: FONT M ET AL: "Indoles and pyridazino(4,5-b)indoles as nonnucleoside analog inhibitors of HIV-1 reverse transcriptase" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 30, no. 12, 1995, páginas 963-971, XP002210360 ISSN: 0223-5234

**2) Referencia a la Sección III**

Las reivindicaciones 27-28 se refieren a la materia objeto considerada por esta Autoridad a ser cubierta por las provisiones de la Regla 67.1(iv) PCT. Por lo tanto, no se formulará ninguna opinión con respecto a la aplicabilidad industrial de la materia objeto de estas reivindicaciones (Artículo 34(4)(a)(I) PCT).

**3) Novedad (Referencia a la sección V)**

D1 describe derivados de piperazina azaindoleoxoacéticos sustituidos; compuestos similares se describen en la presente solicitud, pero son, sin embargo, derivados de diazaindol-dicarbonil-piperazinilo.

Los derivados de diazaindol también no se describen en el documento D2.

efecto inesperado se podría considerar como una indicación de no-evidencia.

En el presente caso, no se indican tales efectos o propiedades en la solicitud.

Por otra parte, ningún dato experimental muestra que también los compuestos de fórmula (I) - en donde Q se selecciona del radical de piridazina (segunda definición, también definida como la solución (B) en la reivindicación 5) - sea una solución al problema técnico anteriormente mencionado, encontrándose en la presente solicitud.

Por consiguiente, la materia objeto de las presentes reivindicaciones 1-28 no cumplen con el criterio del Artículo 33(3) PCT.

**5) Aplicabilidad industrial (Referencia a la sección V)**

Para la valoración de las presentes reivindicaciones 27-28 en la cuestión si son industrial aplicables, ningún criterio unificado existe en los Países Contratantes del PCT. La patentabilidad puede también ser dependiente sobre la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable la materia objeto de las reivindicaciones al uso de un compuesto en tratamiento médico, pero puede permitir, sin embargo, las reivindicaciones a un compuesto conocido para primer uso en

**OPINIÓN ESCRITA DE LA  
AUTORIDAD DE BÚSQUEDA  
INTERNACIONAL (HOJA SEPARADA)**

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No. de Solicitud Internacional  
PCT/US2004/037213

447

el tratamiento médico y el uso de tal compuesto para la  
fabricación de un medicamento para un nuevo tratamiento  
médico.

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, New Jersey 08543-4000  
ETATS-UNIS D'AMERIQUE

FEB 23 2005

Docketed Item

Due Date

Attorney

IMPORTANT NOTIFICATION

|                                                                   |                                                                             |
|-------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Date of mailing (day/month/year)<br>15 February 2005 (15.02.2005) |                                                                             |
| Applicant's or agent's file reference<br>10080PCT                 |                                                                             |
| International application No.<br>PCT/US04/037213                  | International filing date (day/month/year)<br>04 November 2004 (04.11.2004) |
| International publication date (day/month/year)                   | Priority date (day/month/year)<br>26 November 2003 (26.11.2003)             |
| Applicant<br>BRISTOL-MYERS SQUIBB COMPANY et al                   |                                                                             |

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(e) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(e) 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<br>or PCT receiving Office | Date of receipt<br>of priority document |
|-------------------------------|--------------------------|-------------------------------------------------------|-----------------------------------------|
| 26 November 2003 (26.11.2003) | 60/525,624               | US                                                    | 02 February 2005 (02.02.2005)           |

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

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449

10080-US-PS P

VOLLES



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| APPL NO.   | FILING OR 371<br>(c) DATE | ART UNIT | FIL FEE REC'D | ATTY. DOCKET NO | DRAWINGS | TOT CLMS | IND CLMS |
|------------|---------------------------|----------|---------------|-----------------|----------|----------|----------|
| 80/525,624 | 11/26/2003                |          | 160           | 10080 PSP       |          |          |          |

CONFIRMATION NO. 1068

23914  
STEPHEN B. DAVIS  
BRISTOL-MYERS SQUIBB COMPANY  
PATENT DEPARTMENT  
P O BOX 4000  
PRINCETON, NJ 08543-4000

FILING RECEIPT



\*0C000000011854600\*

Date Mailed: 01/09/2004

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-748-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

John A. Bender, Middletown, CT;  
Zhong Yang, Middletown, CT;  
John F. Kadow, Wallingford, CT;  
Nicholas A. Mearwell, East Hampton, CT;

RECEIVED  
BMS PATENT LAW

JAN 12 2004

If Required, Foreign Filing License Granted: 01/08/2004

Docketed Item FLR

Due Date (WV)

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Diazaindole-dicarbonyl-piperazinyl antiviral agents

LICENSE FOR FOREIGN FILING UNDER  
Title 35, United States Code, Section 184

43/450

Page 2 of 2

**Title 37, Code of Federal Regulations, 5.11 & 5.15**

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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## PCT REQUEST

Original (for SUBMISSION)

|         |                                                                                                                                         |                                                                                                  |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| 0       | For receiving Office use only                                                                                                           |                                                                                                  |
| 0-1     | International Application No.                                                                                                           |                                                                                                  |
| 0-2     | International Filing Date                                                                                                               |                                                                                                  |
| 0-3     | Name of receiving Office and "PCT International Application"                                                                            |                                                                                                  |
| 0-4     | Form PCT/RO/101 PCT Request                                                                                                             |                                                                                                  |
| 0-4-1   | Prepared Using                                                                                                                          | PCT-SAFE [EASY mode]<br>Version 3.50 (Build 0002.163)                                            |
| 0-5     | Petition<br>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                                                                                                   | 10080PCT                                                                                         |
| I       | Title of invention                                                                                                                      | DIAXATINDOLE-DICARBONYL-PIPERAZINYL<br>ANTIVIRAL AGENTS                                          |
| II      | Applicant                                                                                                                               |                                                                                                  |
| II-1    | This person is                                                                                                                          | applicant only                                                                                   |
| II-2    | Applicant for                                                                                                                           | all designated States except US                                                                  |
| II-4    | Name                                                                                                                                    | BRISTOL-MYERS SQUIBB COMPANY                                                                     |
| II-5    | Address                                                                                                                                 | Route 206 and Province Line Road<br>Princeton, New Jersey 08543-4000<br>United States of America |
| II-6    | State of nationality                                                                                                                    | US                                                                                               |
| II-7    | State of residence                                                                                                                      | US                                                                                               |
| II-8    | Telephone No.                                                                                                                           | 609-252-4000                                                                                     |
| II-9    | Facsimile No.                                                                                                                           | 609-252-4526                                                                                     |
| III-1   | Applicant and/or inventor                                                                                                               |                                                                                                  |
| III-1-1 | This person is                                                                                                                          | applicant and inventor                                                                           |
| III-1-2 | Applicant for                                                                                                                           | US only                                                                                          |
| III-1-4 | Name (LAST, First)                                                                                                                      | BENDER, John, A.                                                                                 |
| III-1-5 | Address                                                                                                                                 | 21 Brookview Lane<br>Middletown, Connecticut 06457<br>United States of America                   |
| III-1-6 | State of nationality                                                                                                                    | US                                                                                               |
| III-1-7 | State of residence                                                                                                                      | US                                                                                               |



## PCT REQUEST

Original (for SUBMISSION)

|        |                                                                                                                                                                                                                                |                                                                                                               |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| II-2   | Applicant and/or inventor                                                                                                                                                                                                      | applicant and inventor                                                                                        |
| II-2-1 | This person is                                                                                                                                                                                                                 | US only                                                                                                       |
| II-2-2 | Applicant for                                                                                                                                                                                                                  | US only                                                                                                       |
| II-2-4 | Name (LAST, First)                                                                                                                                                                                                             | YANG, Khong                                                                                                   |
| II-2-5 | Address                                                                                                                                                                                                                        | 11-2 West Meadow Lane<br>Middletown, Connecticut 06457<br>United States of America                            |
| II-2-6 | State of nationality                                                                                                                                                                                                           | CH                                                                                                            |
| II-2-7 | State of residence                                                                                                                                                                                                             | US                                                                                                            |
| II-3   | Applicant and/or inventor                                                                                                                                                                                                      | applicant and inventor                                                                                        |
| II-3-1 | This person is                                                                                                                                                                                                                 | US only                                                                                                       |
| II-3-2 | Applicant for                                                                                                                                                                                                                  | US only                                                                                                       |
| II-3-4 | Name (LAST, First)                                                                                                                                                                                                             | KADON, John, F.                                                                                               |
| II-3-5 | Address                                                                                                                                                                                                                        | 9 Quarry Run<br>Wallingford, Connecticut 06492<br>United States of America                                    |
| II-3-6 | State of nationality                                                                                                                                                                                                           | US                                                                                                            |
| II-3-7 | State of residence                                                                                                                                                                                                             | US                                                                                                            |
| II-4   | Applicant and/or inventor                                                                                                                                                                                                      | applicant and inventor                                                                                        |
| II-4-1 | This person is                                                                                                                                                                                                                 | US only                                                                                                       |
| II-4-2 | Applicant for                                                                                                                                                                                                                  | US only                                                                                                       |
| II-4-4 | Name (LAST, First)                                                                                                                                                                                                             | MEANWELL, Nicholas, A.                                                                                        |
| II-4-5 | Address                                                                                                                                                                                                                        | 15 Valli Drive<br>East Hampton, Connecticut 06424<br>United States of America                                 |
| II-4-6 | State of nationality                                                                                                                                                                                                           | GB                                                                                                            |
| II-4-7 | State of residence                                                                                                                                                                                                             | US                                                                                                            |
| IV-1   | Agent or common representative; or<br>address for correspondence<br>The person identified below is hereby/<br>has been appointed to act on behalf of<br>the applicant(s) before the competent<br>International Authorities as: | agent                                                                                                         |
| IV-1-1 | Name (LAST, First)                                                                                                                                                                                                             | DUBOFF, Samuel                                                                                                |
| IV-1-2 | Address                                                                                                                                                                                                                        | Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| IV-1-3 | Telephone No.                                                                                                                                                                                                                  | 203-677-6974                                                                                                  |
| 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                                                                      |

