SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO f
Liduslnaytomercio IiI000IlnhiiliIi]o SUPERINTENCENCIA

No 06-023144. -00003-0000
Fecha: 2009-05-12 11:10:34 Dep. 2020 NUECREACIONI
Ira. 11 PATENTEJYII Eve: 379 FASENACIONALII
Act. 329 CTOINFORMACION Folios: 10

FORMULARIO UNICO DE CORRECIONES Y MOUIFIAIuNt
2000-10

I I SOLICITUD DE:

I I Corrección de Error Material I X I Modiflcación a una Solicitud.

I 2 I Nombre: CELGENE CORPORATION IDENTIFICACION

SOLICITANTE Dirección: 7 Powder Horn Drive C.0 (J NIT
TelØfono: G.E. 0 Otro 0 E-mail

NUmero

Domicilio: Warren, Estado de New Jersey, E.U.A.

I 3 I Nombre: LUIS FEUPE CASTILLO GIBSONE IDEN11FICACION

REPRESENTANTE Direcciôn: Carrara 13 No. 37-43 Piso 12 C.0 NIT 0
0 APODERADO
TelØfono: 2857460 Fax: 285 92 67

G.E. Otro 0 E-mail infotcastillocirau.com
Numero 79.397.879 T.P. ERROR:

de BogotÆ del C.S.J.

I 4 INümero de Expediente
.06-23.144

IS IDescrlpcion de la correcclôn o modlflcaclón solicitada Se adjunta un nuevo capitulo
reMndlcatorlo pam que sea tenido en cuenta al momento de efectuar el examen de
fondo de esta solicitud. Este captuIo reemplaza al previamente presentado con ml escrito
del pasado 27 de Febrero de 2009

I 6 1 Comprobante de pago NO ’2i)/, Fecha

I I Anexos:

EJ Comprobante de pago de Ia lase

El Poderes, si fuere el caso
Certificado de existencia representaciôn legal de las partes, cuando seen personas juridicas.

I B I
NOMBRE LUIS FEUPE CASTILLO G. FIRMA

G.0 Z’39787_q-17 -6-8995 8995de deBogota del C.S.J.
Instrucciones pam el diligenclamlento del presente formularlo, ver reveiso de esta pØgina.

ReMndicaciones

1. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-pipendin-2,6-diona
cnstalina que tiene un patrOn de difracciOn de polvo de Rayos-X que comprende picos a aproximadamente 8, 14.5y 16 grados 20.

2. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de la reivindicaciOn 1, donde el patrOn comprende picos a aproximadamente 7.9, 14.4 y 15.9 grados 20.

3. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-pipendin-2,6-diona
cnstalina de la reivindicaciOn 1, donde el patrOn comprende ademÆs picosa aproximadamente 17.5, 20.5, 24 y26 grados 20.

4. La 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cnstalina de la reivindicaciOn 1, donde el patrOn comprende picos a 17.6, 20.6, 24.1 y 26.0 grados 20.

5. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina de las reivindicaciones 1-4, que tiene un termograma por calorimetrIa diferencial de bamdo que comprende un endotermo con maxima de aproximadamente 270°C.

6. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cnstalina, que tiene un patrOn de difracciOn de polvo de Rayos-X correspondiente al patrOn de difracciOn de polvo de Rayos-X de la Figura 1.

7. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cnstalina, que tiene un espectro infrarrojo correspondiente al espectro infrarrojo representativo de la Figura 2.

8. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cnstalina, que tiene un espectro Raman correspondiente al espectro Rama representativo de la Figura 3.

9. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de cualquiera de las reivindicaciones 1-8 que no es solvatada.

10. La 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina que tiene un patron de difracciOn de polvo de rayos-X que comprende picos a aproximadamente 16, 22y27 grados 20.

11. La 3-(4-amino-1-oxo-I,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de la reivindicaciOn 10, donde el patrOn comprende picos a 15.8, 22.2y 26.7 grados2o.

12. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de la reivindicaciOn 10, donde el patrOn comprende ademÆs picos a aproximadamente 18 grados 20.

13. La 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de la reivindicaciOn 12, donde el patrOn comprende un pico a 18.2 grados 20.

14. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un termograma de calorimetria diferencial de bamdo que comprende endotermos con mÆximas a aproximadamente 146°C y 268°C.

15. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cnstalina que pierde cerca del 3.1 % de volÆtiles en una base de pesocuando se calienta a aproximadamente 175°C.

16. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-il)-pipendin-2,6-diona
cristalina que tiene un patron de difracciOn de polvo de Rayos-X correspondiente a los patrones de difracciOn de polvo de rayos X representativos de las Figuras 6, 32, 33 y 34.

17. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cnstalina que tiene un espectro infrarrojo correspondiente al espectro infrarrojo representativo de la Figura 7.

18. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-pipendin-2,6-diona
cristalina que tiene un espectro Raman correspondiente al espectro Raman representativo de la Figura 8.

19. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-pipendin-2,6-diona
cnstalina que tiene aproximadamente 0.46 moles de agua por mole de de 3-(4-amino-I-oxo-1,3-dihidro-isoindol-2-il)-piperidin-I,6-diona.

01,

20. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-pipendin-2,6-diona
cristalina de cualquiera de las reivindicaciones 10-19, que es hemihidratada.

21. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina que tiene un patron de difracciOn de polvo de Rayos-X que comprende picos a aproximadamente 8, 15.5 y25 grados 29.

22. La La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de la reivindicaciOn 21, donde el patrOn comprende picos a 7.9, 15.8 y 24.9 grados 20.

23. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina de la reivindicaciOn 21 022 que tiene un termograma por calonmetrIa diferencial de bamdo que comprende endotermos con mÆximas aproximadamente a 150°C y 269°C

24. 3-(4-amino.-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cnstalina que tiene un patron de difracciOn de polvo de rayos-X correspondiente al patrOn de difracciOn de polvo de rayos-X representativo de la Figura 12.

25. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-pipendin-2,6-diona
cristalina que tiene un espectro infrarrojo correspondiente al espectro infrarrojo representativo de la Figura 13.

26. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina que tiene un espectro Raman correspondiente al espectro Raman representativo de la Figura 14.

27. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de cualquiera de las reivindicaciones 21-26 que es solvatada.

28. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un patrOn de difracciOn de rayos-x que comprende picos a aproximadamente 12, 27 y28 grados 20.

29. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-djona
cnstalina de la reivindicaciOn 28, donde el patrOn comprende picos a 11.9, 26.5 y 27.8 grados 20.

30. La 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidjn-2,6-djona
cristalina de la reivindicaciOn 28 029 que tiene un termograma por calorimetrIa

3

diferencial de bamdo que comprende endotermos con mÆximas entre 122°C y 270°C.

31. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un patron de difracciOn de polvo de rayos-x correspondiente al patrOn de difracciOn de polvo representativo de la Figura 18.

32. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina que tiene un espectro infrarrojo correspondiente al espectro infrarrojo representativo de la Figura 19.

33. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un espectro Raman correspondiente al espectro Raman representativo de la Figura 20.

34. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de cualquiera de las reivindicaciones 28-33, que es solvatada.

35. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un patron de difracciOn de polvo de rayos-x que comprende picos a aproximadamente 20, 24.5 y29 grados 20

36. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
c,istalina de (a reivindicaciOn 35, donde el patron comprende picos a 20.0 24.7 y 28.6 grados 20

37. La 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-pipendin-2,6-diona
cristalina de las reivindicaciones 35 0 36 que tiene un termograma por calorimetria diferencial de bamdo que comprende endotermos con mÆximas entre 99°C y 269°C

38. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina que tiene un patrOn de difracciOn de polvo de rayos-x correspondiente a los patrones de difracciOn de polvo de rayos-x representativos de las Figuras 23 y 35.
39. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-dioria
cristalina de cualquiera de las reivindicaciones 35-38 que es dihidratada.

40. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina que tiene un patrOn de difracciOn de polvo de rayos-x que comprende picos a aproximadamente 19, 19.5 y25 grados 20

4

41. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina de la reivindicapión 40, donde el patron comprende picos a 18.9, 19.7 y 24.9 grados 20

42. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina de la reivindicación 40 41, que tiene un termograma por calorimetria diferencial de barrido que comprende un endotermo con un mÆximo de aproximadamente 269°C.

43. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un patrOn de difracciOn de polvo de rayos-x correspondiente al patrOn de difracciOn de polvo de rayos-x representativo de la Figura 26.

44. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-djona
cristalina de cualquiera de las reivindicaciones 40-43, que no es solvatada.

45. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un patrOn de difracciOn de polvo de rayos-x que comprende picos a aproximadamente 21, 23y 24.5 grados 20.

46. La 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina de la reivindicaciOn 45, donde el patron comprende picos a 21.3, 22.5 y 24.3 grados 20.

47. La 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina de la reivindicación 45 46 que tiene un termograma por calorimetria diferencial de barrido que comprende un endotermo a aproximadamente 248°C.

48. 3-(4-amino-1-oxo-1,3-dihidro-isoindol-2-il)-piperidin-2,6-diona
cristalina que tiene un patrOn de difracciOn de polvo de rayos-x correspondiente al patrOn de difracciOn de polvo de rayos-x representativo de la Figura 28
49. La 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina de cualquiera de las reivindicaciones 45-48 que no es solvatada.

50. 3-(4-amino-1 -oxo-1,3-dihidro-isoindol-2-it)-piperidin-2,6-diona
cristalina que tiene un patron de difracciOn de polvo de rayos-x que comprende picos a aproximadamente 15, 26y31 grados 20

51. La 3-(4-amino-I-oxo-1, 3-dihidro-isoindol-2-iI)-piperidin-2,6-diona
cristalina de la reivindicaciôn 50 donde el patron comprende picos a I 5.2, 25.6 y 30.7 grados 29.

