



REYES & REYES

A B O G A D O S

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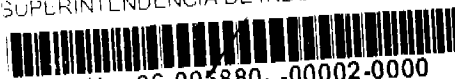
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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REGISTRO DE MARCAS Y DISEÑOS INDUSTRIALES
UNION REGISTRADA DE MARCAS Y DISEÑOS INDUSTRIALES

REF:

Expediente 06-095-880

TÍTULO SOLICITADO:

“COMBINACIONES PARA TRATAMIENTO DE INFECCIÓN DE VIRUS DE INMUNODEFICIENCIA HUMANA (VIH).”

PUBLICACIÓN:

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SOLICITANTE:

BRISTOL – MYERS SQUIBB COMPANY

APODERADO:

JUAN PABLO CADENA SARMIENTO

TRÁMITE:

SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada en los siguientes términos:

I. RATIFICACIÓN

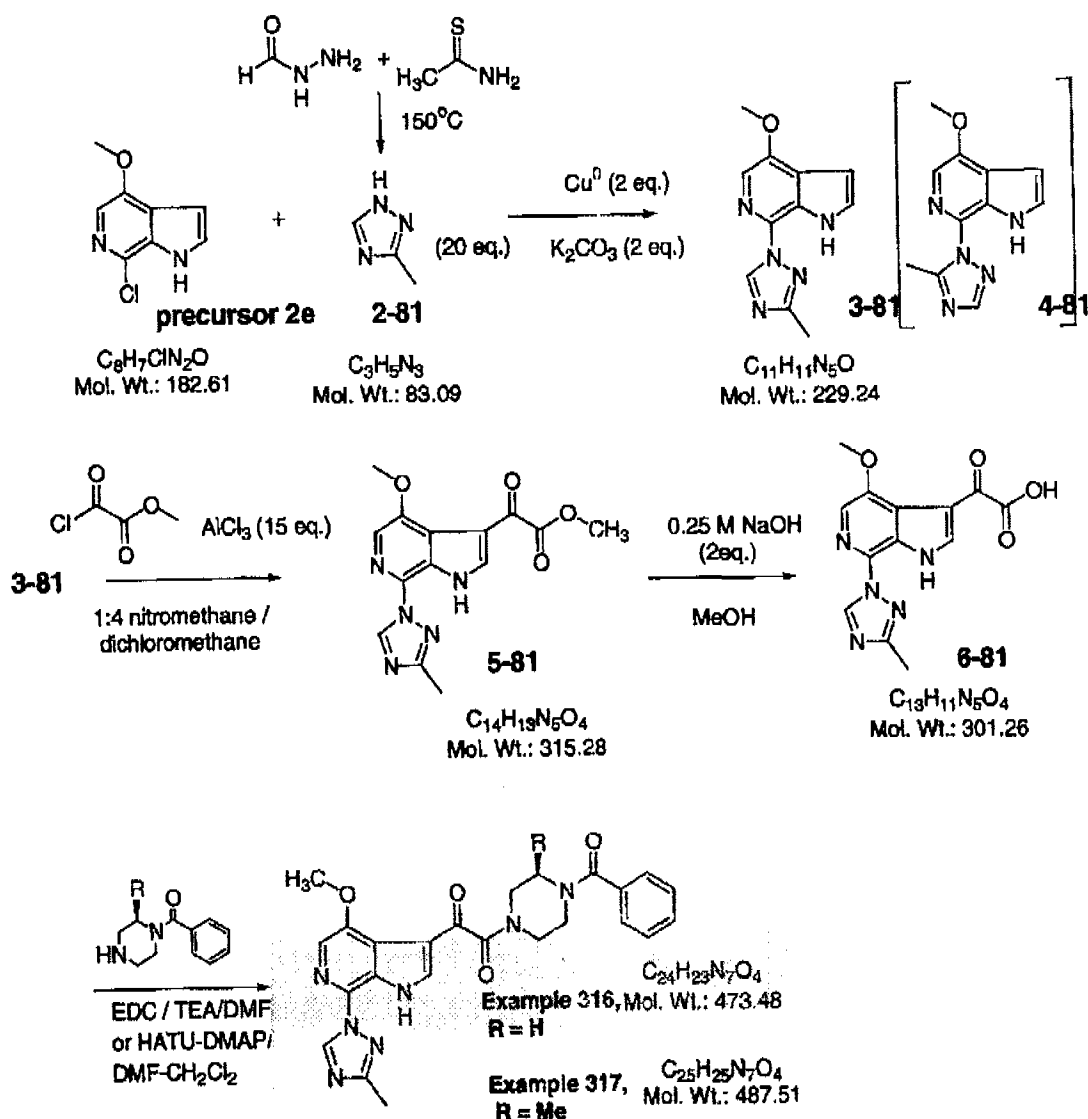
Comendidamente me permito exponer a continuación los argumentos que permitirán demostrar que la solicitud de la referencia, que reivindica la utilización de 1-benzoil-4-[2-[4-metoxi-7-(3-metil-1H-1,2,4-triazol-1-il)-1H-pirrolo[2,3-c]piridin-3-il]-1,2-dioxetil]-piperazina en combinación con otros agentes antivirales y sus

respectivas formulaciones farmacéuticas, incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

II. COMPLEMENTO DE INFORMACIÓN.

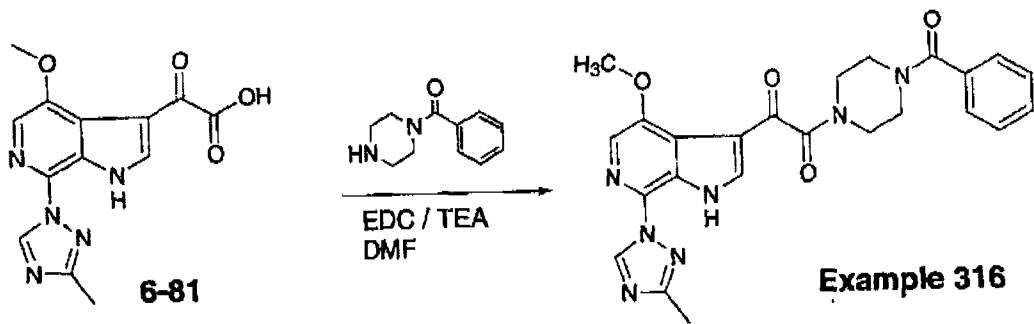
- En primer lugar, se conoce con anterioridad que la sustancia que busca reivindicar la solicitud colombiana en trámite (1-benzoil-4-[2-[4-metoxi-7-(3-metil-1H-1,2,4-triazol-1-il)-1H-pirrol-2-il]-1,2-dioxetil]-piperazina), es un inhibidor de unión del HIV-1 con potencia como antiviral demostrada en una variedad de ensayos clínicos y de laboratorio, como lo demuestra la publicación internacional WO 04/014380 publicada el 19 de febrero de 2004 y titulada "COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED AZAINDOLEOXOACETIC PIPERAZINE DERIVATIVES", veamos:

Scheme 81



En este esquema se puede observar claramente la existencia y la obtención del compuesto "316" ó 1-benzoil-4-[2-[4-metoxi-7-(3-metil-1H-1,2,4-triazol-1-il)-1H-pirrolo[2,3c] piridin-3-il]-1,2-dioxietil]-piperazina, ahora revelado en la solicitud en trámite y reivindicado en su correspondiente reivindicación 1; también, más adelante en la página 448 de la anterioridad en mención, se describe el proceso de preparación del compuesto "316", veamos:

Preparation of Example 316



Entonces, es claro que el compuesto 1-benzoil-4-[2-[4-metoxi-7-(3-metil-1H-1,2,4-triazol-1-il)-1H-pirrolo[2,3c] piridin-3-il]-1,2-dioxietil]-piperazina, pertenece al estado del arte y en consecuencia carece de novedad y nivel inventivo.

Adicionalmente, en la anterioridad tantas veces citada (pág 57, 63), encontramos toda la información relacionada con su actividad antiviral contra VIH y su utilidad como fármaco para el tratamiento de la infección por dicho virus, ya sea solo o en combinación con todos y cada uno de los agentes antivirales que menciona la solicitud colombiana en trámite en su capítulo reivindicatorio, en especial las reivindicaciones 1, 3, 7, 9, 12, 19, 21, 23, 25 en adelante.

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

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

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

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- Además si cada una de las sustancias que se mencionan y que se pueden combinar con dicho principio activo, tales como abacavir¹, didanosina², emtricitabina, lamivudina³, stavudina⁴, tenofovir⁵, zalcitabina⁶, zidovudina⁷

¹ Nucleoside reverse transcriptase inhibitor (NRTI). Prepn: S. M. Daluge, EP 349242 (1990 to Wellcome Found.); idem, US 5034394 (1991 to Burroughs Wellcome). Asymmetric synthesis: M. T. Crimmins, B. W. King, J. Org. Chem. 61, 4192 (1996). Pharmacology and biological profile: S. M. Daluge et al., Antimicrob. Ag. Chemother. 41, 1082 (1997). Review of antiviral activity and clinical evaluations: R. H. Foster, D. Faulds, Drugs 55, 729-736 (1998). Clinical trial of triple nucleoside regimen in HIV patients: S. Staszewski et al., J. Am. Med. Assoc. 285, 1155 (2001).