|          |                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IV-2-1   | Name(s)                                                                                                                                                                                                                                                                                | <b>first named agent</b><br>KFFERSON, James (52,867); GOLIAN, Paul, D. (42,591); HABAJKO, Susanna (32,880); BAXAM, Deanna (45,266); BELFIELD, Jing (45,914); BOGIE, Terence (44,544); BUCHHOLZ, Briana (39,123); D'ANICO, Stephen (46,652); DAVIS, Stephen (26,693); DUNCAN, Laurelee (44,096); DUNCAN, Sammy (46,675); GIBBONS, Maureen (44,121); KILCOYNE, John (33,100); KLEIN, Christopher (34,363); KORSER, Elliott (32,705); LAMERDIE, John (44,858); LANGE, Keith (44,201); O'BRIEN, Maureen (42,043); PROVOOST, Jonathan (44,292); RODNEY, Burton (22,076); SHER, Audrey (39,024); VANATTEN, Mary, K. (39,408); WINSLOW, Anastasia (40,875); ALGIERI, Aldo (31,697); MAKUJINA, Shah (41,174); RYAN, Richard (30,491); VOLLES, Warren, K. (33,810); WINGO, Pamela, A. (48,256); GREENBLATT, Gary, D. (47,609); GU, Henry, H. (55,227); PATEL, Rena (41,412); CHIN, Jennifer, T. (47,487); WANG, Joseph, C. (44,391); WILLE, Louis, J. (32,954); PARLET, Nickki, L. (44,996) |
| <b>V</b> | <b>DESIGNATIONS</b>                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| V-1      | The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| VI-1     | Priority claim of earlier national application                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| VI-1-1   | Filing date                                                                                                                                                                                                                                                                            | 26 November 2003 (26.11.2003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| VI-1-2   | Number                                                                                                                                                                                                                                                                                 | 60/525,624                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| VI-1-3   | Country                                                                                                                                                                                                                                                                                | US                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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PCT REQUEST

Original (for SUBMISSION)

|       |                                                                                                                                                                                                |                                       |  |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|--|
| VI-2  | Priority document request<br>The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): | VI-1                                  |  |
| VI-1  | International Searching Authority Chosen                                                                                                                                                       | European Patent Office (EPO) (ISA/EP) |  |
| VII   | Declarations                                                                                                                                                                                   | Number of declarations                |  |
| VII-1 | Declaration as to the identity of the inventor                                                                                                                                                 | -                                     |  |
| VII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent                                                                       | 1                                     |  |
| VII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application                                                           | 1                                     |  |
| VII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America)                                                                                         | -                                     |  |
| VII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty                                                                                                                 | -                                     |  |

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PCT REQUEST

Original (for SUBMISSION)

|                   |                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VII-2-1           | Declaration: Entitlement to apply for and be granted a patent<br>Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(i) and 51bis.1(a)(ii)).<br>In a case where the declaration under Rule 4.17(iv) is not appropriate:<br>Name (LAST, First) | in relation to this international application<br><br>BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following: |
| VIII-2-1(i)<br>v) |                                                                                                                                                                                                                                                                                                                                | an assignment from BENDER, John, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 23 December 2003 (23.12.2003)                                                       |
| VIII-2-1(i)<br>v) |                                                                                                                                                                                                                                                                                                                                | an assignment from YANG, Khong to BRISTOL-MYERS SQUIBB COMPANY, dated 23 December 2003 (23.12.2003)                                                            |
| VIII-2-1(i)<br>v) |                                                                                                                                                                                                                                                                                                                                | an assignment from KADOW, John, F. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 January 2004 (05.01.2004)                                                         |
| VIII-2-1(i)<br>v) |                                                                                                                                                                                                                                                                                                                                | an assignment from MEANWELL, Nicholas, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 January 2004 (05.01.2004)                                                  |
| VIII-2-1(i)<br>x) | This declaration is made for the purpose of:                                                                                                                                                                                                                                                                                   | all designations except the designation of the United States of America                                                                                        |

|                |                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VII-3-1        | <p>Declaration: Entitlement to claim priority</p> <p>Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(II) and 51bis.1(a)(II))</p> <p>Name</p> | <p>in relation to this international application</p> <p>BRISTOL-MYERS SQUIBB COMPANY</p> <p>is entitled to claim priority of earlier application No. 60/525,624 by virtue of the following:</p>                                                                                                                                                                                                                                                                                                                                                  |
| VII-3-10<br>v) |                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>an assignment from BENDER, John, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 23 December 2003 (23.12.2003)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| VII-3-10<br>v) |                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>an assignment from YANG, Zhong to BRISTOL-MYERS SQUIBB COMPANY, dated 23 December 2003 (23.12.2003)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| VII-3-10<br>v) | ..                                                                                                                                                                                                                                                                                                                                                                                                                              | <p>an assignment from KADOW, John, F. to BRISTOL-MYERS-SQUIBB COMPANY, dated 05 January 2004 (05.01.2004)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| VII-3-10<br>v) |                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>an assignment from MEANWELL, Nicholas, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 January 2004 (05.01.2004)</p>                                                                                                                                                                                                                                                                                                                                                                                                                             |
| VII-3-10<br>x) | <p>This declaration is made for the purpose of:</p>                                                                                                                                                                                                                                                                                                                                                                             | <p>AP: (BW GH GM KE LS MW NX NA SD SL SZ TZ UG XM XW ), EA: (AN AS BY KG KE MD RU TJ TM ), EP: (AT BE BG CH LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC ML PT RO SE SI SK TR ), OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG ), AE AG AL AM AT AU AX BA BB BG BR BW BY BE CA CHA LI CN CO CR CU CZ DE DK DN DE EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KX LC LK LR LS LT LU LV MA MD MG MK MN MW MX ME NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SJ TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW</p> |

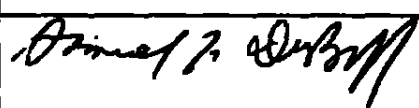
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PCT REQUEST

Original (for SUBMISSION)

|       |                                                            |                                                                                     |                             |
|-------|------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------|
| IX    | Check list                                                 | number of sheets                                                                    | electronic file(s) attached |
| IX-1  | Request (including declaration sheets)                     | 8                                                                                   | ✓                           |
| IX-2  | Description                                                | 159                                                                                 | -                           |
| IX-3  | Claims                                                     | 15                                                                                  | -                           |
| IX-4  | Abstract                                                   | 1                                                                                   | ✓                           |
| IX-5  | Drawings                                                   | 0                                                                                   | -                           |
| IX-7  | TOTAL                                                      | 183                                                                                 |                             |
|       | 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-SAFE physical media                                    | -                                                                                   | ✓                           |
| IX-18 | other                                                      |                                                                                     |                             |
| IX-18 | other                                                      | Postcard receipt;<br>Certificate of<br>Express Mailing;<br>Certification            |                             |
| IX-19 | Figure of the drawings which should accompany the abstract |                                                                                     |                             |
| IX-20 | Language of filing of the international application        | English                                                                             |                             |
| X-1   | Signature of applicant, agent or common representative     |  |                             |
| X-1-1 | Name (LAST, First)                                         | DUBOFF, Samuel                                                                      |                             |
| X-1-2 | Name of signatory                                          |                                                                                     |                             |
| X-1-3 | Capacity                                                   |                                                                                     |                             |

FOR RECEIVING OFFICE USE ONLY

|        |                                                                                                                                         |        |
|--------|-----------------------------------------------------------------------------------------------------------------------------------------|--------|
| 10-1   | Date of actual receipt of the purported international application                                                                       |        |
| 10-2   | Drawings:                                                                                                                               |        |
| 10-2-1 | Received                                                                                                                                |        |
| 10-2-2 | Not received                                                                                                                            |        |
| 10-3   | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application |        |
| 10-4   | Date of timely receipt of the required corrections under PCT Article 11(2)                                                              |        |
| 10-5   | International Searching Authority                                                                                                       | ISA/EP |
| 10-6   | Transmittal of search copy delayed until search fee is paid                                                                             |        |