62. La cantidad terapØutica o profilacticamente efectiva de la
reivindicación 61 donde el cancer es un tumor sólido 0 un tumor Ilevado por la sangre.

63. Una cantidad terapØutica o profilÆcticamente efectivade la 3-(4-
amino-I-oxo-I,3-dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina de cualquiera de las reivindicaciones 1-55 en la preparacion de una composiciôn farmacØutica para el tratamiento o prevenciôn de angiogenesis no deseada, una enfermedad inflamatoria, enfermedad autoinmune o enfermedad inmune.

64 Una cantidad terapØutica o profilÆcticamenteefectiva de la 3-(4-
amino-I-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina de cualquiera de las reivindicaciones 1-55 en la preparación de una composición farmacØutica para el tratamiento o prevención de un sindrome mielodisplÆstico.

65. Una cantidad terapŒuticao profilÆcticamenteefectiva de la 3-(4-
amino-I-oxo-I,3-dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina de cualquiera de las reivindicaciones 1-55 en la preparaciôn de una composición farmacØutica para el tratamiento o prevenciOn de una enfermedad mieloproliferativa.

66. Una cantidad terapeutica o profilÆcticamenteefectiva de la 3-(4-
amino-I-oxo-1,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina de cualquiera de las reivindicaciones 1-55 en la preparaciôn de una composiciôn farmacØutica para el tratamiento o prevenciOn del dolor.

67. Una cantidad terapØutica o profilÆcticamenteefectiva de la 3-(4-
amino-I-oxo-I,3-dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina de cualquiera de las reivindicaciones 1-55 en la preparacion de una composiciôn farmacØutica para el tratamiento o prevenciôn de una generacion macular.

68. Las cantidades terapØuticas o profilÆcticamente efectivas de las
reivindicaciones 61, 62, 63, 64, 65, 66 67 donde la 3-(4-amino-I-oxo-I,3-dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina es administrada por via oral, parenteral, transdermal, mucosal, nasal, tOpica o subllingual.

69. Las cantidades terapØuticas 0 profilÆcticamenteefectivas de la
reivindicación 68 donde la 3-(4-amino-1 -oxo-I,3-dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina es administrada por via oral.

7

StiPERINTENDEI4CIA DE INDIJSTRIA Y CONERCID

NIT 800176089-2

- StAY COMCIO
RE0 OFICIAI. DE CAJA

MAYO 12 BE 2009 SuPERINTENDF

03F EAGION1

Nt 329

PC FCAIOS.

- -

MIS CONS ISNACION;*fl*

DEPUSITANTE TIPO PASO BArICO CiJENTA No. PASO FECHA P60 Vr. PASO

1?7

CASTILiD SkAti Y ASOCTADOSCONSI6NAC!GN BAr4CO DE BOSOTA 062754387 115283022 12/0512009 1,015,000.00

***;* C 0 N Cu E P 1 0 ISM

- -

CAfl. RENTISTICO CONCEPTO TOTAL CONCEPTO

1 50005-01-03 CANSIO DE N0DALIO.40 Y 9001FICA 12 NARCAS Y LENAS COERCIAiES 111,000.00
TOTAL: 111000.00

SON: CIENTO ONCE NIL PESOS

RESPONSABLE

RECISO DE CAM APLICADO AL EXPEDIENTE No.

\5cfJ

ME11MI111010111

US006281230111

(12) United States Patent (10) Patent No.: US 69281,230 B! Muller et aL (45) Date of Patent: Aug. 28,2001

(54) ISOLNDOUNES, METHOD OF USF, AND
PHARMACEUTICAL COMPOSITIONS

(75) Inventors. George W. Muller, Bridgewater, David
L Stirling, Branchburg; Roger
Shen-Chu Chen, Edison, all of NJ
(US)

(73) Assignee: Celgene Corporation, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) AppI. No.: 09/543,809

(22) Filed: Apr. 6, 2000

Related U.S. Application Data

(62) Division of application No. 091230,389, filed as application No. PCT/tJS97I13375 on Jul. 24, 1997, now abandoned,

which is a continuation of application No. 081690,258, filed on Au& 22, 1996, now Pat No. 5,798,368, which is a continuation of application No. 08)701,499, flIed on Jul. 24,

1996, now Pat. No. 5,635,517
(60) Provisional application No. 60/048,278, filed on May 30,
1997.