² Hypoxanthine nucleoside with antiviral activity; metabolic product of dideoxyadenosine, q.v. Enzymatic prep from dideoxyadenosine: W. Plunkett, S. S. Cohen, Cancer Res. 35, 1547 (1975). Synthesis: G. W. Koszalka, T. A. Krenitsky, EP 206497 (1986 to Wellcome Found.); R. R. Webb et al., Nucleosides Nucleotides 7, 147 (1988). In vitro inhibition of HIV-I: H. Mitsuya, S. Broder, Proc. Nat. Acad. Sci. USA 83, 1911 (1986); of HIV-II: D. D. Richman, Antimicrob. Ag. Chemother. 31, 1879 (1987). Antiretroviral spectrum in vitro: J. E. Dahlberg et al., Proc. Nat. Acad. Sci. USA 84, 2469 (1987). Cellular pharmacology in cloned human T-cells: G. Ahluwalia et al., Biochem. Pharmacol. 36, 3797 (1987). HPLC determn in human plasma: G. Ray, E. Murrill, Anal. Letters 20, 1815 (1987). Clinical evaluations in AIDS: J. S. Lambert et al., N. Engl. J. Med. 322, 1333 (1990); T. P. Cooley et al., ibid. 1340. Comprehensive description: M. N. Nassar et al., Anal. Profiles Drug Subs. Excip. 22, 185-227 (1993).

³ Reverse transcriptase inhibitor. Prepn: J. A. V. Coates et al., WO 91 17159 C.A. 117, 111989 (1991). Synthesis of enantiomers: J. W. Beach et al., J. Org. Chem. 57, 2217 (1992); of (-)-enantiomer: D. C. Humber et al., Tetrahedron Letters 33, 4625 (1992). HPLC determn in urine: D. M. Morris, K. Selinger, J. Pharmaceut. Biomed. Anal. 12, 255 (1994). Clinical trial in hepatitis B: F. Nevens et al., Gastroenterology 113, 1258 (1997). Review of pharmacology and clinical efficacy in HIV infection: C. M. Perry, D. Faulds, Drugs 53, 657-680 (1997).

⁴ Analog of thymidine, q.v.; reverse transcriptase inhibitor. Prepn: J. P. Horwitz et al., J. Org. Chem. 31, 205 (1966); J. W. Beach et al., ibid. 57, 3887 (1992). Large scale production: J. E. Starrett et al., EP 334368; eidem, US 5130421 (1989, 1992 both to Bristol-Myers). In vitro activity against HIV and toxicology: M. M. Mansuri et al., Antimicrob. Ag. Chemother. 34, 637 (1990). Mechanism of action study: H.-T. Ho, M. J. M. Hitchcock, ibid. 33, 844 (1989). Disposition and metabolism: E. M. Cretton et al., ibid. 37, 1816 (1993). Clinical pharmacokinetics: M. N. Dudley et al., J. Infec. Dis. 166, 480 (1992). HPLC determn in plasma and urine: J. S. Janiszewski et al., J. Chromatog. 577, 151 (1992). Clinical evaluation in AIDS and ARC: M. J. Browne et al., J. Infec. Dis. 167, 21 (1993).

⁵ Acyclic phosphonate nucleotide analog; reverse transcriptase inhibitor. Prepn: I. Rosenberg et al., Coll. Czech. Chem. Commun. 53, 2753 (1988); A. Holy et al., ibid. 60, 1390 (1995); L. M. Schultze et al., Tetrahedron Letters 39, 1853 (1998). Prepn of ester prodrug: M. N. Arimilli et al., Antivir. Chem. Chemother. 8, 557 (1997); idem et al., WO 98 04569; eidem, US 5922695 (1998, 1999 both to Gilead Sci.). Antiretroviral activity in vitro: J. Balzarini et al., Biochem. Biophys. Res. Commun. 219, 337 (1996). Metabolism and pharmacokinetics of prodrugs: J.-P. Shaw et al., Pharm. Res. 14, 1824 (1997). Clinical evaluation in HIV-infected patients: S. G. Deeks et al., Antimicrob. Ag. Chemother. 42, 2380 (1998).

⁶ Pyrimidine nucleoside analog with antiviral activity. Prepn: J. P. Horwitz et al., J. Org. Chem. 32, 817 (1967); R. Marumoto, M. Honjo, Chem. Pharm. Bull. 22, 128 (1974). Prepn and structure-activity study: T.-S. Lin et al., J. Med. Chem. 30, 440 (1987). In vitro inhibition of viral DNA synthesis: P. C. van der Vliet, M. M. Kwant, Biochemistry 20, 2628 (1981); of HIV-1 virus replication: H. Mitsuya, S. Broder, Proc. Nat. Acad. Sci. USA 83, 1911 (1986). Phosphorylation by human cells: D. A. Cooney et al., Biochem. Pharmacol. 35, 2065 (1986). Metabolism by human cells: M. C. Starnes, Y. Cheng, J. Biol. Chem. 262, 988 (1987). Potential application in acquired immunodeficiency syndrome (AIDS): E. De Clercq, J. Med. Chem. 29, 1561 (1986).

⁷ Pyrimidine nucleoside analog; reverse transcriptase inhibitor. Prepn: J. P. Horwitz et al., J. Org. Chem. 29, 2076 (1964); R. P. Glinski et al., ibid. 38, 4299 (1973). See also: J. L. Rideout et al., US 4724232 (1988 to Burroughs Wellcome). Total synthesis: C. K. Chu et al., Tetrahedron Letters 29, 5349 (1988). In vitro antiviral and antitumor activity: E. De Clercq et al., Biochem. Pharmacol. 29, 1849 (1980); vs HIV-1 virus: H. Mitsuya et al., Proc. Nat. Acad. Sci. USA 82, 7096 (1985). Clinical pharmacokinetics: R. W. Klecker et al., Clin. Pharmacol. Ther. 41, 407 (1987). Toxicology studies: K. M. Ayers, Am. J. Med. 85, Suppl. 2A, 186 (1988). Comprehensive description: M. L. Sethi, Anal. Profiles Drug Subs. 20, 729-765 (1991). Review of clinical experience: G. X. McLeod, S. M. Hammer, Ann. Int. Med. 117, 487-501 (1992); in prevention of perinatal HIV transmission: R. Sperling, Infect. Dis. Obstet. Gynecol. 6, 197-203 (1998).

(inhibidores de transcriptaza inversa nucleosídicos), delavirdina⁸, efavirenz⁹, nevirapina¹⁰ (inhibidores de transcriptasa inversa no nucleosídicos), amprenavir¹¹, atazanavir, indinavir¹², lopinavir¹³, nelfinavir¹⁴, ritonavir¹⁵, saquinavir¹⁶, fosamprenavir (inhibidores de proteasa), enfuvirtide, T-1249

⁸ Bisheteroarylpiperazine (BHAP) reverse transcriptase inhibitor. Prepn: D. L. Romero et al., WO 91 09849 (1991 to Upjohn). Structure-activity studies: D. L. Romero et al., *J. Med. Chem.* 36, 1505 (1993). In vitro activity vs HIV-1: T. J. Dueweke et al., *Antimicrob. Ag. Chemother.* 37, 1127 (1993); P. J. Pagano, K.-T. Chong, *J. Infect. Dis.* 171, 61 (1995). Enzyme kinetic studies: I. W. Althaus et al., *Biochem. Pharmacol.* 47, 2017 (1994).

⁹ Nonnucleoside HIV-1 reverse transcriptase inhibitor. Prepn: S. D. Young et al., EP 582455; eidem, US 5519021 (1994, 1996 both to Merck). Pharmacology: S. D. Young et al., *Antimicrob. Ag. Chemother.* 39, 2602 (1995). Enantioselective synthesis: A. S. Thompson et al., *Tetrahedron Letters* 36, 8937 (1995). Total synthesis and resolution of enantiomers: L. A. Radesca et al., *Syn. Commun.* 27, 4373 (1997). Ionization behavior: S. R. Rabel et al., *Pharm. Dev. Technol.* 1, 91 (1996). Clinical trial as component of combination therapy in HIV-1 infection in adults: S. Staszewski et al., *N. Engl. J. Med.* 341, 1865 (1999); in children: S. E. Starr et al., *ibid.* 1874.