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10080PCT

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PCT REQUEST

Original (for SUBMISSION)

FOR INTERNATIONAL BUREAU USE ONLY

|      |                                                                |  |
|------|----------------------------------------------------------------|--|
| 11-1 | Date of receipt of the record copy by the International Bureau |  |
|------|----------------------------------------------------------------|--|

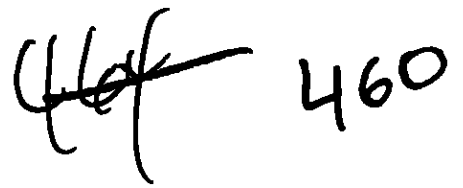
4167 459

## PETITORIO PCT

Original (para PRESENTACION)

|         |                                                                                                                                                           |                                                                                                        |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 0       | Para uso de la Oficina receptora solamente                                                                                                                |                                                                                                        |
| 0-1     | No. de Solicitud Internacional                                                                                                                            |                                                                                                        |
| 0-2     | Fecha de presentación internacional                                                                                                                       |                                                                                                        |
| 0-3     | Nombre de la oficina receptora y "Solicitud Internacional de PCT"                                                                                         |                                                                                                        |
| 0-4     | Forma -PCT/RO/101 Petición del PCT                                                                                                                        |                                                                                                        |
| 0-4-1   | Uso preparado                                                                                                                                             | PCT-SAFE [modelo EASY<br>Versión 3.50 (Forma 0002.163)]                                                |
| 0-5     | Petitorio<br>El abajo firmante solicita que la presente solicitud Internacional sea procesada de acuerdo al Tratado de Cooperación en Materia de Patentes |                                                                                                        |
| 0-6     | Oficina receptora (especificada por el solicitante)                                                                                                       | Oficina de Patentes y Marcas de los Estados Unidos de Norteamérica (USPTO) (RO/US)                     |
| 0-7     | Referencia de archivo del solicitante o agente                                                                                                            | 10080PCT                                                                                               |
| I       | Título de la invención                                                                                                                                    | AGENTES ANTIVIRALES DE DIAZAINDOL-DICARBONIL-PIPERAZINILO                                              |
| II      | Solicitante                                                                                                                                               |                                                                                                        |
| II-1    | Esta persona es:                                                                                                                                          | sólo el solicitante                                                                                    |
| II-2    | Para el solicitante                                                                                                                                       | todos los países designados excepto los US                                                             |
| II-4    | Nombre                                                                                                                                                    | BRISTOL-MYERS SQUIBB COMPANY                                                                           |
| II-5    | Dirección                                                                                                                                                 | Route 206 and Province Line Road<br>Princeton, New Jersey 08543-4000<br>Estados Unidos de Norteamérica |
| II-6    | País de Nacionalidad                                                                                                                                      | US                                                                                                     |
| II-7    | País de residencia                                                                                                                                        | US                                                                                                     |
| II-8    | Teléfono No.                                                                                                                                              | 609-252-4000                                                                                           |
| II-9    | Facsimile No. 1                                                                                                                                           | 609-252-4526                                                                                           |
| III-1   | Solicitante y/o inventor                                                                                                                                  |                                                                                                        |
| III-1-1 | Esta persona es:                                                                                                                                          | solicitante e inventor                                                                                 |
| III-1-2 | Solicitante para                                                                                                                                          | sólo los EU                                                                                            |
| III-1-4 | Nombre (APELLIDO, primer nombre)                                                                                                                          | BENDER, John, A.                                                                                       |
| III-1-5 | Dirección:                                                                                                                                                | 21 Brookview Lane<br>Middletown, Connecticut 06457<br>Estados Unidos de Norteamérica                   |
| III-1-6 | País de nacionalidad                                                                                                                                      | US                                                                                                     |
| III-1-7 | País de residencia                                                                                                                                        | US                                                                                                     |





## PETITORIO PCT

Original (para PRESENTACION)

|         |                                                                                                                                                                                           |                                                                                                                                                                                               |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III-2   | Solicitante y/o inventor                                                                                                                                                                  | solicitante e inventor<br>sólo los EU<br>YANG, Zhong<br>11-2 West Meadow Lane<br>Middletown, Connecticut 06457<br>Estados Unidos de Norteamérica                                              |
| III-2-1 | Esta persona es:                                                                                                                                                                          |                                                                                                                                                                                               |
| III-2-2 | Solicitante para                                                                                                                                                                          |                                                                                                                                                                                               |
| III-2-4 | Nombre (APELLIDO, primer nombre)                                                                                                                                                          |                                                                                                                                                                                               |
| III-2-5 | Dirección:                                                                                                                                                                                |                                                                                                                                                                                               |
| III-2-6 | País de nacionalidad                                                                                                                                                                      | CN                                                                                                                                                                                            |
| III-2-7 | País de residencia                                                                                                                                                                        | US                                                                                                                                                                                            |
| III-3   | Solicitante y/o inventor                                                                                                                                                                  | solicitante e inventor<br>sólo los EU<br>KADOW, John, F.<br>9 Quarry Run<br>Wallingford, Connecticut 06492<br>Estados Unidos de Norteamérica                                                  |
| III-3-1 | Esta persona es:                                                                                                                                                                          |                                                                                                                                                                                               |
| III-3-2 | Solicitante para                                                                                                                                                                          |                                                                                                                                                                                               |
| III-3-4 | Nombre (APELLIDO, primer nombre)                                                                                                                                                          |                                                                                                                                                                                               |
| III-3-5 | Dirección:                                                                                                                                                                                |                                                                                                                                                                                               |
| III-3-6 | País de nacionalidad                                                                                                                                                                      | US                                                                                                                                                                                            |
| III-3-7 | País de residencia                                                                                                                                                                        | US                                                                                                                                                                                            |
| III-4   | Solicitante y/o inventor                                                                                                                                                                  | solicitante e inventor<br>sólo los EU<br>MEANWELL, Nicholas, A.<br>15 Valli Drive<br>East Hampton, Connecticut 06424<br>Estados Unidos de Norteamérica                                        |
| III-4-1 | Esta persona es:                                                                                                                                                                          |                                                                                                                                                                                               |
| III-4-2 | Solicitante para                                                                                                                                                                          |                                                                                                                                                                                               |
| III-4-4 | Nombre (APELLIDO, primer nombre)                                                                                                                                                          |                                                                                                                                                                                               |
| III-4-5 | Dirección:                                                                                                                                                                                |                                                                                                                                                                                               |
| III-4-6 | País de nacionalidad                                                                                                                                                                      | GB                                                                                                                                                                                            |
| III-4-7 | País de residencia                                                                                                                                                                        | US                                                                                                                                                                                            |
| IV-1    | Agente o representante común; o dirección para la correspondencia<br>Ningún agente o representante común es/ha sido designada; la siguiente dirección debe utilizarse especialmente como: | agente<br><br>DUBOFF, Samuel<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>Estados Unidos de Norteamérica<br>203-677-6974<br>203-677-6900<br>25,969 |
| IV-1-1  | Nombre (APELLIDO, primer nombre)                                                                                                                                                          |                                                                                                                                                                                               |
| IV-1-2  | Dirección                                                                                                                                                                                 |                                                                                                                                                                                               |
| IV-1-3  | Teléfono No.                                                                                                                                                                              |                                                                                                                                                                                               |
| IV-1-4  | Facsímile No.                                                                                                                                                                             |                                                                                                                                                                                               |
| IV-1-5  | Registro del Agente No.                                                                                                                                                                   |                                                                                                                                                                                               |

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## PETITORIO PCT

Original (para PRESENTACION)