(51) hit. CC....A61K 31/445; C07D 401/04

(52) US. CL.._514/323; 546/201

(58) FIeld of Search............................ 514/323; 546/201

(56) References Cited

U.S. PATENT DOCUMENTS

4,590,189 5/1986 Hiraga et aL.
4,808,402 2/1989 Leibovich at at.
4,849,441 7/1989 Okazaki at al..
5,385,901 1/1995 Kaplan at at.
5,463,063 10/1995 Muller et at.
5,502,066 3/1996 Heinemann at at.
5,593,990 1/1997 D’Amato.
5,605,914 2/1997 Muller.
5,629,327 511997 D’Aniato.
5,635,517 6/1997 Muller et at...__..._. 514)323
5,658,940 8/1997 Muller at at.
5,698,579 12/1997 Muller.
5,703,098 12/1997 Muller at at.
5,712,291 1/1998 D’Amato.
5,728,845 3/1998 Muller at at.
5,736,570 4/1998 Muller at at.
5,798,368 8/1998 Muller et at.
5,801,195 9/1998 Muller at at.
5,874,448 2/1999 Muller et at......._. 514/323
5,877,200 3/1999 Muller.
5,929,117 7/1999 Muller at at.
5,968,945 10/1999 Muller at at.
6,011,050 112000 Muller et at..
6,020,358 2/2000 Muller at at.
6,046,221 412000 Muller et at.
6,071,948 6/2000 D’Amato.

FOREIGN PATENT DOCUMENTS

WO 95/01348 1/1995 (WO).

OTHER PUBLICATIONS

Corral, L et at, "Differential Cytokine Modulation and T Cell Activation by Two Distinct Classes of Thalidomide Analogues That Are Potent Inhibitors of TNF- 1"9 The Journal of Immunology, pp. 380-386, 1999.
Corral, L et at., "Immunomodulation by thalidomide and thalidomide analogues", Annals of the Rheumatic Diseases, vol. 58, Suppl. 1, pp. 1107-1113, 1999.
Corral, L. et at, "Selection of Novel Analogs of Thalido-mide with Enhanced Tumor Necrosis Factor Inhibitory Activity", Molecular Medicine, vol. 2, No. 4, 1996-

Craig, 99&Craig,J.C., "Abcolute Configuration of the Enantiomeis of 7-Chloro-4-[[4-diethylamino)-1-methylbuty]amino] quinoline (chioroquine)", 3. Org. Chem., vol. 53, pp. 1167-1170,1988.
Feiser, Louis F., Experiments in Organic Chemistry, 3rd edition, p. 75, 1955.
He, Weixuan et at, "Synthesis of Thalidomide Analogs and Their Biological Potential for Treatment of Graft Versus Host Disease (GyRO)". 206th American Chemical Society National Meeting, Med. Chem. AbsL 216, 1993.
Koch, IL, The Arene Oxide Hypothesis of Thalidomide Action. Considerations on the Molecular Mechanism of Action of the "Classical" Teratogen*, Sci. Pharm., vol. 49, pp. 67-99 (1981).
Koch, It, 4 Thalidomide and Congeners as Anti-Inflamma-tory Agents, Progress in Medicinal Chemistry, vol- M, pp-166-242 (1985).
Miyachi, H. et al., Novel Biological Response Modifiers: Phtha]imides with Tumor Necrosis Factor- Production--RegulatingAclivity,J. Med. Chem., pp. 2858-2865 (1997). Miyacbi, H.. et al.,TumorNecrosisFactor-Alpha Production Enhancing Activity of Substituted 3’-Mcthylthalidomide: Influence of Substituents at the Phihaloyl Moiety on the Activity of Stereoselectivity, Chem. Pharm. Bull., 46(7), pp. 1165-1168(1998).
Muller, George at at,Amino-Substituted Thalidomide Ann-logs. Potent Inhibitors of TNF- Production, Binorganic & Medicinal Chem. Letters 9, pp. 1625-1630(1999). Niwayania, Satomi et at, Potent inhibition of Tumor Necro-sis Factor- Production by Tetrailuorothalidomide and Tetr-lfluorophtalimides, J. Med. Chem., pp. 3044-3045 (1996). Smith, R. L. et at, Studies on the Relationship Between the Chemical Structure and Embryotoxic Activity of Thalido-mide and Related Compounds, Symp. Enibryopathic Act. Drugs, pp. 194-209 (1965).

(List continued on next page.)

Prunary ExwninerCharanjit S. Aulakh
(74) Attorney, Agem or FinnMathews, Collins Sherpherd & Gould

(57) ABSTRACT

Subxithire’i 1,-2-(Z6.dioxopiperidin-3-yl)isoindolixtes are useful in treating inflammation, inflammatory disease, autoimmune disease, and oncogenic or cancerous conditio in a mammal. ’Typical embodiments are 1-oxo-2.(2, - dioxopiperidin3-yl)-4-aminoisoincloline and 1-oxo-2-(2, dioxo-3-methylpiperidin-3- 1

26 Claims, No Drawings

US 6,281,230 Bi

a1

R2

H2

R?

, 0-.

a4

Amino compounds can be prepared through catalytic hydrogenation of the corresponding nitro compoun–

EA

The nitro intermediates of Formula IA are known or can be obtained though conventional processes. For example, a nitrophthalic anhydride is allowed to react with a-aniinoglutarimide hydrochloride {alternatively named as 2,6-dioxopiperidin-3-ylarmmonium chloride} in the pres-ence of sodium acetate and glacial acetic acid to yield an intermediate of Formula LA in which X and Y are both c=O.

