

9900470-7



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| (51) International Patent Classification <sup>6</sup> :<br><b>C07D 233/44, A61K 31/415, C07D 233/88</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  | <b>A1</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | (11) International Publication Number: <b>WO 98/14432</b><br>(43) International Publication Date: <b>9 April 1998 (09.04.98)</b> |
| (21) International Application Number: <b>PCT/EP97/05322</b><br>(22) International Filing Date: <b>24 September 1997 (24.09.97)</b><br>(30) Priority Data: <b>96202749.6</b> ✓ <b>2 October 1996 (02.10.96)</b> ✓ <b>EP</b><br>(34) Countries for which the regional or international application was filed: <b>DE et al.</b><br>(71) Applicant (for all designated States except US): <b>JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE)</b><br>(72) Inventors; and<br>(75) Inventors/Applicants (for US only): <b>FREYNE, Eddy, Jean, Edgard [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). FERNANDEZ-GADEA, Francisco Javier [ES/ES]; Sagra No. 20, Cerro de las Perdices (Bargas), E-45593 Toledo (ES). ANDRES-GIL, José Ignacio [ES/ES]; Vesubiana No. 22, Getafe-Sector 3, E-28905 Madrid (ES).</b><br>(74) Agent: <b>QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  | (81) Designated States: <b>AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</b><br><br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |                                                                                                                                  |
| (54) Title: <b>PDE IV INHIBITING 2-CYANOIMINOIMIDAZOLE DERIVATIVES</b> ✓                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                  |
| <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                  |
| (57) Abstract<br><br><p>The present invention concerns 2-cyanoiminoimidazole derivatives having formula (I) the <i>N</i>-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein <math>R^1</math> and <math>R^2</math> each independently are hydrogen; <math>C_{1-6}</math>alkyl; difluoromethyl; trifluoromethyl; <math>C_{3-6}</math>cycloalkyl; a saturated 5-, 6- or 7-membered heterocycle containing one or two heteroatoms selected from oxygen, sulfur or nitrogen; indanyl; 6,7-dihydro-5<i>H</i>-cyclopentapyridinyl; bicyclo[2.2.1]-2-heptenyl; bicyclo[2.2.1]heptanyl; <math>C_{1-6}</math>alkylsulfonyl; arylsulfonyl; or substituted <math>C_{1-10}</math>alkyl; <math>R^3</math> is hydrogen, halo or <math>C_{1-6}</math>alkyloxy; <math>R^4</math> is hydrogen; halo; <math>C_{1-6}</math>alkyl; trifluoromethyl; <math>C_{3-6}</math>cycloalkyl; carboxyl; <math>C_{1-6}</math>alkyloxycarbonyl; <math>C_{3-6}</math>cycloalkylaminocarbonyl; aryl; Het<sup>1</sup>; or substituted <math>C_{1-6}</math>alkyl; or <math>R^4</math> is -O-<math>R^7</math> or -NH-<math>R^8</math>; <math>R^5</math> is hydrogen, halo, hydroxy, <math>C_{1-6}</math>alkyl or <math>C_{1-6}</math>alkyloxy; <math>R^6</math> is a hydrogen or <math>C_{1-6}</math>alkyl; or <math>R^4</math> and <math>R^6</math>, or <math>R^4</math> and <math>R^5</math> taken together may form a bivalent radical; -A-B- is -CR<sup>10</sup>-CR<sup>11</sup>- or -CHR<sup>10</sup>-CHR<sup>11</sup>-; L is hydrogen; <math>C_{1-6}</math>alkyl; <math>C_{1-6}</math>alkylcarbonyl; <math>C_{1-6}</math>alkyloxycarbonyl; substituted <math>C_{1-6}</math>alkyl; <math>C_{3-6}</math>alkenyl; substituted <math>C_{3-6}</math>alkenyl; piperidinyl; substituted piperidinyl; <math>C_{1-6}</math>alkylsulfonyl or arylsulfonyl; having PDE IV and cytokine inhibiting activity. The invention also relates to processes for preparing the compounds of formula (I) and pharmaceutical compositions thereof.</p> |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                  |