|        |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IV-2   | Agente(s) adicional(es)                                                                                                                                                                                                                                                                                                | Agente(s) adicional(es) con la misma dirección como el primer agente nombrado<br>EPPERSON, James (52,867); GOLIAN, paul, D. (42,591); BABAJKO, Suzanne(32,880);<br>BAXAM, Deanna(45,266);<br>BELFIELD, Jing (45, 914);<br>BOGIE, Terence (44,544);<br>BUCHHOLZ, Briana (39,123);<br>D'AMICO, Stephen (46,652);<br>DAVIS, Stephen (26, 693);<br>DUNCAN, Laurelee (44,095);<br>DUNCAN, Sammy (46, 675);<br>GIBBONS, Maureen (44,121);<br>KILCOYNE, John (33, 100);<br>KLEIN, Christopher (34,363);<br>KORSEN, Elliott (32,705);<br>LAMERDIN, John (44, 858);<br>LANGE, Keith (44,201);<br>O'BRIEN, Maureen (42, 043);<br>PROVOOST, Jonathan (44,292);<br>RODNEY, Burton (22,076);<br>SHER, Audrey (39,024); VANATTEN, Mary, K. (39,408); WINSLOW, Anastasia (40,875);<br>ALGIERE, Aldo (31,697);<br>MAKUJINA, Shah (41,174);<br>RYAN, Richard (30,491); VOLLES, Warren, K.(33,810); MINGO, Pamela, A.(48,256);<br>GREENBLATT, Gary, D.(47,509); GU, Henry, H.(55,227); PATEL, Rena (41,412);<br>CHIN, Jennifer, T. (47,487); WANG, Joseph, C.(44,391); WILLE,Louis, J.(32,954);<br>PARLET, Nickki, L. (44,996) |
| V      | DESIGNACIONES                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| V-1    | La presentación de esta solicitud constituida bajo la Regla 4.9(a), la designación de todos los Países Contratantes unidos por el PCT en la fecha de presentación internacional, para la concesión de cada tipo de protección disponible y, donde es aplicable, para la concesión de las patentes regional y nacional. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| VI-1   | Reivindicación de prioridad de la solicitud regional anterior                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| VI-1-1 | Fecha de Presentación                                                                                                                                                                                                                                                                                                  | 26 de noviembre de 2003 (26.11.2003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| VI-1-2 | Número                                                                                                                                                                                                                                                                                                                 | 60/525,624                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| VI-1-3 | País                                                                                                                                                                                                                                                                                                                   | US                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|--|
| VI-3   | Petición del documento de prioridad<br>La Oficina de recepción es solicitada para preparar y transmitir a la Oficina Internacional una copia certificada de la solicitud(es) anterior, identificada anteriormente como el artículo(s): | VI-1                                       |  |
| VII-1  | Seleccionar la autoridad de búsqueda internacional                                                                                                                                                                                     | Oficina de Patentes Europea (EPO) (ISA/EP) |  |
| VIII   | Declaraciones                                                                                                                                                                                                                          | Número de declaraciones                    |  |
| VIII-1 | Declaración en cuanto a la identidad del inventor                                                                                                                                                                                      | -                                          |  |
| VIII-2 | Declaración en cuanto al derecho del solicitante de acuerdo a la fecha de presentación internacional para solicitar y a ser concedida una patente                                                                                      | 1                                          |  |
| VIII-3 | Declaración en cuanto al derecho del solicitante de acuerdo a la fecha de presentación internacional para reivindicar la prioridad de la solicitud más reciente.                                                                       | 1                                          |  |
| VIII-4 | Declaración del inventor (sólo para los fines de la designación de los Estados Unidos de América).                                                                                                                                     | -                                          |  |
| VIII-5 | Declaración en cuanto a descripciones nocivas o excepciones para la falta de novedad.                                                                                                                                                  | -                                          |  |

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## PETITORIO PCT

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|                  |                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                               |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VIII-2-1         | <b>Declaración: Derechos de aplicación para y otorgar una patente</b><br>Declaración del derecho del solicitante, así como la fecha de presentación internacional, para aplicar y otorgar una patente (Reglas 4.17(ii) y 5.1bis.1(a)(ii)), en un caso donde la declaración bajo la Regla 4.17(iv) no sea apropiada:<br>Nombre (ULTIMO, Primero): | con relación a esta solicitud internacional<br><br>BRISTOL-MYERS SQUIBB COMPANY<br>tiene los derechos de solicitar y que se le otorgue una patente en virtud de lo siguiente: |
| VIII-2-1<br>(ii) |                                                                                                                                                                                                                                                                                                                                                  | una cesión de BENDER, John, A. a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>23 de diciembre de 2003 (23.12.2003)                                                       |
| VIII-2-1<br>(ii) |                                                                                                                                                                                                                                                                                                                                                  | una cesión de YANG, Zhong a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>23 de diciembre de 2003 (23.12.2003)                                                            |
| VIII-2-1<br>(ii) |                                                                                                                                                                                                                                                                                                                                                  | una cesión de KADOW, John, F. a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>05 de enero de 2004 (05.01.2004)                                                            |
| VIII-2-1<br>(ii) |                                                                                                                                                                                                                                                                                                                                                  | una cesión de MEANWELL, Nicholas, A. a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>05 de enero de 2004 (05.01.2004)                                                     |
| VIII-2-1<br>(ix) | Se hace esta declaración para los<br>propósitos de:                                                                                                                                                                                                                                                                                              | Todas las designaciones excepto la designación de los Estados<br>Unidos de Norte América                                                                                      |

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## PETITORIO PCT

Original (para PRESENTACION)

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VIII-3-1         | <b>Declaración: Autorizada para las reivindicaciones de prioridad</b><br>Declaración como la autorización del solicitante, como en la fecha de presentación internacional, para la reivindicación de prioridad de la presente solicitud especificada más adelante, donde la solicitud no es la solicitud que se presentó en la presente solicitud o donde el nombre del solicitante cambió hace tiempo la presentación de la presente solicitud (Reglas 4.17(iii) y 5.1bis.1(a)(iii));<br>Nombre: | con relación a esta solicitud internacional<br><br>BRISTOL-MYERS SQUIBB COMPANY<br>tiene los derechos para reivindicar la prioridad de la solicitud anterior No. 60/525,624 en virtud de lo siguiente:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| VIII-3-1<br>(iv) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | una cesión de BENDER, John, A. a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>23 de diciembre de 2003 (23.12.2003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| VIII-3-1<br>(iv) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | una cesión de YANG, Zhong a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>23 de diciembre de 2003 (23.12.2003)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| VIII-3-1<br>(iv) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | una cesión de KADOW, John, F. a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>05 de enero de 2004 (05.01.2004)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| VIII-2-1<br>(ii) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | una cesión de MEANWELL, Nicholas, A. a<br>BRISTOL-MYERS SQUIBB COMPANY, con fecha del<br>05 de enero de 2004 (05.01.2004)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| VIII-3-1<br>(ix) | Se hace esta declaración para los propósitos de:                                                                                                                                                                                                                                                                                                                                                                                                                                                  | AP: (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW); EA: (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM); EP: (AT, BE, BG, CH&LI, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR); OA: (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG); AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW |

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| IX    | Lista de verificación                                 | Número de hojas                                                        | Archivo(s) electrónico anexo |
|-------|-------------------------------------------------------|------------------------------------------------------------------------|------------------------------|
| IX-1  | Petitorio(incluyendo hojas de declaración)            | 8                                                                      | ✓                            |
| IX-2  | Descripción                                           | 159                                                                    | -                            |
| IX-3  | Reivindicaciones                                      | 15                                                                     | -                            |
| IX-4  | Extracto                                              | 1                                                                      | ✓                            |
| IX-5  | Dibujos                                               | 0                                                                      | ✓                            |
| IX-7  | Total                                                 | 183                                                                    |                              |
|       | Artículos que la acompañan                            | Documento(s) de papel anexo                                            | Archivo(s) electrónico anexo |
| IX-8  | Costo de la hoja de cálculo                           | ✓                                                                      | -                            |
| IX-9  | Poder separado original del abogado                   | ✓                                                                      | -                            |
| IX-17 | PCT-SAFE medio físico                                 | -                                                                      | ✓                            |
| IX-18 | otro                                                  |                                                                        |                              |
| IX-18 | otro                                                  | Recepción postal; certificado de envío de correo expres; certificación |                              |
| IX-19 | Figura de los dibujos que deben acompañar al extracto |                                                                        |                              |
| IX-20 | Idioma del archivo de la solicitud internacional      | Inglés                                                                 |                              |
| X-1   | Firma del solicitante, agente o representante común   | (Rubrica)                                                              |                              |
| X-1-1 | Nombre (ULTIMO, Primero)                              | DUBOFF, Samuel                                                         |                              |
| X-1-2 | Nombre del que firma                                  |                                                                        |                              |
| X-1-3 | Capacidad                                             |                                                                        |                              |

PARA USO DE LA OFICINA RECEPTORA SOLAMENTE

|        |                                                                                                                                                                        |        |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| 10-1   | Fecha del recibo real de la solicitud internacional alegada                                                                                                            |        |
| 10-2   | Dibujos                                                                                                                                                                |        |
| 10-2-1 | Recibido                                                                                                                                                               |        |
| 10-2-2 | No recibido                                                                                                                                                            |        |
| 10-3   | Fecha corregida del vencimiento del recibo real a los documentos o dibujos recibidos posteriormente pero a tiempo que complementan la solicitud internacional alegada: |        |
| 10-4   | Fecha del recibo a tiempo de las correcciones requeridas bajo el artículo 11(2) del PCT                                                                                |        |
| 10-5   | Autoridad de Búsqueda Internacional                                                                                                                                    | ISA/EP |
| 10-6   | Transmisión de copia de búsqueda retardada hasta que la cuota de búsqueda sea pagada                                                                                   |        |

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Original (para PRESENTACION)

PARA USO DE LA OFICINA INTERNACIONAL SOLAMENTE

|      |                                                                       |  |
|------|-----------------------------------------------------------------------|--|
| 11-1 | Fecha del recibo de la copia de registro por la Oficina Internacional |  |
|------|-----------------------------------------------------------------------|--|