¹⁰ Non-nucleoside reverse transcriptase inhibitor (NNRTI) of the dipyrindodiazepinone class. Prepn: K. D. Hargrave et al., EP 429987 (1991 to Boehringer, Ing; Thomae); eidem, US 5366972 (1994 to Boehringer, Ing.); eidem, *J. Med. Chem.* 34, 2231 (1991). Inhibition of HIV-1 reverse transcriptase: V. J. Merluzzi et al., *Science* 250, 1411 (1990). Studies of structure-activity and binding site: P. M. Grob et al., *AIDS Res. Hum. Retroviruses* 8, 145 (1992). Clinical pharmacokinetics: S. H. Cheeseman et al., *Antimicrob. Ag. Chemother.* 37, 178 (1993). Review of clinical experience: A. Carr, D. A. Cooper, *Adv. Exp. Med. Biol.* 394, 299-304 (1996); of safety profile: R. B. Pollard et al., *Clin. Ther.* 20, 1071-1092 (1998). Clinical trial in prevention of perinatal HIV-1 transmission: L. A. Guay et al., *Lancet* 354, 795 (1999).

¹¹ Second generation HIV protease inhibitor. Prepn: R. D. Tung et al., WO 94 05639; eidem, US 5585397 (1994, 1996 both to Vertex). Crystal structure of complex with HIV protease: E. E. Kim et al., *J. Am. Chem. Soc.* 117, 1181 (1995). Review of design strategy: M. A. Navia et al., *Int. Antiviral News* 3, 143-145 (1995); of pharmacology and clinical evaluation: J. C. Adkins, D. Faulds, *Drugs* 55, 837-842 (1998).

¹² Member of the novel hydroxyaminopentane amide class of HIV-1 protease inhibitors. Prepn: J. P. Vacca et al., EP 541168; eidem, US 5413999 (1993, 1995 both to Merck & Co.); B. D. Dorsey et al., *J. Med. Chem.* 37, 3443 (1994). Diastereoselective synthesis: D. Askin et al., *Tetrahedron Letters* 35, 673 (1994); P. E. Maligres et al., *ibid.* 36, 2195 (1995). Crystal structure of HIV-II protease complex: Z. Chen et al., *J. Biol. Chem.* 269, 26344 (1994). Antiviral activity and pharmacokinetics: J. P. Vacca et al., *Proc. Nat. Acad. Sci. USA* 91, 4096 (1994). HPLC determn in plasma and urine: E. Woolf et al., *J. Chromatog. A* 692, 45 (1995). Metabolism in humans: S. K. Balani et al., *Drug Metab. Dispos.* 23, 266 (1995).

¹³ HIV protease inhibitor; analog of ritonavir, q.v. Prepn: H. L. Sham et al., WO 97 21685; idem et al., US 5914332 (1997, 1999 both to Abbott); E. J. Stoner et al., *Org. Process Res. Dev.* 3, 145 (1999). Protease inhibition and pharmacokinetics: H. L. Sham et al., *Antimicrob. Ag. Chemother.* 42, 3218 (1998). In vitro metabolism study: G. N. Kumar et al., *Drug Metab. Dispos.* 27, 86 (1999). Pharmacokinetic enhancement by ritonavir: G. N. Kumar et al., *ibid.* 902. Clinical evaluation in HIV-infection: R. L. Murphy, *Antiviral Ther.* 4, Suppl. 3, 85 (1999).

¹⁴ HIV protease inhibitor. Prepn: B. A. Dressman et al., WO 95 09843; eidem, US 5484926 (1995, 1996 both to Agouron). Physical properties: M. Longer et al., *J. Pharm. Sci.* 84, 1090 (1995). HIV protease inhibition and antiviral activity: A. K. Patick et al., *Antimicrob. Ag. Chemother.* 40, 292 (1996). Preclinical pharmacokinetics and tissue distribution: B. V. Shetty et al., *ibid.* 110. Review of pharmacology and clinical efficacy in HIV infection: A. Bardsley-Elliott, G. L. Plosker et al., *Drugs* 59, 581-620 (2000).

¹⁵ Peptidomimetic HIV-1 protease inhibitor. Prepn: D. J. Kempf et al., WO 94 14436; eidem, US 5541206 (1994, 1996 both to Abbott). Antiretroviral spectrum, pharmacokinetics: idem et al., *Proc. Nat. Acad. Sci. USA* 92, 2484 (1995). Structural model for drug resistance: M. Markowitz et al., *J. Virol.* 69, 701 (1995). HPLC determn in biological fluids: R. M. W. Hoetelmans et al., *J. Chromatog. B* 705, 119 (1998). Review of clinical experience: A. P. Lea, D. Faulds, *Drugs* 52, 541-546 (1996). Clinical trial with nucleoside analogs in HIV-infected children: S. A. Nachman et al., *J. Am. Med. Assoc.* 283, 492 (2000).

¹⁶ Selective HIV protease inhibitor. Prepn: J. A. Martin, S. Redshaw, EP 432695; eidem, US 5196438 (1991, 1993 both to Hoffmann-LaRoche); K. E. B. Parkes et al., *J. Org. Chem.* 59, 3656 (1994). In vitro HIV proteinase inhibition: N. A. Roberts et al., *Science* 248, 358 (1990). Antiviral properties: J. C. Craig et al., *Antiviral Res.* 16, 295 (1991); S. Galpin et al., *Antiviral Chem.*

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(inhibidores de fusión), Sch-C, Sch-D, TAK-220, PRO-140, UK-427,857 (CCR5 inhibidores), AMD-3100 (CXCR4 inhibidor) y PA-457 (inhibidor de la maduración); son sustancias cuyos mecanismos de acción y propiedades antivirales (contra HIV) son reconocidos con anterioridad, resulta obvia la combinación de dichos principios activos para el tratamiento de la infección por HIV, ya que como toda persona medianamente versada en la materia reconoce, la eficacia de dicha combinación depende de la complementariedad de dichos mecanismos de acción; y por lo tanto formular farmacéuticamente la combinación de dichos principios activos resulta totalmente carente de nivel inventivo.

- Por último, aunque es bien sabido por el Despacho, al punto de haber basado varias decisiones sobre patentes en ese argumento, me permito hacer notar que según el artículo 14 de la Decisión 486 de 2000, las patentes sólo pueden concederse sobre productos o procedimientos, siempre que estos, además, sean nuevos, tengan nivel inventivo y sean susceptibles de aplicación industrial. Una simple lectura del capítulo reivindicatorio de la solicitud colombiana en trámite (específicamente las reivindicaciones 1 a 18), pretende sin más, y sin que sea dado hacer interpretaciones extensivas, obtener exclusiva sobre un USO de composiciones farmacéuticas y principios activos, pretensión inaceptable de acuerdo con las normas citadas.

De igual manera, hago notar que respecto de estas mismas reivindicaciones el uso pretendido tiene el agravante de serlo como parte de métodos de tratamiento, adicionalmente, las reivindicaciones propiamente relacionadas con métodos igualmente se encuentran prohibidas por las normas andinas vigentes si se tiene en cuenta que según el artículo 20 literal d) de la decisión 486 expone literalmente que *"No serán patentables: Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o animales."*

En conclusión la solicitud colombiana en trámite busca reivindicar una sustancia con actividad antiviral cuya obtención y aplicación ya se encontraban suficientemente descritas en el estado de la técnica, con lo que incurre en una

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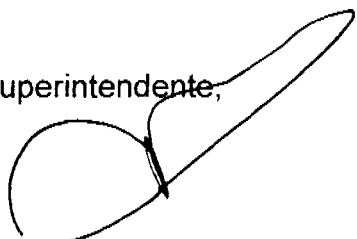
total falta de novedad y de nivel inventivo, si se tiene en cuenta el hecho que se propone su combinación con otros agentes antivirales ya descritos de la misma manera en la anterioridad WO 04/014380, o que cualquier persona medianamente versada en la materia asociaría dichos agentes como una alternativa terapéutica para la infección de VIH teniendo en cuenta sus mecanismos de acción.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS

- La publicación WO 04/014380 titulada "COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED AZAINDOLEOXOACETIC PIPERAZINE DERIVATIVES" paginas 57 a 63, 444, 448 y capítulo reivindicatorio.

