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COLOMBIA

ESCOBAR-URIBE ASOCIADOS
Intellectual Property

As: 2605/PCT.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-098325-00006-0000

Doctor

GIANCARLO MARCENARO JIMÉNEZ

Superintendente Delegado Para la Propiedad Industrial

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EXPEDIENTE: 03-098.325

ASUNTO: Solicitud de patente a nombre de
Novartis AG.

Estimado Doctor:

En mi calidad de apoderada de la sociedad solicitante de la patente de la referencia manifiesto a usted lo siguiente:

1. Mediante memorial radicado en ese despacho el 21 de diciembre de 2005, el cual no ha sido resuelto aún, solicité que se realizara el examen de patentabilidad.
2. En vista de que han transcurrido 2 años sin que se haya atendido dicha solicitud, ruego a usted se sirva dar las instrucciones del caso para que se proceda de inmediato a resolver este asunto.

Cordialmente,


JIMENA ESCOBAR URIBE
CC 39.779.452 de Usaquén.
T.P. 68228

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-098325

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **554** DE

FECHA **29 DE JULIO DE 2005** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **25 DE OCTUBRE DEL 2005**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

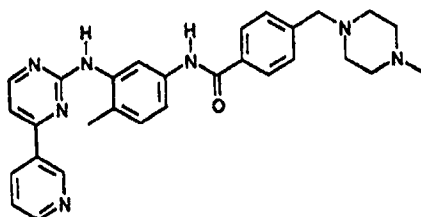
SI _____

NO__ _X_ _____

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data: 1764/97 18 July 1997 (18.07.97) CH			
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(54) Title: CRYSTAL MODIFICATION OF A N-PHENYL-2-PYRIMIDINEAMINE DERIVATIVE, PROCESSES FOR ITS MANUFACTURE AND ITS USE



(I)

(57) Abstract

The invention relates to a new crystalline form of the methanesulfonic acid-addition-salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl-benzamide of formula (I), which may be used for example for tumour therapy.

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On the basis of the described properties, the ~~methanesulfonic acid addition salt of a compound of formula I, such as especially the β -crystal form thereof, may be used not only as a tumour-inhibiting substance, for example in small cell lung cancer, but also as an agent to treat non-malignant proliferative disorders, such as atherosclerosis, thrombosis, psoriasis, scleroderma, and fibrosis, as well as for the protection of stem cells, for example to combat the haemotoxic effect of chemotherapeutic agents, such as 5-fluoruracil, and in asthma. It may especially be used for the treatment of diseases which respond to an inhibition of the PDGF receptor kinase.~~

In addition, the methanesulfonic acid addition salt of a compound of formula I, such as especially its β -crystal form C, ~~prevents the development of multidrug resistance in cancer therapy with other chemotherapeutic agents or abolishes a pre-existing resistance to other chemotherapeutic agents.~~ Also regardless of the effect described hereinbefore, the methanesulfonic acid addition salt of a compound of formula I, such as especially the β -crystal form thereof, ~~may be used to advantage in combination with other antitumor agents.~~

Also abl kinase, especially v-abl kinase, is inhibited by 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide and its methanesulfonate salt. The inhibition of v-abl tyrosine kinase is determined by the methods of N. Lydon *et al.*, *Oncogene Research* 5, 161-173 (1990) and J. F. Geissler *et al.*, *Cancer Research* 52, 4492-8 (1992). In those methods [Val⁵]-angiotensin II and [γ -³²P]-ATP are used as substrates. 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]benzamide here shows an IC₅₀ of 38 nM.

By analogy, the salt of a compound of formula I also inhibits BCR-abl kinase (see *Nature Medicine* 2, 561-566 (1996)) and is thus suitable for the treatment of BCR-abl-positive cancer and tumour diseases, such as leukaemias (especially chronic myeloid leukaemia and acute lymphoblastic leukaemia, where especially apoptotic mechanisms of action are found), and also shows effects on the subgroup of leukaemic stem cells as well as potential for the purification of these cells *in vitro* after removal of said cells (for example, bone marrow removal) and reimplantation of the cells once they have been cleared of cancer cells (for example, reimplantation of purified bone marrow cells).

In addition, the methanesulfonic acid addition salt of a compound of formula I shows useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as especially obliterative bronchiolitis (OB), i.e. a chronic rejection of allogenic lung transplants. In contrast to patients without OB, those with OB often show an elevated PDGF concentration in bronchoalveolar lavage fluids. If 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide methanesulfonate, especially in the β -crystal form, is administered to rats with tracheal allogenic transplants, for example in a dose of 50 mg/kg i.p., it can be shown after removal of 10 transplants per group after 10 and 30 days for morphometric analysis of possible epithelial lesions and occlusion of the airways, and investigation for immunohistochemical pathways of action that, although the methanesulfonic acid addition salt of a compound of formula I has no significant effect on epithelial necrosis or infiltration by inflammatory cells, it does markedly reduce fibroproliferation and occlusion of the lumen compared with controls. ~~Synergistic effects with other immunomodulatory or anti-inflammatory substances are possible, for example when used in combination with ciclosporin, rapamycin, or ascomycin, or immunosuppressant analogues thereof, for example ciclosporin A (CsA), ciclosporin G, FK-506, rapamycin, or comparable compounds; corticosteroids; cyclophosphamide; azathioprine; methotrexate; brequinar; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualin; immunosuppressant antibodies, especially monoclonal antibodies for leucocyte receptors, for example MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 or their ligands; or other immunomodulatory compounds, such as CTLA4Ig.~~ If CsA (1 mg/kg s.c.), for example, is combined with the acid addition salt of formula I (50 mg/kg), synergism may be observed.

The methanesulfonic acid addition salt of a compound of formula I is also effective in diseases associated with vascular smooth-muscle cell migration and proliferation (where PDGF and PDGF-R often also play a role), such as restenosis and atherosclerosis. These effects and the consequences thereof for the proliferation or migration of vascular smooth-muscle cells *in vitro* and *in vivo* can be demonstrated by administration of the methanesulfonic acid addition salt of a compound of formula I and also by investigating its effect on the thickening of the vascular intima following mechanical injury *in vivo*.