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## PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the International application)

|         |                                                                                                    |                                                           |
|---------|----------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| 0       | For receiving Office use only                                                                      |                                                           |
| 0-1     | International Application No.                                                                      |                                                           |
| 0-2     | Date stamp of the receiving Office                                                                 |                                                           |
| 0-4     | Form PCT/ROH01 (Annex)                                                                             |                                                           |
| 0-4-1   | PCT Fee Calculation Sheet Prepared Using                                                           | PCT-SAFE [EASY mode]<br>Version 3.50 (Build 0002.163)     |
| 0-9     | Applicant's or agent's file reference                                                              |                                                           |
| 2       | Applicant                                                                                          |                                                           |
| 12      | Calculation of prescribed fees                                                                     |                                                           |
| 12-1    | Transmittal fee T                                                                                  | ⇒ 300                                                     |
| 12-2-1  | Search fee S                                                                                       | ⇒ 1000                                                    |
| 12-2-2  | International search to be carried out by                                                          | EP                                                        |
| 12-3    | International filing fee (first 30 sheets) H                                                       | 1134                                                      |
| 12-4    | Remaining sheets                                                                                   | 153                                                       |
| 12-5    | Additional amount (A)                                                                              | 12                                                        |
| 12-6    | Total additional amount R                                                                          | 1836                                                      |
| 12-7    | H + R = I                                                                                          | 2970                                                      |
| 12-12   | EASY Filing reduction R                                                                            | -81                                                       |
| 12-13   | Total international filing fee (I-R)                                                               | ⇒ 2889                                                    |
| 12-14   | Fee for priority document                                                                          |                                                           |
|         | Number of priority documents requested                                                             | 1                                                         |
| 12-15   | Fee per document (O)                                                                               | 20                                                        |
| 12-16   | Total priority document fee: P                                                                     | ⇒ 20                                                      |
| 12-17   | TOTAL FEES PAYABLE (T+S+H+P)                                                                       | ⇒ 4209                                                    |
| 12-19   | Mode of payment                                                                                    | authorization to charge deposit account                   |
| 12-20   | Deposit account instructions                                                                       |                                                           |
|         | The receiving Office                                                                               | United States Patent and Trademark Office (USPTO) (RO/US) |
| 12-20-1 | Authorization to charge the total fees indicated above                                             | ✓                                                         |
| 12-20-2 | Authorization to charge any deficiency or credit any overpayment in the total fees indicated above | ✓                                                         |
| 12-20-3 | Authorization to charge the fee for priority document                                              | ✓                                                         |
| 12-21   | Deposit account No.                                                                                | 19-3880                                                   |
| 12-22   | Date                                                                                               | 04 November 2004 (04.11.2004)                             |
| 12-23   | Name and signature                                                                                 | DUBOFF, Samuel<br><i>Samuel P. Duboff</i>                 |



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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

REMARKS

|        |                   |                                                                                                      |
|--------|-------------------|------------------------------------------------------------------------------------------------------|
| 13-1-1 | Applicant Remarks | Abstract contains chemical structures. Please charge any additional fees to deposit account 19-3880. |
|--------|-------------------|------------------------------------------------------------------------------------------------------|

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PCT

Original (for SUBMISSION)

|         |                                     |                                                                                                                                                                 |
|---------|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13-1-1  | Applicant Remarks                   | Abstract contains chemical structures.                                                                                                                          |
| 13-1-2  | Applicant Remarks                   | Please charge any additional fees to deposit account 19-3880.                                                                                                   |
|         |                                     |                                                                                                                                                                 |
| 13-2-6  | Validation messages<br>Declarations | Green?<br>Manually inputted data. Please verify the contents of the information provided.                                                                       |
|         | Validation messages<br>Declarations | Green?<br>Manually inputted data. Please verify the contents of the information provided.                                                                       |
| 13-2-7  | Validation messages<br>Contents     | Green?<br>The international application contains no drawings. Please verify.                                                                                    |
| 13-2-8  | Validation messages<br>Fees         | Green?<br>Please confirm that fee schedule utilized is the latest available                                                                                     |
| 13-2-9  | Validation messages<br>Payment      | Green?<br>Please ensure that you have a valid deposit account with the receiving Office selected.                                                               |
| 13-2-10 | Validation messages<br>Annotate     | Green?<br>All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication. |

The invention comprises substituted indazole-dicarbonyl-piperazinyl derivatives of general Formula I  
[PLEASE INSERT CHEMICAL STRUCTURE HERE]

(I)  
wherein:

Q is selected from the group consisting of  
[PLEASE INSERT CHEMICAL STRUCTURE HERE]

- - may represent a bond;

T is -C(O)- or -CH(CN)-; and

-Y- is selected from the group consisting of  
[PLEASE INSERT CHEMICAL STRUCTURE HERE]

compositions thereof and their use for treating HIV infection.

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PCT POWER OF ATTORNEY

Duplicate of Original

|       |                                                                                                                    |                                                       |
|-------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| D-1   | PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 80.4) |                                                       |
| D-1-1 | Prepared Using                                                                                                     | PCT-SAFE [EASY mode]<br>Version 3.50 (Build 0002.163) |

## PCT POWER OF ATTORNEY

Duplicate of Original

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|        |                                                |                                                                                                                                   |
|--------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| 1      | The undersigned applicant(s)                   | BRISTOL-MYERS SQUIBB COMPANY                                                                                                      |
| 1-1-1  | hereby appoints (appoint) the following person | DUBOFF, Samuel<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-2  | hereby appoints (appoint) the following person | EPPELSON, James<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America  |
| 1-1-3  | hereby appoints (appoint) the following person | GOLIAN, Paul, D.<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-1-4  | hereby appoints (appoint) the following person | BARAJKO, Suzanne<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-1-5  | hereby appoints (appoint) the following person | RAHAM, Deanna<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America    |
| 1-1-6  | hereby appoints (appoint) the following person | BELFIELD, Jing<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-7  | hereby appoints (appoint) the following person | BOGIE, Terence<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-8  | hereby appoints (appoint) the following person | BUCHHEIZ, Briana<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-1-9  | hereby appoints (appoint) the following person | D'AMICO, Stephen<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-1-10 | hereby appoints (appoint) the following person | DAVIS, Stephen<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-11 | hereby appoints (appoint) the following person | DUNCAN, Laurelee<br>Bristol-Myers Squibb Company<br>P.O. Box 4000                                                                 |

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PCT POWER OF ATTORNEY

Duplicate of Original

|        |                                                |                                                                                                                                     |
|--------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
|        |                                                | Princeton, New Jersey 08543-4000<br>United States of America                                                                        |
| 1-1-12 | hereby appoints (appoint) the following person | DUNCAN, Sammy<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America      |
| 1-1-13 | hereby appoints (appoint) the following person | GIBBONS, Maureen<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-14 | hereby appoints (appoint) the following person | KILCOYNE, John<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America     |
| 1-1-15 | hereby appoints (appoint) the following person | KLEIN, Christopher<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-1-16 | hereby appoints (appoint) the following person | KORSEN, Elliott<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America    |
| 1-1-17 | hereby appoints (appoint) the following person | LANERDIN, John<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America     |
| 1-1-18 | hereby appoints (appoint) the following person | LANGE, Keith<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America       |
| 1-1-19 | hereby appoints (appoint) the following person | O'BRIEN, Maureen<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-20 | hereby appoints (appoint) the following person | PROVOOST, Jonathan<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-1-21 | hereby appoints (appoint) the following person | RODNEY, Burton<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America     |
| 1-1-22 | hereby appoints (appoint) the following person | SHER, Audrey<br>Bristol-Myers Squibb Company<br>P. . Box 4000<br>Princeton, New Jersey 08543-4000                                   |

## PCT POWER OF ATTORNEY

Duplicate of Original

|        |                                                |                                                                                                                                       |
|--------|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
|        |                                                | United States of America                                                                                                              |
| 1-1-23 | hereby appoints (appoint) the following person | VANATTEN, Mary, K.<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-24 | hereby appoints (appoint) the following person | WINSLOW, Anastasia<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-25 | hereby appoints (appoint) the following person | ALGERI, Aldo<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America         |
| 1-1-26 | hereby appoints (appoint) the following person | MAKUSJINA, Shah<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America      |
| 1-1-27 | hereby appoints (appoint) the following person | RYAN, Richard<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America        |
| 1-1-28 | hereby appoints (appoint) the following person | VOLLIS, Warren, K.<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-29 | hereby appoints (appoint) the following person | MINGO, Pamela, A.<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America    |
| 1-1-30 | hereby appoints (appoint) the following person | GREENBLATT, Gary, D.<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-1-31 | hereby appoints (appoint) the following person | GU, Henry, H.<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America        |
| 1-1-32 | hereby appoints (appoint) the following person | PATEL, Rena<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America          |
| 1-1-33 | hereby appoints (appoint) the following person | CHIN, Jennifer, T.<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |

10080PCT

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## PCT POWER OF ATTORNEY

Duplicate of Original

|        |                                                                    |                                                                                                                                            |
|--------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 1-1-34 | hereby appoints (appoint) the following person                     | <b>MANG, Joseph, C.</b><br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America   |
| 1-1-35 | hereby appoints (appoint) the following person                     | <b>WILLIE, Louis, J.</b><br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America  |
| 1-1-36 | hereby appoints (appoint) the following person                     | <b>PARLET, Nickki, L.</b><br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, New Jersey 08543-4000<br>United States of America |
| 1-2    | as                                                                 | agent                                                                                                                                      |
| 1-3    | to represent the undersigned before                                | all the competent International Authorities                                                                                                |
| 1-4    | In connection with the international application identified below: |                                                                                                                                            |
| 1-4-1  | Title of invention                                                 | <b>DIAZABINDOLE-DICARBONYL-PIPERAZINYL ANTIVIRAL AGENTS</b>                                                                                |
| 1-4-2  | Applicant's or agent's file reference                              | <b>10080PCT</b>                                                                                                                            |
| 1-4-3  | International application number (if already available)            |                                                                                                                                            |
| 1-4-4  | filed with the following Office as receiving Office                | <b>United States Patent and Trademark Office (USPTO) (RO/US)</b>                                                                           |
| 1-5    | and to make or receive payments on behalf of the undersigned       |                                                                                                                                            |
| 2-1    | Signature of applicant, agent or common representative             | <i>Richard P. Ryan</i>                                                                                                                     |
| 2-1-1  | Name                                                               | <b>BRISTOL-MYERS SQUIBB COMPANY</b>                                                                                                        |
| 2-1-2  | Name of signatory                                                  | <b>Richard P. Ryan</b>                                                                                                                     |
| 2-1-3  | Capacity                                                           | <b>Senior Patent Counsel</b>                                                                                                               |
| 3      | Date                                                               | <b>03 November 2004 (03.11.2004)</b>                                                                                                       |



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CERTIFICATION

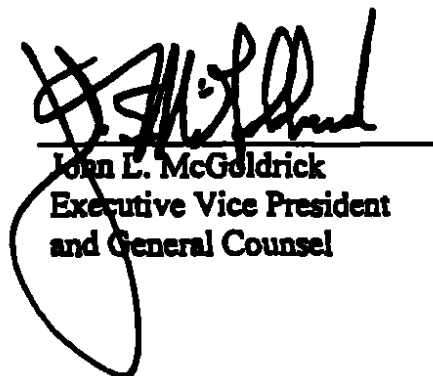
The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Suzanne Babajko  
Stephen B. Davis  
Blair Q. Ferguson  
John M. Kilcoyne  
Christopher Klein  
David Morse  
Richard Ryan

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 22<sup>nd</sup> day of May 2002.

  
Secretary

  
John L. McGeldrick  
Executive Vice President  
and General Counsel

477

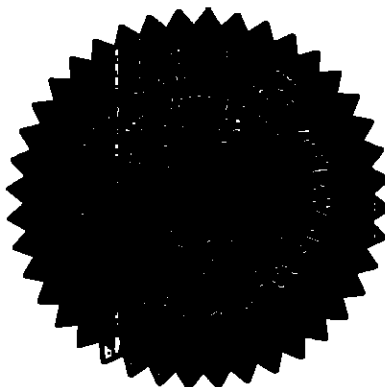
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:  
MAURA O KNOBL
3. ACTING IN THE CAPACITY OF:  
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:  
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 3RD DAY OF MAY 2006
7. BY: Bradley I. Abelow, NEW JERSEY TREASURER
8. NO. A258533
9. SEAL/STAMP:
10. SIGNATURE



*Bradley Abelow*

**AFFIDAVIT**

I, Briana C. Bergen, Senior Patent Counsel, Patent Department, Bristol-Myers Squibb Company, do hereby certify that this document is a notarized true and accurate copy of the assignment signed by the inventors.

Briana C. Bergen  
Briana C. Bergen

STATE OF NEW JERSEY       )  
                                          )  
COUNTY OF MERCER       )       ss.

Subscribed before me on this 19<sup>th</sup> day of April, 2006

Maura O. Knobl  
Notary Public

(SEAL)

**MAURA O. KNOBL**  
**NOTARY PUBLIC OF NEW JERSEY**  
My Commission Expires July 23, 2008



487  
479

UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231



\*700060088\*

JANUARY 12, 2004

PTAS

BRISTOL-MYERS SQUIBB COMPANY  
STEPHEN B. DAVIS  
P.O. BOX 400  
PATENT DEPARTMENT  
PRINCETON, NJ 08543-4000

UNITED STATES PATENT AND TRADEMARK OFFICE  
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 01/12/2004

REEL/FRAME: 014249/0720  
NUMBER OF PAGES: 5

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

## ASSIGNOR:

BENDER, JOHN A.

DOC DATE: 12/23/2003

## ASSIGNOR:

YANG, ZHONG

DOC DATE: 12/23/2003

## ASSIGNOR:

KADOW, JOHN F.

DOC DATE: 01/05/2004

## ASSIGNOR:

MEANWELL, NICHOLAS A.

DOC DATE: 01/05/2004

## ASSIGNEE:

BRISTOL-MYERS SQUIBB COMPANY  
LAWRENCEVILLE-PRINCETON ROAD  
PRINCETON, NEW JERSEY 08543-4000

014249/0720 PAGE 2

SERIAL NUMBER: 60525624  
PATENT NUMBER:

FILING DATE: 11/26/2003  
ISSUE DATE:

ANTIONE ROYALL, EXAMINER  
ASSIGNMENT DIVISION  
OFFICE OF PUBLIC RECORDS

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11:02PM

1/12/04 9:02 PAGE 4/4 RightFAX

BUS PRIORITY 203 572 5900

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10000 P&P

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FORM PTO-1085  
(Rev. 9-93)

RECORDATION FORM COVER SHEET

U.S. DEPARTMENT OF COMMERCE  
Patent and Trademark Office

OMB No. 0851-0011 (exp. 4/04)

PATENTS ONLY

To the Honorable Director of the US Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

John A. Bander, Zhong Yang, John F. Kadow,  
Nicholas A. Mearwell

2. Name and address of receiving party(ies)

Name: Bristol-Myers Squibb Company

Internal Address: \_\_\_\_\_

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger  
☐ Security Agreement ☐ Change of Name  
☐ Other \_\_\_\_\_

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

Execution Date: 12/23/03, 12/23/03, 1/5/04, 1/5/04

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: \_\_\_\_\_

A. Patent Application No.(s)

USPN 60/525,824 filed November 28, 2003

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Stephen B. Davis

Internal Address: Bristol-Myers Squibb Company

Patent Department

Street Address: P.O. Box 4000

City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) \$ 40

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

18-3880 (in the name of Bristol-Myers Squibb Company)

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Samuel J. DuBoff

Name of Person Signing  
Reg. No. 25,999

Samuel J. DuBoff  
Signature

1/12/04  
Date

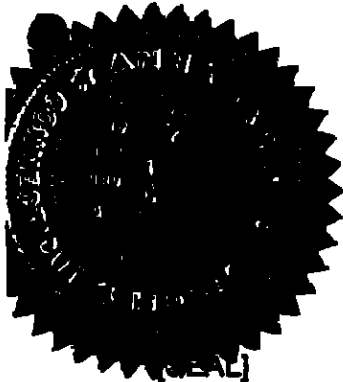
☐ Certificate of mailing on reverse side

Total number of pages including cover sheet, attachments, and document: 5

Mail documents to be recorded with required cover sheet information to:  
Mail Stop Assignment Recordation Services, Director of the US Patent and Trademark Office  
PO Box 1450, Alexandria, VA 22319-1450

STATE OF Connecticut     )  
                                      ) ss. Wallingford  
COUNTY OF New Haven    )

On the 23rd day of December, 2003, before me came John A. Bender, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



Annamarie Bodisch  
Notary Public

ANNAMARIE BODISCH  
Notary Public  
My Commission Expires March 31, 2005

STATE OF Connecticut     )  
                                      ) ss. Wallingford  
COUNTY OF New Haven    )

On the 23rd day of December, 2003, before me came Zhong Yang, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



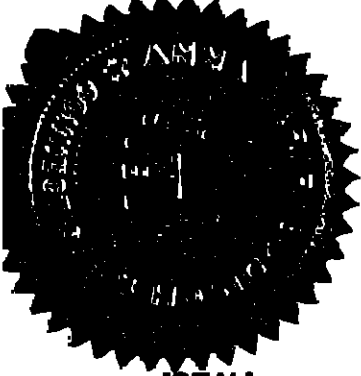
[SEAL]

Annamarie Bodisch  
Notary Public

ANNAMARIE BODISCH  
Notary Public  
My Commission Expires March 31, 2005

STATE OF Connecticut     )  
                                          ) ss. Wallingford  
COUNTY OF New Haven     )

On the 5th day of January, 2004, before me came John F. Kadow, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



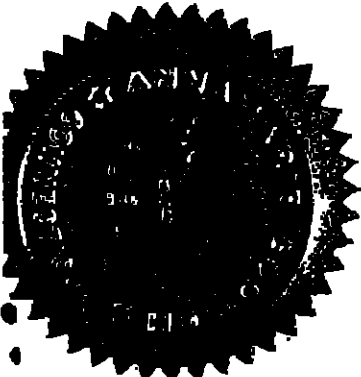
[SEAL]