In a second route, a lower alkyl ester ofnitro-ortho-toluic acid is brominated with N-bromosuccinimide under the influence of light to yield a lower aikyl 2-(bromomethyl) nitrobenzoate. This is allowed to react with 2,6-dioxopiperidiu-3-ammonium chloride in, for example, dim-ethylformamide in the presence of triethylamine to yield an intermediate of Formula II in which one of X is 0=0 and the other is Cl!,.
Alternatively, if one of R1, R2, R3, and 1(4 is protected amino, the protecting group can be cleaved to yield the corresponding compound in which one ofR1, R2, R3, and 1(4 is amino. Protecting groups utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at some stage of the synthesis in order to protect groups which otherwise might be altered in the course of chemical manipulations. Such protecting groups are removed at a later stage of the synthesis and compounds bearing such protect-ing groups thus are of importance primarily as chemical intermediates (although some derivatives also exhibit bio-logical activity). Accordingly the precise structure of the protecting group is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number’ of standard works including, for example, "Protective Groups in Organic Chemistry", Ple-num Press, London and N.Y., 1973; Greene, Th. W. "Pro-tective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides",Vol 1, Scbr&ler and Lubke,Academic Press, London and New York, 1965; "Methoden der alga-nisehen Chemie", Houben-Weyl, 4th Edition. %bl.15/I, Georg Theme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference. An amino group can be protected as an amide utilizing an acyl group which is selectively removable under mild conditions, especially benzyloxycarbonyl, formyl, or a lower alkanoyl group which is branched in 1-or a position to the carbenyl group, particularly tertiary alkanoyl such as pivaloyl, a lower alkanoyl group which is substituted in the position a to the carbonyl group, as for example trifluoroacetyl.

The compounds of the present invention possess a center of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral adsorbent Alternatively, the individual iso-mers can be prepared in chiral form orseparated chemically 10 from a mixture by forming salts with a chiral acid, such as the individual enantiomers of lO-camphorsulfonic acid, camphoric acid, 4x-bromocanlphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing 15 one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other, i.e., in a form having an optical purity of >95%.
The present invention also pertains to the physiologically acceptable non-toxic acid addition salts ofthe compounds of
o Formula I. Such saltsinclude those derived from organic and
inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesuiphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, maleic acid, maleic acid, sorbic
25 acid, aconitic acid, salicylic acid, phthalic acid, enibonic
acid, enanthic acid, and the like.
Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms contain-ing from 1 to 100 mg of drug per unit dosage. Isotonic saline 30 solutions containing from 20 to 100 mg/niL can be used for parenteral administration which includes intramuscular, inirathecal, intravenous and intra-arterial routes of admin-istration.. Rectal administration can be effected through the use of suppositories formulated from conventional carriers 35 such as cocoa butter.
Pharmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipi-ent. In preparing such compositions the active ingredients 40 are usually mixed with or diluted by an excipient orenclosed within such a carrier which can be in the form of a capsule or sachet When the excipient serves as a diluent, it may be a solid,semi-solid, orliquid material which acts as a vehicle, carrier, or medium for the active ingredient Thus, the 45 compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solu-tions and sterile packaged powders. Examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, so mannitol, starch, gum acacia, calcium silicate, microcrys-talline cellulose, polyvinylpyrrolidinone, cellulose, water, syrup, and methyl cellulose, the formulations can addition-ally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and
ss suspending agents, preserving agents such as methyl- and
propylhydroxybenzoates, sweetening agents or flavoring agents.

The following examples will serve to further typify the nature of this invention but should not be construed as a 60 limitation in the scope thereof, which scope is defined solely by the appended claims.

EXAMPLE 1

1,3-Dioxo-2-(2,6-dioxopiperidin-3-yl)-5-
65 aminoisoindoline
A mixture of 1,3dioxo-2-(2,6-dioxopiperidin-3-yl)-5-nitroisoindoline {alternatively named as N-(2.6-

OUO!P
V

ouo9ppddJCq1w
- - 4’Cz-u!Iopuos!oxo1-onmv-L,)-
LI ThUSIVXH

W1’N s6i’ ’H ’966c ’3

pUUO 9J ’N SO ’ii 1J9 ’3:EOENTHET3 iojpj
1VX%z145)n1w099
’s!iu 1!qZ) (bofH%ro
/N3fl3 06/01 ’mu ’UWPiW T ’U013iU1 il ’Win
0SP6c ’S13/d-AON WM ’TkIH ’VLZZ ’0V1f ’61 ’SlitS ¶65011 ’L5911 ’6L8Z1 ’z1 ’9901