Señor Superintendente,



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For two-letter codes and other abbreviations, refer to the "Guid-
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WO 2004/014380 A1

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

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

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

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

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

ANTIVIRALS

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

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

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

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	GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
5			
	HB Y097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
10			
	Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
15	Recombinant Human Interferon Beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC
	Interferon alfa-n3	Interferon Sciences	ARC, AIDS
20	Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
25			
	ISIS 2922	ISIS Pharmaceuticals -	CMV retinitis
	KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
30	Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
35			
	Lobucavir	Bristol-Myers Squibb	CMV infection

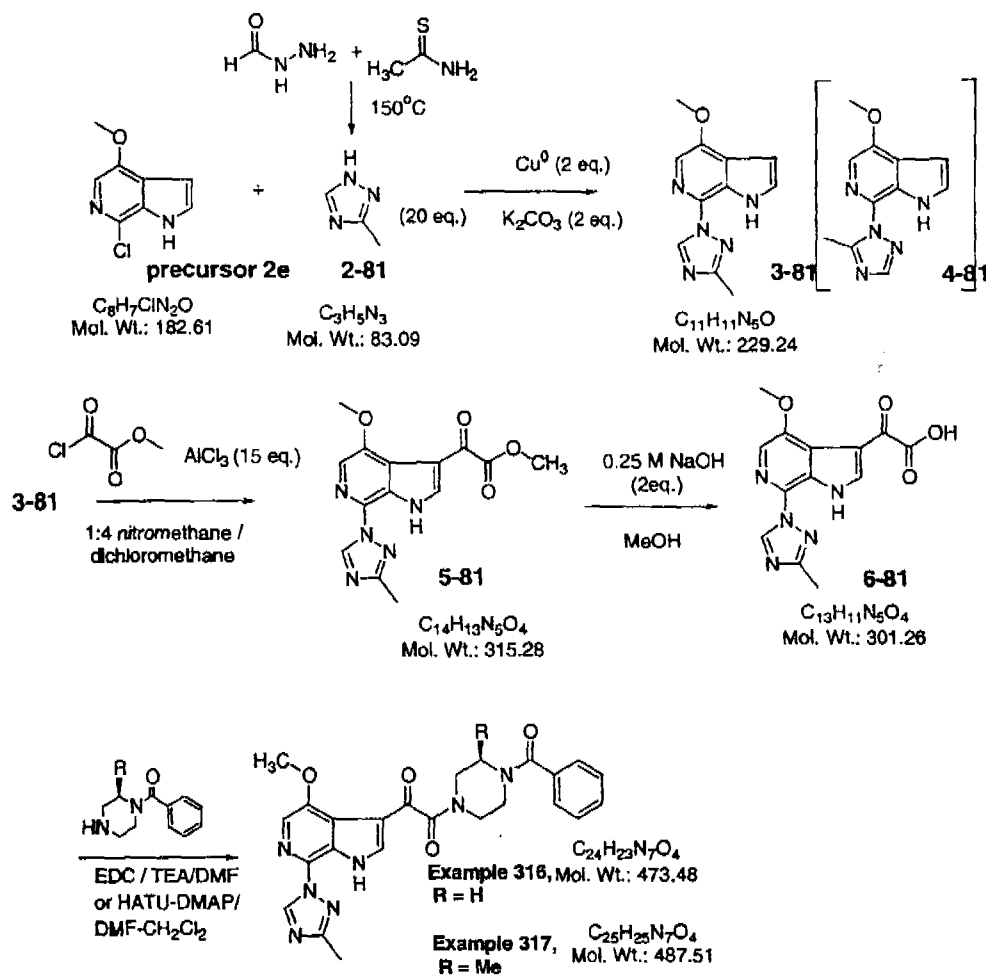
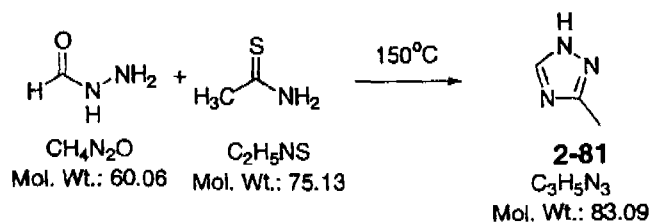
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	Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
5	Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
10	Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
15	Peptide T Octapeptide Sequence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

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16D

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

Scheme 81

Preparation of 3-methyl-1,2,4-triazole (2-81)

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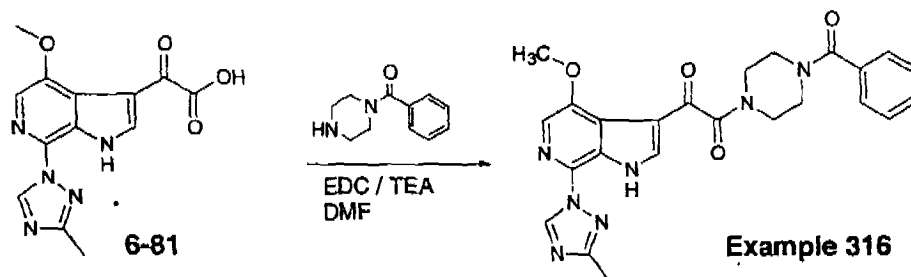
Procedure: A solid mixture of formic hydrazide (68 g, 1.13 mol) and thioacetamide (85 g, 1.13 mol) in a 500mL-RBF was heated with stirring at 150°C (oil bath temp.) for 1.5 hrs with a gentle stream of nitrogen, removing H_2S and water (about 18 mL of liquid collected) formed during the reaction. The reaction mixture was distilled under reduced pressure, collecting 60.3 g (0.726 mol, Y. 63.3%) of the title compound at

10

quickly to remove MeOH, and the residual solution was extracted with EtOAc to remove any neutral impurities. To the aqueous phase was added 1N HCl (68 mL, 68 mmol) to neutralize the product. The resultant mixture was frozen and lyophilized to obtain 14.1 g (33.7 mmol, Y. 99.2%) of the title compound **6-81**, containing 2 mole equivalents of NaCl as off-white solid. This material was used in the subsequent reaction without further purification. The sodium salt of the title compound **6-81** was obtained by C-18 reverse phase column chromatography after sodium bicarbonate treatment: HPLC >97% (AP, uv at 254nm); HRMS (Na salt, ESI⁺) *m/z* calcd for C₁₃H₁₀N₅O₄ (M-H), 300.0733; found 300.0724 (Δ -3 ppm); ¹H NMR (Na salt, DMSO-*d*₆, 500 MHz) δ ppm 2.37 (3H, s, Me), 3.83 (3H, s, CH₃O), 7.56 (1H, s, H-5), 8.03 (1H, s, H-2), 9.32 (1H, s, triazole-H-5); ¹³C NMR (Na salt, DMSO-*d*₆, 125.7 MHz) δ ppm 13.8 (triazole-Me), 57.2 (OMe), 114.8 (C-3), 120.0 (C-5), 125.1, 143.5 (C-5'), 149.8 (C-4), 160.0 (C-3'), 171.7, 191.3.

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Preparation of Example 316



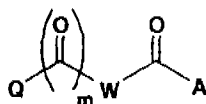
Procedure: To a solution of the acid **6-81** (3.01 g, 10 mmol) and benzoylpiperazine hydrochloride (3.39 g, 15 mmol) in DMF (50 mL) was added triethylamine (10.1 g, 100 mmol, 10 eq.), followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 5.75 g, 30 mmol) under N₂ and the mixture stirred at room temperature for 22 h after sonication and at 40°C for 2 h. The mixture was concentrated *in vacuo* to remove DMF and TEA, and to the residual solution was added water (200 mL) under stirring and sonication. The precipitates formed were collected, washed with water and dried *in vacuo* to obtain 2.8 g (5.9 mmol, Y. 59%) of the title compound **Example 316** as off-white solid. The filtrate was extracted with CH₂Cl₂ (x2). The CH₂Cl₂ extracts were dried (Na₂SO₄), filtered and concentrated to gum which was triturated with Et₂O to obtain a solid. This solid was

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CLAIMS

What is claimed is:

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

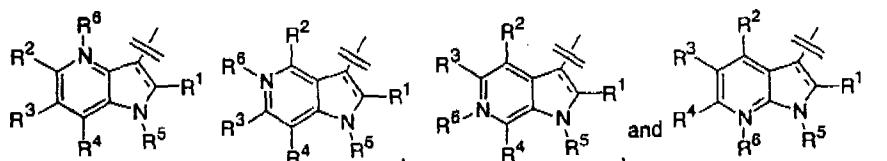


I

wherein:

10

Q is selected from the group consisting of:



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

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

20

m is 1 or 2;

R^5 is hydrogen or $(\text{CH}_2)_n\text{CH}_3$, $-\text{C(O)}(\text{CH}_2)_n\text{CH}_3$, $-\text{C(O)O}(\text{CH}_2)_n\text{CH}_3$, $-\text{C(O)}(\text{CH}_2)_n\text{N}(\text{CH}_3)_2$ wherein n is 0-5;

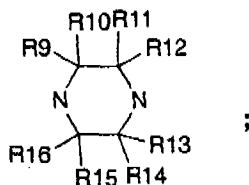
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R^6 is O or does not exist;

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- A is selected from the group consisting of C₁₋₆alkoxy, aryl and heteroaryl; in which said aryl is phenyl or naphthyl; said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, benzoimidazolyl and benzothiazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different members selected from the group consisting of amino, nitro, cyano, hydroxy, C₁₋₆alkoxy, -C(O)NH₂, C₁₋₆alkyl, -NHC(O)CH₃, halogen and trifluoromethyl;

- 10 -W- is



- B is selected from the group consisting of -C(=NR⁴⁶)(R⁴⁷), C(O)NR⁴⁰R⁴¹, aryl, heteroaryl, heteroalicyclic, S(O)₂R⁸, C(O)R⁷, XR^{8a}, (C₁₋₆)alkylNR⁴⁰R⁴¹, (C₁₋₆)alkylCOOR^{8b}; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group F; wherein aryl is naphthyl or substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;

q is 0, 1, or 2;