Annamarie Bodisch  
Notary Public

ANNAMARIE BODISCH  
Notary Public  
My Commission Expires March 31, 2005

STATE OF Connecticut     )  
                                          ) ss. Wallingford  
COUNTY OF New Haven     )

On the 5th day of January, 2004, before me came Nicholas A. Meanwell, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



[SEAL]

Annamarie Bodisch  
Notary Public

ANNAMARIE BODISCH  
Notary Public  
My Commission Expires March 31, 2005



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486

**TRADUCCIÓN AL ESPAÑOL del documento de cesión de la solicitud de patente a  
Bristol-Myers Squibb Company, firmado por los cedentes y el cesionario.**

---

**APOSTILLE**

**(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)**

1. **PAÍS: ESTADOS UNIDOS DE AMÉRICA**
2. **ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR  
MAURA O KNOBL**
3. **ACTUANDO EN CAPACIDAD DE  
NOTARIO PÚBLICO DE NEW JERSEY**
4. **LLEVA EL SELLO/TIMBRE DE:  
EVELYN VAZQUEZ, NOTARIO**

**CERTIFICADO**

5. **EN TRENTON, NEW JERSEY**
6. **EL 3 DE MAYO DE 2006**
7. **POR: Bradley I. Abelow, TESORERO DE NEW JERSEY**
8. **NO. A258533**
9. **SELLO/TIMBRE**
10. **FIRMA**

**Bradley Abelow (firma)**

491  
487

**Declaración Juramentada por escrito**

Yo, Briana C. Bergen, Asesor Principal de Patentes, Departamento de Patentes - Bristol-Myers Squibb Company certifico que esta una copia notariada, verdadera y precisa de la cesión firmada por los inventores.

\_\_\_\_\_  
(Firma)  
Briana C. Bergen

ESTADO DE NEW JERSEY            )  
                                                  )  
CONDADO DE MERCER            )           ss.

Firmado ante mi este 19 de abril de 2006

(Firma)  
Notario Público

[Sello]

Hay un sello que dice:  
MAURA O. KNOBL  
NOTARIO PÚBLICO DE NEW JERSEY  
Mi comisión expira Julio 23 de 2008

492  
488

ENERO 17 DE 2004

BISTOL-MYERS SQUIBB COMPANY  
STEPHEN B. DAVIS  
CASILLA POSTAL 4000  
DEPARTAMENTO DE PATENTES  
PRINCETON, NJ 08543-4000

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS  
INFORME DE GRABACIÓN DE DOCUMENTO DE CESION

EL DOCUMENTO ADJUNTO HA SIDO GRABADO POR LA DIVISIÓN DE CESIONES DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS. HAY DISPONIBLE UNA COPIA COMPLETA EN MICROFILME EN EL CUARTE DE BÚSQUEDA DE CESIONES EN EL NÚMERO DE ROLLO Y CUADRO REFERENCIADOS ABAJO.

POR FAVOR REVISE TODA LA INFORMACIÓN CONTENIDA EN ESTE INFORME. LA INFORMACIÓN CONTENIDA EN ESTE INFORME DE GRABACIÓN REFLEJA LOS DATOS PRESENTES EN EL SISTEMA DE ASIGNACIÓN DE PATENTES Y MARCAS. SI USTED ENCUENTRA CUALQUIER ERROR O TIENE PREGUNTAS CONCERNIENTES A ESTE INFORME, PUEDE CONTACTAR AL EMPLEADO CUYO NOMBRE APARECE EN ESTE INFORME AL 703-308-9723. POR FAVOR ENVÍE LA SOLICITUD DE CORRECCIÓN A: OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS, DIVISIÓN DE CESIONES, ASIGNACIÓN DE CASILLAS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C.20231.

FECHA DE GRABACIÓN: 01/12/2004      ROLLO/CUADRO: 014249/0720  
NÚMERO DE PÁGINAS: 5

RESUMEN: CESIÓN DE INTERÉS DEL CEDENTE (VER DOCUMENTO PARA DETALLES).

CEDENTE:  
BENDER, JOHN A.      FECHA DE DOC: 12/23/2003

CEDENTE:  
YAMG, ZHONG      FECHA DE DOC: 12/23/2003

CEDENTE:  
KADOW, JOHN, F.      FECHA DE DOC: 01/05/2004

CEDENTE:  
MEANWELL, NICHOLAS A.      FECHA DE DOC: 01/05/2004

CESIONARIO:  
BRISTOL-MYERS SQUIBB COMPANY  
LAWRENCEVILLE-PRINCETON ROAD  
PRINCETON, NEW JERSEY 08543-4000

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014249/0720 PAGINA 2

NÚMERO DE SERIE: 80525824  
NÚMERO DE PATENTE:

FECHA DE PRESENTACIÓN: 11/26/2003  
FECHA DE EMISIÓN:

ANTIONE ROYALL, EXAMINADOR  
DIVISIÓN DE CESIONES  
OFICINA DE REGISTROS PÚBLICOS

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|                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                              |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----------------------------------------------------------------------------------------------|--|
| <b>FORMULARIO PTO-1585</b><br>(Rev. 8-93)<br>OMB No. 0651-0011 (exp. 4/94)<br><b>TU0059 (PSP)</b>                                                                                                                                                                                                                                                                                                                                          |  | <b>PORTADA DEL FORMULARIO DE REGISTRO SOLO PATENTES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                              |  | <b>Departamento de Comercio de los Estados Unidos</b><br><b>Oficina de Marcas y Patentes</b> |  |
| Al Honorable Comisionado de Marcas y Patentes: por favor registre los documentos originales adjuntos o copias de los mismos.                                                                                                                                                                                                                                                                                                               |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                              |  |
| <b>1. Nombre de la(s) parte(s) cedente(s):</b><br>John A. Bender, Zhong Yang, John F. Kadow, Nicholas A. Meanwell                                                                                                                                                                                                                                                                                                                          |  | <b>2. Nombre y dirección de la(s) parte(s) que recibe(n)</b><br>Nombre: <u>Bristol-Myers Squibb Company</u><br>Dirección Interna: _____<br>_____<br>Dirección: <u>Lawrenceville-Princeton Road</u><br>_____<br>Ciudad: <u>Princeton</u> Estado: <u>NJ</u> ZIP: <u>08543-4000</u>                                                                                                                                                                                                                     |  |                                                                                              |  |
| Se adjunta(n) nombre(s) adicional(es) de la(s) parte(s) cedente(s)<br><input type="checkbox"/> SI <input checked="" type="checkbox"/> No                                                                                                                                                                                                                                                                                                   |  | <b>¿Se adjunta(n) nombre(s) y dirección(es) adicional(es)?</b><br><input type="checkbox"/> SI <input checked="" type="checkbox"/> No                                                                                                                                                                                                                                                                                                                                                                 |  |                                                                                              |  |
| <b>3. Naturaleza del traspaso:</b><br><input checked="" type="checkbox"/> Cesión <input type="checkbox"/> Fusión<br><input type="checkbox"/> Acuerdo de Seguridad <input type="checkbox"/> Cambio de Nombre<br><input type="checkbox"/> Otro: _____                                                                                                                                                                                        |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                              |  |
| Fecha de Ejecución: <u>12/23/03, 12/23/03, 1/5/04, 1/5/04</u>                                                                                                                                                                                                                                                                                                                                                                              |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                              |  |
| <b>4. Número(s) de Solicitud o número(s) de Patente:</b><br>Si este documento está siendo entregado junto con una nueva solicitud, la fecha de ejecución de la solicitud es: _____<br><br>A. Solicitud(es) de Patente No(s).<br><u>USSN 80/525,624 presentada en noviembre 28 de 2003</u><br><br>B. No(s). de Patente<br><br><b>¿Se adjuntan números adicionales?</b> <input type="checkbox"/> SI <input checked="" type="checkbox"/> No   |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                              |  |
| <b>5. Nombre y dirección de la parte a quien se le debe enviar la correspondencia de los documentos concernientes:</b><br>Nombre: <u>Stephen B. Davis</u><br>Dirección Interna: <u>Bristol-Myers Squibb Company</u><br><u>Departamento de Patentes</u><br>Dirección: <u>Apartado Postal 4000</u><br>Ciudad: <u>Princeton</u> Estado: <u>NJ</u> ZIP: <u>08542-4000</u>                                                                      |  | <b>6. Número total de solicitudes y patentes involucradas:</b><br><u>1</u><br><b>7. Tarifa Total (37 CFR 3.41) \$ <u>40</u></b><br><input type="checkbox"/> Adjunta<br><input checked="" type="checkbox"/> Autorización para ser cargada a una cuenta de depósito y cualquier otra tarifa adicional requerida.<br><b>8. Número de cuenta depósito:</b><br><u>19-3880 (a nombre de Bristol-Myers Squibb Company)</u><br>(Anexar copia por duplicado de esta página si se paga por cuenta de depósito) |  |                                                                                              |  |
| <b>NO USAR ESTE ESPACIO</b>                                                                                                                                                                                                                                                                                                                                                                                                                |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                              |  |
| <b>9. Declaración y firma:</b><br>Hasta donde se y creo, la información anterior es veraz y correcta y cualquier copia adjunta es una copia veraz del documento original.<br><br><u>Samuel J. DeBoff</u> (Firma) <u>1/12/04</u><br>Nombre del suscrito Firma Fecha<br>Reg. No. 25,999<br><input type="checkbox"/> Certificado de envío por el reverso<br><br>Número total de páginas incluyendo la portada, anexos, y documentos: <u>5</u> |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                              |  |