’i’5591 ’6v1L1 ’cgzLIg IINN 3E1 XHT
w)1--90z ’(Hr ’m)/Zz-liZ ’(Hi
’WS-Z6Z ’(HZ ’ZN 88Z PilE 0L1[’PP)LTi’ ’Zn
TEl PilE ’PP)ZV ’ZH SL=r ’P)8L9
’Zn CL1 ’P)069 ’(HI ’Zfl 9Lf’061L *oITg
IIWN H 3 065Z-9SSZ din pqos oqm
in pnpozd MR jo (%Tc) 9 9V*O pop o PO.W pin pWilhjg’ Win OE Mg OMOM 1JCqlil101 UI PMMqS mmpqos 0UJ 01WA
Ut 033UO3 na apnig Oqi pilE inaiq pIIJJ
mmomizw mLL,wnciq Siaj uD2o4L(qjo ind lit smmddL, M p uozp4Cq in* (-tm 01)9) 10=ql= u
(21C0)DIpa %0T pa (ioww o-i) ouoW-9’z03WEdid
(uC-z-uuopm0s1oiiu-i-ox0-T)-i-(s) jo alnxw y
U0!P

9’Z-ilUW!(1-tUfl0PU00Uii’0XO1)i(S) 1 ’01tT ’N ’4)LE ’H
Z65S ’3 1mLQt1 E1i ’N ’i-I S65S’3:sONtnffI5
103 P3IED 1’’V X%00T)UitU L9E b)o1i%roIN3EHD

1)5f1) ’wu UtZ ’11W/1U ’101W t’mw 05P6t ’813/’IM -0A0N SIMEM ’3iJH EVZZ ’9115 ’Ei’8t ’ZOLZI
’096Z1 ’SV051 ’89’i’SI ’OVLST ’EE’Ci’I ’56591 ’690LT

’6CZLT9 (Pp05140) WJN 3 ’(Hz
’w)6yz-w7 ’(Hi ’zH P1lE 561"f
’PP)96t ’zit pm 61’=(’ZN
9L’f’OWL ’(Hi ’Zn E-L ’(Hi ’Zn pm
’pP)cts-61’s ’(Hi JmN H
ç g din 2 pnpwd Jo (%cL) 9 rZ OAIZ

pm

usjqui stzj. -(-in (t’) oppqqo OUilj1Clpaw qm papowa sum mCuj snoonbu oqI pm (-1w ooz) inam aoir am pomod

SuM. 01flZlW 11U U04 5103 3 00t’- 0405- Ia poims W

04

’ss’oc’3 pun03 ’89t1 ’N 9t’H zwos
’3:f’j103 P0i) 1UUV 69i’Z
’56’9Z1 ’19’6ZT ’01051 ’/_L1’5I ’01El ’S55i’1 ’96’59T

’(H ’Zn 101 PME gf ’p)sti’-swi’ ’(Hz ’O56i’

(’jw 09) 3)L1014D 9U0JdIfl0W UT (jotuw 66 ’2 90 nuwa7q2

mm

(%i’666)9tm
41wf’i11

S9 1-7d-UA0N WORM ’alan Xn6 s)9-1 ’(i* ’wY?zz-6vz

in

01

’S

si’ j7 ’Win OçTx6-5 ’SIDPFd3*WN 104’M ’D’1dH 69ZZ ’9(155

’s)oo-i’
pm pm

’S

OS 04

OS i’

pm

i’

US 6,281,230 Bi

27

tetrafluoroisoindoline through a sieve of0.2 mm mesh width and the two components are intimately mixed for 10 min-utes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 nun width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.
EXAMPLE 36

A0.2% injection or infusion solution can be prepared, for example, in the following manner

- 15

1.o-2-(2,6.doxo-3-methyI 5.0 g pipeiirite-3-yl).4,5,6,7-telxaftuoxo-
fsoiudoline

sodium cbtorids 2S g
phosphate buffer pH 7.4 300.0 g
demineralized water to 25(10.0 mL 20

1-Oxo-2-(2,6-dioxo-3.methylpiperldin-3-yl)-4,5,6,7-tetrafluoroisoindoline is dissolved in 100 mL of water and filtered through a microfilter. The buffer solution is added and the whole ismade up to 2500 mLwith water. To prepare dosage unit forms, portions of 1.0 or 23 mL each are introduced into glass ampoules (each containing respec-tively 2.0 or 5.0 mg of imide).
What is claimed is:

1. A method of treating inflammation, Inflammatory dis-ease or autoimmune disease in a mammal which comprises administering thereto an effective amount of a compound of the formula:

rnrk,A,-?.NK

28

9. The method according to claim 2 wherein said disease issepsis.
10. The method according to claim 2 wherein said disease
is lupus.
S U. The method according to claim 2 wherein said disease
is erythema nodosum leprosum.
12. The method according to claim 2 wherein said com-pound is administered orally or pareuterally.
13. The method according to claim 2 wherein said corn-
10 pound is administered in combination with a therapeutic agent
14. The method according to claim 2 in which said compound is administered in the form of a physiologically acceptable non-toxic acid addition salt
15. The method according to claim 2 in which said compound has the R-configuration.
16. The method according to claim 2 in which said compound has the S-configuration.
17. The method according to claim 2 in which said compound is administered in a single or multiple dosage regimen as a pharmaceutical composition containing from 1 to 100 mg. of said compound.
18. A method of treating an oncogenic or cancerous condition in a mammal which comprises administering 25 thereto an effective amount of a compound of the formula:

0 0

30

NH2 0

35 in which R6 is hydrogen or methyl.
19. The method according to claim iS in which said compound has the formula:

NH2

’ *zctt L,-L040
CH_ N-&ONH

in which R6 is hydrogen or methyl.
2. The method according to claim 1 in which said com-
pound has the formula: 45 H2

9 Ca N-&NH 0.

Nil2

3. The method according to claim 2 wherein said disease
is rheumatoid arthritis.

4. The method according to claim 2 wherein said disease
is osteoarthritis.

5. The method according to claim 2 wherein said disease is Inflammatory bowel disease.
6. The method according to claim S wherein said inflam-matory bowel disease is Crohn’s disease.
7. The method according to claim 5 wherein said inflam-matory bowel disease is ulcerative colitis.
S. The method according to claim 2 wherein said disease is an arthritic condition.

20. The method according to claim 19 wherein said compound is administered orally or parenterally.
so 21. The method according to claim 19 in which said
compound is administered in combination with a therapeutic agent

22. The method according to claim 21 wherein said therapeutic agent is a steroid, neoplastic agent or antibiotic.
ss 23. The method according to claim 19 in which said
compound is administered in the form of a physiologically acceptable non-toxic acid addition salt
24. The method according to claim 19 in which said compound has the R-conflguration.
60 25. The method according to claim 19 in which said
compound has the S-configuration.
26. The method according to claim 1.9 in which said compound is administered in a single or multiple dosage regimen as a pharmaceutical composition containing from I as to 100 mg. of said compound.

17a etlición

EDITOR1AI MEDICA cnainericaui

JUNIN S31 - BUNS AIRES
ROG0TA - CARACAS - MADRID - MEXICO - SANTIAGO LW CHILE - SˆO PAULO

1.

TWO 11

Mu* P

--

___

__ till JlJJUL1rL
P "4k 1 19 11’ 19% 15’ i.
4’ 1910 P4iOu. 11% 1? 4& 1961 1ff d1c,

. t.
1975
1910

E11Tt*1ALM*A PANALANA S;A.

ZW. MA1O AVAWO MAIIM)
Is £a. LUCIA MKCNA L* GUEMRO

MUL A1JTO TA
PMI&a4"IL1NaO*IacMmdra

F&-kAde Fiissà 7IL-j-L.’.
UuiTr!4

Uss,4e1USPXX. evucfdn dela

Oih MI iwv

N E dcvd o d.Iii4.kU ti& VSP) y* di kaIFu,alui (PIfl.

3006

-. I1LL

ISBN 95O*1$5-1 r1imo I) 91BI6X(rmo2)

IMPRESO EN LA ARØEWIINA

He ii d qa ipoi 1$ ley 11323.
Todoe.,sirseiiaos.

Este Lio rbp#i. Ł psies ...... 4 ’
nitnaumMi4ia-ep*no.

giel*ciosss S2 4--.. .
S.A.

C J917. JVIM1. A PANAM1CANA SA.

E dc 1n,lr

ci di I*v&i1!aPasmflcsa SA.
Sa k $3l Buisos Ales

OWNWAMOM

4I.L1riqtii.IritrI niliiLft WI1I11IiI’lt

1908 PREPARADO FARMACtjTICO Y SU ELABORACION

aspeft apJwa co acopaoe 4eSarWJlO
En estecapftulo heiiios de ocupan tie Iacvahia-
citi łcoqufmicaquc tiene lugaren la eMpdet-ftnmulactdn y adents pttaremos considezicidu a
algunos componentes especrales de Is fotmulwrdn
que pueden ieçnr discrecidu en su seleacidn

II’

Uag;’7Ai,;i9 L

ci6n. En eft evaIuid las

:DesCnll1ón

1912

too:

0

PREPARADO MRMAd!JTCO V SO BAMM16N

H& M. cmbk del tanmafiode lasparti-
enempopazaunasuspen

siónacuosade La formaidewindroga expen
nntaL

Æo \\24r

Or

0.1

’5,

LOt’ 20
DIAMtJROW

(Waie cap. 37 sobre AbsiclØn, accióny desffiw de
to *agas).
Cnociendo ci efecto do pamcxón y In constante do disociacæise puede eslimar ci sflio do absorci6n do dna nueva entidad qulmica Presunnendo que en ci cstóinagoelpHesl a3yenei mtestinodelgado5a8, e1amayotfade1oscasos1asdrasactdas(pIç3)se absoiberÆu maspmwen ci estoinago y In,nÆs bsz-casfpK 8)lo hathn mis pmonto to ci tracto mtestmnal, pero existen excqxioms porque algunas drops tkw ma - coeficientes do partictón ylo se monizan mimucho en toda la ganma de pH fismol6gzcos, aunquc siemxe dcspbcgan nun buenabiodmsponibmhdad ape-sar*esto