25

D is selected from the group consisting of (C₁₋₆)alkyl and (C₂₋₆)alkenyl; wherein said (C₁₋₆)alkyl and (C₂₋₆)alkenyl are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of C(O)NR⁵⁵R⁵⁶, hydroxy, cyano and XR⁵⁷;

30

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E is selected from the group consisting of (C₁₋₆)alkyl and (C₂₋₆)alkenyl; wherein said (C₁₋₆)alkyl and (C₂₋₆)alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, -C(O)NR₅₆R₅₇, C(O)R₅₇, SO₂(C₁₋₆)alkyl and SO₂Ph; wherein heteroaryl is a

5 monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;

F is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, aryloxy, (C₁₋₆)thioalkoxy, cyano,

10 halogen, nitro, -C(O)R⁵⁷, benzyl, -NR⁴²C(O)-(C₁₋₆)alkyl, -NR⁴²C(O)-(C₃₋₆)cycloalkyl, -NR⁴²C(O)-aryl, -NR⁴²C(O)-heteroaryl, -NR⁴²C(O)-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴²S(O)₂-(C₁₋₆)alkyl, -NR⁴²S(O)₂-(C₃₋₆)cycloalkyl, -NR⁴²S(O)₂-aryl, -NR⁴²S(O)₂-heteroaryl, -NR⁴²S(O)₂-heteroalicyclic, S(O)₂(C₁₋₆)alkyl, S(O)₂aryl, -S(O)₂NR⁴²R⁴³, NR⁴²R⁴³,

15 (C₁₋₆)alkylC(O)NR⁴²R⁴³, C(O)NR⁴²R⁴³, NHC(O)NR⁴²R⁴³, OC(O)NR⁴²R⁴³, NHC(O)OR⁵⁴, (C₁₋₆)alkylNR⁴²R⁴³, COOR⁵⁴, and (C₁₋₆)alkylCOOR⁵⁴; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C₁₋₆)alkoxy, and aryloxy, are optionally substituted with one to nine same or different halogens or from one to five same or different substituents selected from the group G; wherein

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

25 G is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, aryloxy, cyano, halogen, nitro, -C(O)R⁵⁷, benzyl, -NR⁴⁸C(O)-(C₁₋₆)alkyl, -NR⁴⁸C(O)-(C₃₋₆)cycloalkyl, -NR⁴⁸C(O)-aryl, -NR⁴⁸C(O)-heteroaryl, -NR⁴⁸C(O)-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴⁸S(O)₂-(C₁₋₆)alkyl, -NR⁴⁸S(O)₂-(C₃₋₆)cycloalkyl, -NR⁴⁸S(O)₂-aryl, -NR⁴⁸S(O)₂-heteroaryl, -NR⁴⁸S(O)₂-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide, NR⁴⁸R⁴⁹, (C₁₋₆)alkyl C(O)NR⁴⁸R⁴⁹, C(O)NR⁴⁸R⁴⁹, NHC(O)NR⁴⁸R⁴⁹, OC(O)NR⁴⁸R⁴⁹, NHC(O)OR⁵⁴,

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(C₁₋₆)alkylNR⁴⁸R⁴⁹, COOR⁵⁴, and (C₁₋₆)alkylCOOR⁵⁴; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R⁷ is selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or with from one to three same or different substituents selected from the group F;

wherein for R⁷, R⁸, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R⁸ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₃₋₇)cycloalkenyl, (C₂₋₆)alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₃₋₇)cycloalkenyl, (C₂₋₆)alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

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

R^{8b} is selected from the group consisting of hydrogen, (C₁₋₆)alkyl and phenyl;

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

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

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

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

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R_a and R_b are each independently H, (C₁₋₆)alkyl or phenyl;

R⁴⁶ is selected from the group consisting of H, OR⁵⁷, and NR⁵⁵R⁵⁶;

- 5 R⁴⁷ is selected from the group consisting of H, amino, halogen, phenyl, and (C₁₋₆)alkyl;

R⁴⁸ and R⁴⁹ are independently selected from the group consisting of hydrogen, (C₁₋₆)alkyl and phenyl;

10

R⁵⁰ is selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, and benzyl; wherein each of said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl and benzyl are optionally substituted with one to three same or different halogen, amino, OH, CN or NO₂;

- 15 R⁵⁴ is selected from the group consisting of hydrogen and (C₁₋₆)alkyl;

R^{54'} is (C₁₋₆)alkyl;

- 20 R⁵⁵ and R⁵⁶ are independently selected from the group consisting of hydrogen and (C₁₋₆)alkyl; and

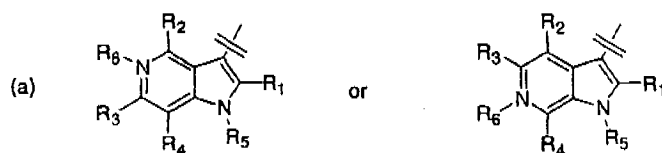
R⁵⁷ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl and phenyl.

- 25 2. A compound of claim 1, including pharmaceutically acceptable salts thereof wherein:

R¹ is hydrogen;

- 30 Q is either:

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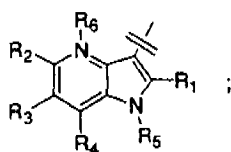
wherein R^2 is selected from the group consisting of hydrogen, halogen, hydroxy, $-O(C_{1-6})$ alkyl, cyano, nitro and XR^{57} ;

5

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

10

(b) Q is:



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

20

and for both (a) and (b):

m is 2;

25 R^5 is hydrogen;

R^6 does not exist;

A is selected from the group consisting of C₁₋₆alkoxy, aryl and heteroaryl; wherein said aryl is phenyl; heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl and isoxazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different members selected from the group consisting of amino, cyano, hydroxy C₁₋₆alkoxy, C₁₋₆alkyl, -NHC(O)CH₃, halogen and trifluoromethyl;

-- represents a carbon-carbon bond;

10 X is NH or NCH₃;

R⁵⁷ is H or (C₁₋₃)alkyl; and

R⁵⁵ and R⁵⁶ are independently H or (C₁₋₆)alkyl.

15

3. A compound of claim 2, including pharmaceutically acceptable salts thereof, wherein:

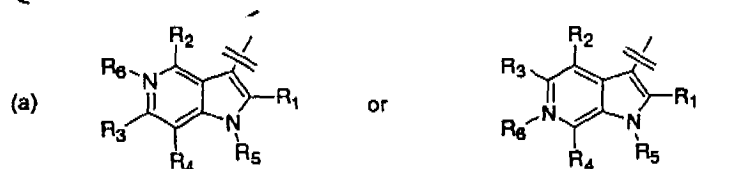
A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C₁₋₆alkyl, hydroxy, or halogen;

20

R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶ are each independently hydrogen or methyl with the proviso that only one is methyl;

25

Q is either:



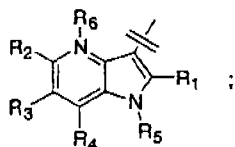
and then R² is selected from the group consisting of hydrogen, halogen and methoxy; and

30

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R₃ is hydrogen; or

(b) Q is:



5

and R² is halogen or hydrogen and R³ is hydrogen;

and for both (a) and (b):

10 R⁴ is selected from the group consisting of B;

B is selected from the group consisting of -C(O)NR⁴⁰R⁴¹, substituted phenyl, heteroaryl, oxazoline, pyrazinone and methylene dioxy or ethylene dioxy fused to a benzene or pyridine; wherein said heteroaryl or phenyl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

15

4. A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

20

B is selected from the group consisting of -C(O)NR⁴⁰R⁴¹, substituted phenyl and heteroaryl; wherein said phenyl is substituted and heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F;

25

F is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, (C₁₋₆)thioalkoxy, cyano, halogen, -C(O)R⁵⁷, benzyl, -NR⁴²C(O)-(C₁₋₆)alkyl, -NR⁴²C(O)-(C₃₋₆)cycloalkyl, -NR⁴²C(O)-aryl, -NR⁴²C(O)-heteroaryl, -NR⁴²C(O)-heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴²S(O)₂-(C₁₋₆)alkyl, -NR⁴²R⁴³, C(O)NR⁴²R⁴³ and COOR⁵⁴; wherein said (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, aryl, heteroaryl, heteroalicyclic,

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(C₁₋₆)alkoxy, are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G;

- G is selected from the group consisting of (C₁₋₆)alkyl, hydroxy, (C₁₋₆)alkoxy, halogen, -NR⁴⁸C(O)-(C₁₋₆)alkyl, -NR⁴⁸C(O)-(C₃)cycloalkyl, 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴⁸S(O)₂-(C₁₋₆)alkyl, NR⁴⁸R⁴⁹, (C₁₋₆)alkyl C(O)NR⁴⁸R⁴⁹, C(O)NR⁴⁸R⁴⁹ and (C₁₋₆)alkylNR⁴⁸R⁴⁹;

R⁴⁰ is hydrogen; and

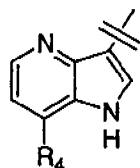
10

R⁴¹ is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, phenyl and heteroaryl; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, phenyl, or heteroaryl are substituted with one to three same or different halogens or one to two same or different substituents selected from the group consisting of methyl, (C₁₋₃)alkoxy,

- 15 heteroaryl and aryl; wherein said aryl or heteroaryl are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group consisting of (C₁₋₆)alkyl, hydroxy, (C₁₋₆)alkoxy, -NR⁴²C(O)-(C₁₋₆)alkyl, NR⁴²R⁴³ and C(O)NR⁴²R⁴³.