Envíe por correo los documentos a registrar con la información requerida de la portada a:  
Parada de Correo Servicios de Registro de cesión, Director de la Oficina de Marcas y patentes de Estados Unidos

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**CESIÓN**

**Nosotros,**

|                             |                     |                                                                                              |
|-----------------------------|---------------------|----------------------------------------------------------------------------------------------|
| <b>John A. Bender</b>       | <b>residente en</b> | <b>21 Brookview Lane<br/>Middletown, Connecticut 06457<br/>Estados Unidos de América</b>     |
| <b>Zhong Yang</b>           | <b>residente en</b> | <b>11-2 West Meadow Lane<br/>Middletown, Connecticut 06457<br/>Estados Unidos de América</b> |
| <b>John F. Kadow</b>        | <b>residente en</b> | <b>9 Quarry Run<br/>Wallingford, Connecticut 06492<br/>Estados Unidos de América</b>         |
| <b>Nicholas A. Meanwell</b> | <b>residente en</b> | <b>15 Valli Drive<br/>East Hampton, Connecticut 06424<br/>Estados Unidos de América</b>      |

en virtud de obligaciones contractuales hasta ahora asumidas por nosotros y/o en buena y valiosa consideración, el recibo y suficiencia de la misma se reconoce aquí, por medio de la presente vendemos y cedemos a Bristol-Myers Squibb Company, una corporación de Delaware, que funciona en Lawrenceville-Princeton Road, Princeton, NJ 08534-4000, sus sucesores, cedentes y representantes legales, todo nuestro derecho, título e interés, el cual incluye el beneficio correcto y completo de tales prioridades que puedan ser concedidas ahora o en adelante a nosotros por leyes locales o tratados, incluyendo cualquier convenio internacional para la protección de propiedad industrial, en y para todos los países del mundo, incluyendo a los Estados Unidos y sus territorios y posesiones, en y a la invención titulada:

**Agentes Antivirales de Diazlandole-Dicarbonil-Piperazinil**

inventado por nosotros y descrito en la solicitud de patente provisional de los Estados Unidos

**Solicitud No. 60/525,624, presentada en Noviembre 26 de 2003,**

incluyendo dicha solicitud de patente no provisional de los Estados Unidos y cualquier solicitud que reivindique prioridad de dicha solicitud provisional, presentada en cualquier país, y cualquier patente que pueda ser emitida y/o otorgada a la misma, y todas las divisiones, continuaciones, reemisiones, certificado de reexaminación y extensiones de la misma en todos los países, dicho interés siendo la propiedad total de dicha invención y de todas dichas solicitudes, patentes (incluyendo patentes reemitidas), extensiones y certificados de reexaminación a ser tenido y disfrutados por Bristol-Myers Squibb

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Company y sus sucesores y cedentes por la totalidad de los términos que sean concedidos y/o emitidos a dicha patente (incluyendo patentes reemitidas), extensiones, y certificados de reexaminación, tan completa y totalmente como los mismos habrían sido tenidos y disfrutados por nosotros si esta venta, cesión y transferencia no hubiera sido hecha;

Y por la presente acordamos comunicar a dicho cesionario o sus representantes cualquier hecho que conozcamos respecto a esta invención, atestiguar en cualquier proceso legal, firmar y/o ejecutar cualquier documento adicional y/o instrumentos que puedan ser necesarios, legales y apropiados en y/o para la presentación y/o procesamiento de todas las solicitudes, incluyendo solicitudes de división, continuación y reemisión, certificados de extensión y reexaminación y/o concesión y/o emisión de la misma y/o de otro modo asegurar el título de dicha invención y de todas dichas solicitudes, patentes (incluyendo reemisión de patentes, certificados de extensión y reexaminación a dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y cesionarios a obtener y hacer cumplir la protección apropiada para dicha invención entonos los países.

Firmado este 23 de diciembre de 2003 por (Firma)  
John A. Bender

Firmado este 23 de diciembre de 2003 por (Firma)  
Zhong Yang

Firmado este 5 de enero de 2004 por (Firma)  
John F. Kadow

Firmado este 5 de enero de 2004 por (Firma)  
Nicholas A. Meanwell

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ESTADO DE Connecticut )  
 ) ss. Wallingford  
CONDADO DE New Haven )

En el 23 de diciembre de 2003 ante mí, vino John A. Bender a quien conozco como la misma persona de ese nombre mencionada en y quien ejecutó el instrumento anterior, y reconoció que lo hizo.

(Firma)  
Notario Público

**Hay un sello que dice:**

**ANAMARIE BODISCH**

## Notario Público

**Mi comisión expira Marzo 31 de 2005**

ESTADO DE Connecticut )  
 ) ss. Wallingford  
CONDADO DE New Haven )

**En el 23 de diciembre de 2003 ante mí, vino Zhong Yang a quien conozco como la misma persona de ese nombre mencionada en y quien ejecutó el instrumento anterior, y reconoció que lo hizo.**

                    (Firma)                      
**Notario Público**

**Hay un sello que dice:**

**ANAMARIE BODISCH**

## Notario Público

**Mi comisión expira Marzo 31 de 2005**



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**[Sello]**

**(Firma)**

**Hay un sello que dice:**

## Notario Público

ESTADO DE Connecticut )  
 ) ss. Wallingford  
CONDADO DE New Haven )

**[Sello]**

**(Firma)**

**Hay un sello que dice:**

## Notario Público

**Mi comisión expira Marzo 31 de 2005**

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
Rad: 06-049957- -00000-0000  
Fec: 2006-05-24 16:38:32 Dep. 2020 NUECREACIONES  
Trib. 11 PATENTENY  
EYE 375 FASENACIONALI  
Act 411 PRESENTACION Folio 499



**Industria y Comercio**  
**SUPERINTENDENCIA**

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**Delegatura de Propiedad Industrial**  
**División de Nuevas Creaciones**

**REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE**

|                                                                                                             | USUARIO | RADICADOR |
|-------------------------------------------------------------------------------------------------------------|---------|-----------|
| PATENTE DE INVENCION (✓) MODELO DE UTILIDAD ( )                                                             | ( )     | ( )       |
| -Indicación de que se solicita la concesión de una patente.✓                                                | ( )     | ( )       |
| -Datos de identificación del solicitante o de la persona que se presenta la solicitud.✓                     | ( )     | ( )       |
| -Descripción de la invención.✓                                                                              | ( )     | ( )       |
| -Dibujos de ser estos pertinentes. NO                                                                       | ( )     | ( )       |
| -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 se presenta la solicitud.                      | ( )     | ( )       |
| -Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | ( )     | ( )       |
| -Comprobante de Pago de las tasas establecidas.                                                             | ( )     | ( )       |
| COMPLETA ( ) INCOMPLETA ( )                                                                                 | ( )     | ( )       |
| ESQUEMA DE TRAZADO ( )                                                                                      |         |           |
| -Indicación de que se solicita el registro de Diseño Industrial.                                            | ( )     | ( )       |
| -Datos de identificación del solicitante o de la persona que se presenta la solicitud.                      | ( )     | ( )       |
| -Representación gráfica del Esquema Trazado.                                                                | ( )     | ( )       |
| -Comprobante de Pago de las tasas establecidas.                                                             | ( )     | ( )       |
| COMPLETA ( ) INCOMPLETA ( )                                                                                 | ( )     | ( )       |

Firma Responsable:

Fecha:

Mayo 24 de 2006.

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**REPUBLICA DE COLOMBIA**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

Bogotá,  
2020

Doctor(a)  
CADENA SARMIENTO JUAN PABLO

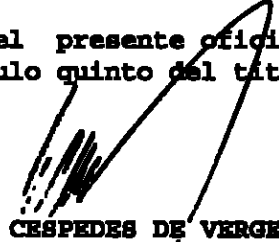
|            |                            |               |
|------------|----------------------------|---------------|
| REFERENCIA | Radicación No.             | 06 49957      |
|            | Solicitud internacional    | US2004/037213 |
|            | Fecha inicio fase nacional | 27/06/2006    |
|            | Trámite                    | 11            |
|            | Evento                     | 378           |
|            | Actuación                  | 430           |
|            | Oficio No.                 | 8831          |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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 No.10 de 2001.

  
ALIX CARMENZA CESPEDES DE VERGEL  
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 1-1-AGO. 2006  
adpal