Polim a

El PORMO& csullafasccrisidisolidadeun

oisuodado qw se que pueden ocurw pot IoincmmsdosordcnamientosthstuitosdeLas moI6c1as doicnCsilidDbmciIaflüsma

3,

pue&serdedistintalformaenlospclirnóspemesto noes necesarroy, enefecto ciertos caminos deforms enlraæan La fminacidn de molØculas dismiss y, pot ende, no eonst*tuyen polunorfismo A Los isdmeros geomØtricos a Iautômcros, aunque scan interconverli-bies y lo bagan en fomia reversible, nose los puedo denomrnarpohmnomfos, sibren pueden comportarse do msnema conftaumente similar.

Uncrfleuo segwnpara clasificarcomopohmórflco a tin sistema es ci siguiente dos poinnorfos saran do estructuiacnsmalmadisnnmapero idØnftcos enci estado lfquido ode vapor Losisômerosdmimicos funden a lempemaluras dishntas, Jo niismo pie Jos pohmoifos, pew los productos fundidoa son do conmposicidn dis-tanta Con ci tiempo cada uno de CStOs produclos fimdidosseconviemteen unamezclaequthbradadelos dos isdunmos y sits composicmones son termodepen-iiintes. Esmdudablequeaigunoscasospublicadosdc pohnunfisma son isomensnros dinimicos porque Ins dos se compoztan do nmanera muy similar PoliznorfimoesIacapacidad demalquia elemer-

FORMA. I

SUSPENSION INIcJAL

PREFORMULACION 1913

FORMA I

SUSPENSION A LAS 6 HORAS

Fig. 764 Miceofot s lei cambio do ’amafto de los t.tistalcs en um suspnsion de la fonna: I de una droga

too compu sb para cnsta1iar en mªs dtUæ sistema
cnMthnocomo sucede con ci carbono, qucŁn ci
dramante cnstaiiza en cisistemacdbio yen ci grafito
en ci sisteina hexagonal En icueral, los distiutos

estabi-

lidad etc. MIN Sc alim&{ica. En icomctido inicial del pifonnuladores detcnnna general, Sc tendrIague poder obtener crista es e for sjJadmgague emi evivando PXiSti en micdLL]lfl.a masdistintas de nun dro ilKaraMlaspropie- foimacæstalina.Por lo general pnraptoducirJacsta-

dadde deseinpcæo de me compuesto. Para hater tizaci6n dc una fortna metaestable e siguen lQ!_jl- esti1l que cmom ci compoxtamiento de los poli- sjuinto procedimicntos:

morfos. Sc ban publicado muchas rescUas sobre el
tema do] polimorfismo. Ademas en In bibliograffa a) Fündase par completo ’inn peq’ieæa cantidad del corn-aparecen machas indicacinnes do b impartancia dat puesto en ’in po.taobjeto y obsŒrvese la solidificación cntre pojjismo en productos fa ne&icos., Los tra- polares cruzadus. Si luego de Ia eongelacidn cspornÆncase bajos dc Kubnert-Brandstauer y col., con esteroides, produce ’ma transforinación espoatlneao SI SC puede inducir barbittiricos y antihistanilnicos representaifan el std- ºsta mediate sembrado a raspado, es probable que LCiSt3II dio mâs intensivo qua Se ha hecho sobre poiimortismo Par to memos dos fonnas pohmóiiicas dcl compuesto. Es lmunc En lnuhte.i MIui, ’l F ’doseAt esencial prcvcrnrla nucicacidn de la fornia estable rnducicn-

do un supercnfriamicrno El superenfriarniento puede indu- Ia espectroscopia inframja, describicron d polirnor- time con ’ma mucstrapequciIa, manteniendoel trozo fundido fismo de esterrndcs, barbituncos v suIfonamIdas.JL seguedos iinos It) par encima del porno de fusion, esjhns de wefn nulariin cufrn inchur.rigrosoa_ dejaruio cuj&joien ci compucsto do lade sin sacudidas

trajpara dotrnuinnila JwPsenri de poIi’noafos an fisicas ames do obscrvarloy medianre enfriamierito rÆpidu

tii:)im4nn,ca.pn inIcde ex- bahdnteseuha mwft dcl cflmpuestosobie uma On

1914 PREPARAOO MR.UTICO ’i $tJ ELAB()RACION

Fg.76S en zee eff 0
tivo enfunción dcl iicmpo para on suspet-.
snacuasade la fornial de una dxogaepen

I I

1$ ii *1 76-6. 4iietndeJa

MINUTOS