- 20 5. A compound of claim 4, including pharmaceutically acceptable salts thereof, wherein:

Q is



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

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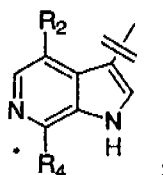
B is selected from the group consisting of $-C(O)NR^{40}R^{41}$ or heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

- 5 6. A compound of claim 5, including pharmaceutically acceptable salts thereof, wherein:

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

7. A compound of claim 4, including pharmaceutically acceptable salts thereof, wherein:

15 Q is



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

20 R^4 is B;

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

25

8. A compound of claim 7, including pharmaceutically acceptable salts thereof, wherein:

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

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9. A compound of claim 8 including pharmaceutically acceptable salts thereof, wherein:

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

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10. A compound of claim 8 including pharmaceutically acceptable salts thereof, wherein:

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

11. A compound of claim 4 wherein:

15 F is selected from the group consisting of (C_{1-6}) alkyl, (C_{3-6}) cycloalkyl (C_{1-6}) alkoxy, hydroxy, heteroaryl, heteroalicyclic, methoxy, $-S(C_{1-3})$ alkyl, halogen, $-C(O)R^{57}$, $C(O)NR^{42}R^{43}$, $-NR^{42}C(O)-(C_{1-6})$ alkyl, $-NR^{42}C(O)-(C_{3-6})$ cycloalkyl, $-NR^{42}C(O)$ -aryl, $-NR^{42}C(O)$ -heteroaryl, $-NR^{42}C(O)$ -heteroalicyclic, 4, 5, or 6 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$ alkyl, $-NR^{42}S(O)_2-(C_{3-6})$ cycloalkyl, $-NR^{42}S(O)_2$ -aryl, 20 $-NR^{42}S(O)_2$ -heteroaryl, $-NR^{42}S(O)_2$ -heteroalicyclic, $NR^{42}R^{43}$, $NR^{55}(C_{1-3})$ alkyl $NR^{55}R^{56}$ and $COOR^{54}$.

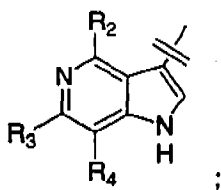
12. A compound of claim 11 wherein:

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

13. A compound of claim 4, including pharmaceutically acceptable salts thereof, wherein:

Q is

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R² is selected from the group consisting of hydrogen and methoxy;

R³ is hydrogen; and

- 5 B is selected from the group consisting of -C(O)NR⁴⁰R⁴¹ and heteroaryl; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

14. A compound of claim 8 wherein R² is fluoro.

10

15. A compound of claim 8 wherein R² is methoxy.

16. A compound of claim 8 wherein:

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

17. A compound of claim 5 wherein:

- B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, 25 pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole, pyridyl, indole, azaindole, and diaza-indole; wherein said heteroaryl is optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F.

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18. A compound of claim 13 wherein:

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

19. A compound of claim 7 wherein:

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

20. A compound of claim 6 wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a
20 substituent selected from the group consisting of hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₃ thioalkoxy, amino, -C(O)H, -COOH, -COOC₁-C₆ alkyl, -NHC(O)- (C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), -C(O)-NH₂, C(O)NHMe, C(O)NMe₂, trifluoromethyl, -NR⁵⁵R⁵⁶, NR⁵⁵R⁵⁶-(C₁-C₆ alkyl)-NR⁵⁵R⁵⁶, -thiazole, pyrrole, piperazine, pyrrolidine and N-pyrrolidone.

25

21. A compound of claim 7 wherein:

B is -C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to
three same or different halogens or a substituent selected from the group consisting of
30 (C₁-C₆ alkyl), amino, -NHC(O)-(C₁-C₆ alkyl), -methoxy, -NHC(C₁-C₆ alkyl) and -N(C₁-C₆ alkyl)₂.

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22. A compound of claim 10 wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C₁-C₆ alkyl), amino, -NHC(O)-
5 (C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), methoxy, -C(O)-NH₂, C(O)NHMe,
C(O)NMe₂, trifluoromethyl, -NHC(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -heteroaryl and a
4, 5, or 6 membered cyclic N-lactam.

23. A compound of claim 9 wherein:

10

B is -C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C₁-C₆ alkyl), amino, -NHC(O)-(C₁-C₆ alkyl), -methoxy, -NHC(C₁-C₆ alkyl) and
-N(C₁-C₆ alkyl)₂.

15

24. A compound of claim 16 wherein:

B is heteroaryl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy,
20 C₁-C₃ thioalkoxy, amino, -C(O)H, -COOH, -COOC₁-C₆ alkyl, -NHC(O)-
(C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), methoxy, -C(O)-NH₂, C(O)NHMe,
C(O)NMe₂, trifluoromethyl, -NR⁵⁵R⁵⁶, NR⁵⁵R⁵⁶-(C₁-C₆ alkyl)-NR⁵⁵R⁵⁶, -thiazole,
pyrrole, piperazine, pyrrolidine and N-pyrrolidone.

25. A compound of claim 13 wherein:

B is -C(O)NH-heteroaryl wherein said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of (C₁-C₆ alkyl), amino, -NHC(O)-(C₁-C₆ alkyl), -methoxy,
30 -NHC(C₁-C₆ alkyl) and -N(C₁-C₆ alkyl)₂.

26. A compound of claim 5 wherein:

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A 78
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B is thienyl.

27. A compound of claim 24 wherein:

- 5 B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₃ thioalkoxy, amino, -C(O)H, -COOH, -COOC₁-C₆ alkyl, -NHC(O)-(C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), -C(O)-NH₂, C(O)NHMe, C(O)NMe₂, trifluoromethyl, -NR⁵⁵R⁵⁶, NR⁵⁵R⁵⁶-(C₁-C₆ alkyl)-NR⁵⁵R⁵⁶, heteroaryl, piperazine,
10 pyrrolidine, N-pyrrolidone and trifluoromethyl.

28. A compound of claim 10 wherein:

B is thienyl.

15

29. A compound of claim 27 wherein:

- B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C₁-C₆ alkyl, amino,
20 -NHC(O)-(C₁-C₆ alkyl), -C(O)-NH₂, C(O)NHMe, C(O)NMe₂ and -NR⁵⁵R⁵⁶.

30. A compound of claim 10 wherein:

- 25 B is thienyl optionally substituted with one to three same or different halogens or a substituent selected from the group consisting of hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₃ thioalkoxy, amino, -C(O)H, -COOH, -COOC₁-C₆ alkyl, -NHC(O)-(C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), methoxy, -C(O)-NH₂, C(O)NHMe, C(O)NMe₂, trifluoromethyl, -NR⁵⁵R⁵⁶, NR⁵⁵R⁵⁶-(C₁-C₆ alkyl)-NR⁵⁵R⁵⁶, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

30

31. A compound of claim 16 wherein:

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1.2.1

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein said heteroaryl is optionally substituted with one to three same or different halogens
5 or a substituent selected from the group F consisting of hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₃ thioalkoxy, amino, -C(O)H, -COOH, -COOC₁-C₆ alkyl, -NHC(O)-(C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), methoxy, -C(O)-NH₂, C(O)NHMe, C(O)NMe₂, trifluoromethyl, -NR⁵⁵R⁵⁶, NR⁵⁵R⁵⁶-(C₁-C₆ alkyl)-NR⁵⁵R⁵⁶, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

10

32. A compound of claim 17 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein
15 said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₃ thioalkoxy, amino, -C(O)H, -COOH, -COOC₁-C₆ alkyl, -NHC(O)-(C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), methoxy, -C(O)-NH₂, C(O)NHMe, C(O)NMe₂, trifluoromethyl, -NR⁵⁵R⁵⁶, NR⁵⁵R⁵⁶-(C₁-C₆ alkyl)-NR⁵⁵R⁵⁶, heteroaryl,
20 piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

33. A compound of claim 18 wherein:

B is heteroaryl selected from the group consisting of thiazole, pyridazine, pyrazine, pyrazole, isoxazole, isothiazole, imidazole, furyl, thienyl, oxazole, oxadiazole, thiadiazole, pyrimidine, pyrazole, triazine, triazole, tetrazole and pyridyl; wherein
25 said heteroaryl is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₃ thioalkoxy, amino, -C(O)H, -COOH, -COOC₁-C₆ alkyl, -NHC(O)-(C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), methoxy, -C(O)-NH₂, C(O)NHMe, C(O)NMe₂, trifluoromethyl, -NR⁵⁵R⁵⁶, NR⁵⁵R⁵⁶.
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(C₁-C₆ alkyl)-NR⁵⁵R⁵⁶, heteroaryl, piperazine, pyrrolidine, N-pyrrolidone and trifluoromethyl.

34. A compound of claim 3 which is depicted in Table 2.

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

36. A compound of claim 3 which is depicted in Table 3.

10 37. A compound of claim 3 which is depicted in Table 4.

38. A compound of claim 3 which is depicted in Table 5.

39. A compound of claim 1 wherein:

15

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; wherein said phenyl or heteroaryl is independently optionally substituted with one to two of the same or different amino, C₁₋₆alkyl, or halogen;

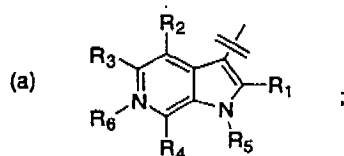
20

-- represents a carbon-carbon bond;

R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶ are each independently hydrogen or methyl, with the proviso that only zero, one, or two is methyl;

25

Q is either:

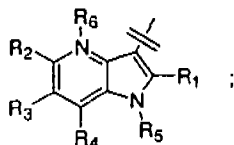


30 R² is selected from the group consisting of hydrogen, halogen, and methoxy; and

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R₃ is hydrogen; or

(b) Q is:



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R² and R³ are hydrogen;

and for both (a) and (b):

10 R⁴ is selected from the group consisting of B;

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

15 substituents selected from the group F;

F is selected from the group consisting of (C₁₋₆)alkyl, heteroaryl, -NR⁴²C(O)-(C₁₋₆)alkyl, -NR⁴²R⁴³ and C(O)NR⁴²R⁴³;

20 R⁵ is hydrogen;

R⁶ does not exist; and

25 R⁴² and R⁴³ are independently selected from the group consisting of hydrogen and (C₁₋₆)alkyl; or R⁴² and R⁴³ taken together with the nitrogen to which they are attached form a heteroalicyclic selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, tetrahydrofuran, tetrahydropyran, azepine and morpholine.

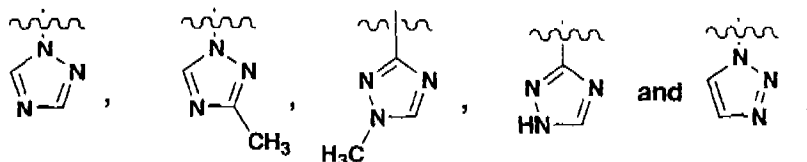
40. A compound of claim 39 wherein:

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R² is H, Cl, F, or methoxy; and

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AS 2

R⁴ is selected from the group consisting of



5 41. A compound of claim 40 wherein:

R² is methoxy or fluoro; and

one of R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, or R¹⁶ is methyl and the others are hydrogen.

10

42. A compound of claim 40 wherein:

R² is methoxy; and

15 R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶ are each hydrogen.

43. A compound of claim 41 wherein:

one of R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, or R¹⁶ is (R)-methyl and the others are
20 hydrogen.

44. A compound of claim 41 wherein:

one of R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, or R¹⁶ is (S)-methyl and the others are
25 hydrogen.

45. A compound of claim 39 wherein:

R² is methoxy, hydrogen, chloro, or fluoro; and

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R⁴ is oxadiazole.

46. A compound of claim 54 wherein:

5 R² is methoxy, hydrogen, chloro or fluoro; and

R⁴ is oxadiazole substituted with a single fluoro, chloro, amino or methyl group.

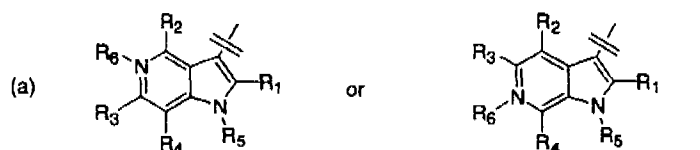
47. A compound of claim 2, including pharmaceutically acceptable salts thereof,
10 wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein said
heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is
optionally substituted with one to two of the same or different amino, C₁₋₆alkyl,
15 hydroxy, or halogen;

R⁹, R¹⁰, R¹¹, R¹², R¹⁵, and R¹⁶ are each hydrogen;

R¹³ and R¹⁴ are each independently hydrogen or methyl with the proviso that only one
20 is methyl;

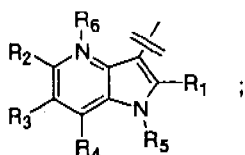
Q is either:



25 R² is selected from the group consisting of hydrogen, halogen and methoxy; and

R₃ is hydrogen; or

(b) Q is:



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

5 and for both (a) and (b):

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

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

15 48. A compound of claim 47, including pharmaceutically acceptable salts thereof,
 wherein:

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

F is selected from the group consisting of (C_{1-6}) alkyl, (C_{3-6}) cycloalkyl, aryl,
 heteroaryl, heteroalicyclic, hydroxy, (C_{1-6}) alkoxy, (C_{1-6}) thioalkoxy, cyano, halogen,
 25 $-C(O)R^{57}$, benzyl, $-NR^{42}C(O)-(C_{1-6})$ alkyl, $-NR^{42}C(O)-(C_{3-6})$ cycloalkyl,
 $-NR^{42}C(O)$ -aryl, $-NR^{42}C(O)$ -heteroaryl, $-NR^{42}C(O)$ -heteroalicyclic, 4, 5, or 6
 membered ring cyclic N-lactam, $-NR^{42}S(O)_2-(C_{1-6})$ alkyl, $-NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$ and
 $COOR^{54}$; wherein said (C_{1-6}) alkyl, (C_{3-6}) cycloalkyl, aryl, heteroaryl, heteroalicyclic,
 (C_{1-6}) alkoxy, are optionally substituted with one to three same or different halogens
 30 or from one to two same or different substituents selected from the group G;

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G is selected from the group consisting of (C₁₋₆)alkyl, hydroxy, (C₁₋₆)alkoxy, halogen, -NR⁴⁸C(O)-(C₁₋₆)alkyl, -NR⁴⁸C(O)-(C₃)cycloalkyl, 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴⁸S(O)₂-(C₁₋₆)alkyl, NR⁴⁸R⁴⁹, (C₁₋₆)alkyl C(O)NR⁴⁸R⁴⁹, C(O)NR⁴⁸R⁴⁹ and (C₁₋₆)alkylNR⁴⁸R⁴⁹;

5

R⁴⁰ is hydrogen;

R⁴¹ is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, phenyl, or heteroaryl; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, phenyl, or heteroaryl are substituted with one to three same or different halogens or one to two same or different methyl, (C₁₋₃)alkoxy, heteroaryl or aryl; wherein said aryl or heteroaryl are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group consisting of (C₁₋₆)alkyl, hydroxy, (C₁₋₆)alkoxy, -NR⁴²C(O)-(C₁₋₆)alkyl, NR⁴²R⁴³ and C(O)NR⁴²R⁴³.

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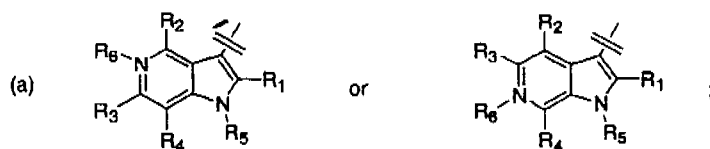
49. A compound of claim 2, including pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is pyridinyl, furanyl or thienyl; and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, C₁₋₆alkyl, hydroxy, or halogen;

R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶ are each independently hydrogen or methyl with the proviso that only one is methyl;

25

Q is either:



30

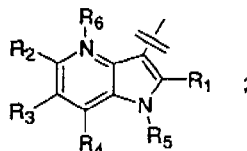
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wherein R^2 is selected from the group consisting of hydrogen, halogen and methoxy;
and

R_3 is hydrogen; or

5

(b) Q is:



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

10

and for both (a) and (b):

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

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

20

50. A compound of claim 49, including pharmaceutically acceptable salts thereof, wherein:

B is selected from the group consisting of pyrazinone and methylene dioxy or ethylene dioxy fused to a benzene ring; wherein said group is optionally substituted with one to three same or different halogens or a substituent selected from the group F consisting of $(C_1-C_6 \text{ alkyl})$, amino, $-NHC(O)-(C_1-C_6 \text{ alkyl})$, $-NHS(O)_2-(C_1-C_6 \text{ alkyl})$, methoxy, $-C(O)-NH_2$, $C(O)NHMe$, $C(O)NMe_2$, trifluoromethyl, $-NHC(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, heteroaryl and a 4, 5, or 6 membered cyclic N-lactam.

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51. A compound of claim 49, including pharmaceutically acceptable salts thereof, wherein:

B is selected from the group consisting of oxadiazole, triazole, pyrazole, pyrazine and
5 pyrimidine; wherein said group is optionally substituted with one to three same or
different halogens or a substituent selected from the group F consisting of
(C₁-C₆ alkyl), amino, -NHC(O)-(C₁-C₆ alkyl), -NHS(O)₂-(C₁-C₆ alkyl), methoxy,
-C(O)-NH₂, C(O)NHMe, C(O)NMe₂, trifluoromethyl, -NHC(C₁-C₆ alkyl),
-N(C₁-C₆ alkyl)₂, -heteroaryl, a 4, 5, or 6 membered cyclic N-lactam and
10 (C₁₋₆)alkylNR⁴⁸R⁴⁹.

52. A compound of claim 49, including pharmaceutically acceptable salts thereof, wherein:

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

53. A compound of claim 50, including pharmaceutically acceptable salts thereof, wherein:

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

54. A compound of claim 1 wherein R⁹, R¹⁰, R¹⁵ and R¹⁶ are each hydrogen; and

R¹¹, R¹², R¹³, and R¹⁴ are each independently hydrogen or methyl with the proviso
25 that up to one can be methyl.

55. A compound of claim 54, including pharmaceutically acceptable salts thereof, wherein one of R¹¹, R¹², R¹³, and R¹⁴ is methyl.

30 56. A compound of claim 55, wherein the carbon atom of the piperazine ring to which the methyl group of R¹¹, R¹², R¹³, and R¹⁴ is attached has an (R) configuration.

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57. A compound of claim 1 wherein R^{11} , R^{12} , R^{13} , and R^{14} are each hydrogen; and R^9 , R^{10} , R^{15} and R^{16} are each independently hydrogen or methyl with the proviso that up to one can be methyl.
- 5 58. A compound of claim 57, wherein one of R^9 , R^{10} , R^{15} and R^{16} is methyl.
59. A compound of claim 58, wherein the carbon atom of the piperazine ring to which the methyl group of R^9 , R^{10} , R^{15} and R^{16} is attached has an (R) configuration.
- 10 60. A compound of claim 1, including pharmaceutically acceptable salts thereof wherein:
- R^1 is hydrogen;
- 15 m is 2;
- R^5 is hydrogen;
- 20 R^6 does not exist;
- A is selected from the group consisting of C_{1-6} alkoxy, aryl and heteroaryl; wherein aryl is phenyl; heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl and isoxazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different amino, cyano, hydroxy C_{1-6} alkoxy, C_{1-6} alkyl, -NHC(O)CH₃, halogen and trifluoromethyl; and

-- represents a carbon-carbon bond.

30

61. A pharmaceutical formulation which comprises an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier.

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62. The pharmaceutical formulation of claim 61, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

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

63. A method for treating mammals infected with a virus, comprising
10 administering to said mammal an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, as claimed in claim 1.

64. The method of claim 63, comprising administering to said mammal an antiviral effective amount of a compound of Formula I in combination with an
15 antiviral effective amount of an AIDS treatment agent selected from the group consisting of: an AIDS antiviral agent; an anti-infective agent; an immunomodulator; and HIV entry inhibitors.

65. The method of claim 63 wherein the virus is HIV.

20

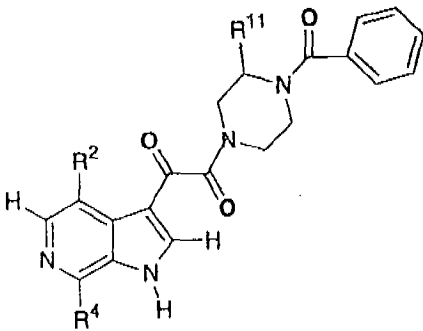
66. The method of claim 64 wherein the virus is HIV.

67. A compound of claim 1 having the Formula Ia, including pharmaceutically acceptable salts thereof,

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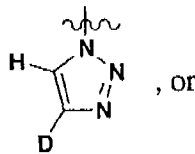
Ia

wherein:

5

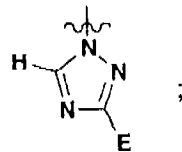
R² is methoxy, fluoro or chloro;

R⁴ is selected from the group consisting of a 1,2,3-triazolyl group having the formula



10

a 1,2,4-triazolyl group having the formula



15

D is hydrogen or C₁-C₃ alkyl;

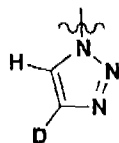
E is selected from the group consisting of hydrogen, (C₁-C₃)alkyl, O(C₁-C₃)alkyl and CH₂OCH₃; and

20

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R¹¹ is either hydrogen or methyl in which the configuration to which the methyl is

attached is (R); with the proviso that when R⁴ is



, then R¹¹ is hydrogen.

68. A compound of claim 67, including pharmaceutically acceptable salts thereof,

5

wherein:

R² is methoxy or fluorine;

D is hydrogen or methyl; and

10 E is hydrogen, methyl or ethyl.

69. A compound of claim 68, including pharmaceutically acceptable salts thereof,

wherein:

15

R² is methoxy;

D is hydrogen or methyl; and

E is hydrogen, methyl or ethyl.

20 70. A compound of claim 69, including pharmaceutically acceptable salts thereof,

wherein:

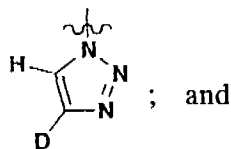
R¹¹ is hydrogen.

25

71. A compound of claim 70, including pharmaceutically acceptable salts thereof,

wherein:

30 R⁴ is

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R¹¹ is hydrogen.

5 72. A compound of claim 71, including pharmaceutically acceptable salts thereof,

wherein:

D is hydrogen.

10

73. A compound of claim 71, including pharmaceutically acceptable salts thereof,

wherein:

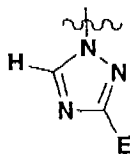
15 D is methyl.

74. A compound of claim 70, including pharmaceutically acceptable salts thereof,

wherein:

20

R⁴ is



25 75. A compound of claim 74, including pharmaceutically acceptable salts thereof,

wherein:

E is hydrogen.

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76. A compound of claim 74, including pharmaceutically acceptable salts thereof,

wherein:

5 E is methyl.

77. A compound of claim 74, including pharmaceutically acceptable salts thereof,

wherein:

10

E is ethyl.

78. A compound of claim 68, including pharmaceutically acceptable salts thereof,

15 wherein:

R^2 is fluoro;

D is hydrogen or methyl; and

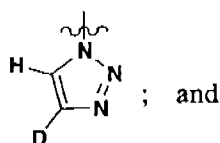
E is hydrogen or methyl.

20

79. A compound of claim 78, including pharmaceutically acceptable salts thereof,

wherein:

25 R^4 is



R^{11} is hydrogen.

30

80. A compound of claim 79, including pharmaceutically acceptable salts thereof,

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wherein:

D is hydrogen.

5 81. A compound of claim 79, including pharmaceutically acceptable salts thereof,

wherein:

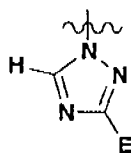
D is methyl.

10

82. A compound of claim 78, including pharmaceutically acceptable salts thereof,

wherein:

15 R⁴ is



83. A compound of claim 82, including pharmaceutically acceptable salts thereof,

20 wherein:

E is hydrogen.

84. A compound of claim 82, including pharmaceutically acceptable salts thereof,

25

wherein:

E is methyl.

30 85. A compound of claim 68, including pharmaceutically acceptable salts thereof,

5/
195

wherein:

R² is methoxy;

D is hydrogen or methyl;

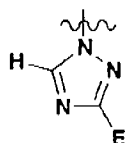
5 E is hydrogen, methyl or ethyl; and

R¹¹ is (R)-methyl.

86. A compound of claim 85, including pharmaceutically acceptable salts thereof,

10 wherein:

R⁴ is



15

87. A compound of claim 86, including pharmaceutically acceptable salts thereof,

wherein:

20 E is hydrogen.

88. A compound of claim 86, including pharmaceutically acceptable salts thereof,

wherein:

25

E is methyl.

89. A compound of claim 86, including pharmaceutically acceptable salts thereof,

wherein:

30

E is ethyl.

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90. A pharmaceutical formulation which comprises an antiviral effective amount of a compound of Formula Ia, including pharmaceutically acceptable salts thereof, as claimed in claim 67, and a pharmaceutically acceptable carrier.

5 91. The pharmaceutical formulation of claim 90, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

(a) an AIDS antiviral agent;

(b) an anti-infective agent;

10 (c) an immunomodulator; and

(d) HIV entry inhibitors.

92. A method for treating mammals infected with the HIV virus, comprising administering to said mammal an antiviral effective amount of a compound of
15 Formula Ia, including pharmaceutically acceptable salts thereof, as claimed in claim 67.

93. The method of claim 92, comprising administering to said mammal an antiviral effective amount of a compound of Formula Ia in combination with an
20 antiviral effective amount of an AIDS treatment agent selected from the group consisting of: an AIDS antiviral agent; an anti-infective agent; an immunomodulator; and HIV entry inhibitors.

2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Sarmiento
Apoderado

Oficio N°: 16

ASUNTO:

Radicación PCT N°	06-95880
Trámite	011
Evento	379
Actuación	440
Folios	058

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano - Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 04 .Jul. 2008.

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