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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
WO 2006/100310 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 31/00* (2006.01)
A61K 31/495 (2006.01)

(21) International Application Number:
PCT/EP2006/061070

(22) International Filing Date: 27 March 2006 (27.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/665,151 25 March 2005 (25.03.2005) US
60/680,405 12 May 2005 (12.05.2005) US

(71) Applicant *(for all designated States except US)*: **TIBOTEC PHARMACEUTICALS LTD** [IE/IE]; Little Island, Co Cork (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SIMMEN, Kenneth Alan** [GB/BE]; Boterbloemenlaan 35, B-3080 Tervuren (BE). **CHAKRAVARTY, Sarvajit** [US/US]; 1888 Miramonte Avenue, California, CA 94040 (US). **HART, Barry** [US/US]; 920 Palo Alto Avenue, CA 94301 (US). **SURLERAUX, Dominique Louis Nestor Ghislain**; -. **LIN, Tse-I**; -. **LENZ, Oliver**; -. **RABOISSON, Pierre, Jean-Marie, Bernard**; -.

(74) Agent: **WANTE, Dirk**; Tibotec-Virco Comm. VA, Generaal De Wittelaan L 11b 3, B-2800 Mechelen (BE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

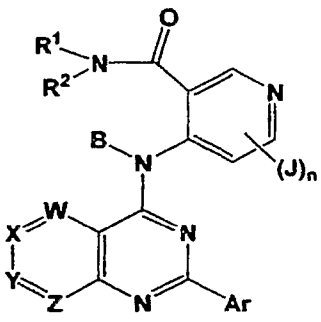
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** HETEROBICYLIC INHIBITORS OF HCV



(I)

(57) **Abstract:** Fused bicyclic pyrimidine compounds having an amide-substituted pyridylamine group at C-4 of the pyrimidine of formula (I) ring are useftul in the treatment of conditions associated with HCV.

WO 2006/100310 A1

HETEROBICYLIC INHIBITORS OF HVC

Field of the Invention

The invention relates to methods of treating disorders associated with hepatitis C infection. More specifically, it concerns certain fused bicyclic pyrimidine compounds that have an amide-substituted 4-pyridylamine group on the pyrimidine ring that are useful in these methods.

Background Art

Transforming growth factor-beta (TGFβ) denotes a superfamily of proteins that includes, for example, TGFβ1, TGFβ2, and TGFβ3, which are pleiotropic modulators of cell growth and differentiation, embryonic and bone development, extracellular matrix formation, hematopoiesis, and immune and inflammatory responses (Roberts and Sporn Handbook of Experimental Pharmacology (1990) 95:419-58; Massague, *et al., Ann. Rev. Cell. Biol.* (1990) 6:597-646). Other members of this superfamily include activin, inhibin, bone morphogenic protein, and Mullerian inhibiting substance. The members of the TGFβ family initiate intracellular signaling pathways leading ultimately to the expression of genes that regulate the cell cycle, control proliferative responses, or relate to extracellular matrix proteins that mediate outside-in cell signaling, cell adhesion, migration and intercellular communication.

Therefore, inhibitors of the TGFβ intracellular signaling pathway are useful treatments for fibroproliferative diseases. Specifically, fibroproliferative diseases include kidney disorders associated with unregulated TGFβ activity and excessive fibrosis including glomerulonephritis (GN), such as mesangial proliferative GN, immune GN, and crescentic GN. Other renal conditions include diabetic nephropathy, renal interstitial fibrosis, renal fibrosis in transplant patients receiving cyclosporin, and HIV-associated nephropathy. Collagen vascular disorders include progressive systemic sclerosis, polymyositis, scleroderma, dermatomyositis, eosinophilic fascitis, morphea, or those associated with the occurrence of Raynaud's syndrome. Lung fibroses resulting from excessive TGFβ activity include adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and interstitial pulmonary fibrosis often associated with autoimmune disorders, such as systemic lupus erythematosus and scleroderma, chemical contact, or allergies. Another autoimmune disorder associated with fibroproliferative characteristics is rheumatoid arthritis. Fibroproliferative conditions can be associated with surgical eye procedures. Such procedures include retinal reattachment surgery accompanying proliferative

vitreoretinopathy, cataract extraction with intraocular lens implantation, and post glaucoma drainage surgery.

In addition, members of the TGFβ family are associated with the progression of various cancers. M.P. de Caestecker, E. Piek, and A.B. Roberts, *J. National Cancer Inst.*, 92(17), 1388-1402 (2000). For example, it has been found that TGFβ1 inhibits the formation of tumors, probably by inhibition of the proliferation of nontransformed cells. However, once a tumor forms, TGFβ1 promotes the growth of the tumor. N. Dumont and C.L. Arteaga, *Breast Cancer Res.*, Vol. 2, 125-132 (2000). Thus inhibitors of the TGFβ pathway are also useful for the treatment of many forms of cancer, such as lung cancer, skin cancer, and colorectal cancer. In particular, they are useful to treat cancers of the breast, pancreas, and brain, including glioma.

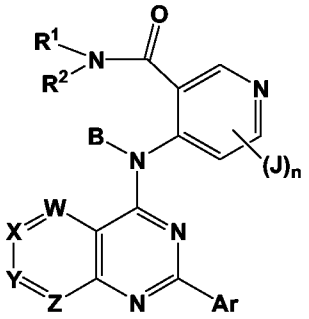
The compounds of the invention herein are derivatives of pyrimidine having an additional ring fused onto the pyrimidine. PCT publication WO01/47921 describes pyrimidine and triazine compounds that are inhibitors of kinase activities associated with various inflammatory conditions, as opposed to the treatment of fibroproliferative disorders described herein. The above mentioned PCT publication describes the use of the disclosed compounds only for treatment of the inflammatory aspects of certain autoimmune diseases. Further, the compounds described differ from those described herein by virtue of the substitutions required on the pyrimidine nucleus; among other distinctions, the compounds disclosed in the PCT publication do not include phenyl bound directly to the pyrimidine ring.

Related compounds, some of which have the 4-pyridylamine group at C-4 on the pyrimidine, are disclosed in two published U.S. Patent Applications, publications no. US 2004-0132159-A1 and US 2005/0004143-A1. Those applications, however, disclose a preference for certain electron-donating substituents on the pyridine ring of the 4-pyridylamine group, including alkyl, amine and alkoxy groups, and do not disclose a preferred position for substituents. The present invention provides compounds specifically including a 4-pyridylamine containing an essential carboxamide group attached at position 3 on the pyridine ring.

U.S. Patent No. 6,476,031 also discloses compounds containing a quinazoline ring, which cam be a fused bicyclic derivative of a pyrimidine; it includes compounds where the quinazoline ring is linked to an aryl group at C-4 of the quinazoline. The compounds are reported to act at the TGFβ site, and the compounds can include a 4-pyridylamine group as the aryl group linked to the quinazoline at C-4. However, that patent only discloses that a quinazoline compound linked to a pyridyl that is unsubstituted: it does not disclose any compounds with a 4-pyridyl that includes an amide substituent such as the ones at the 3-position of the 4-pyridyl group in the compounds of the present invention.

Disclosure of the Invention

The invention is directed to methods, compositions, and novel compounds useful in treating conditions that are characterized by excessive TGFβ activity. These conditions are, most prominently, fibroproliferative diseases, such as conditions associated with hepatitis C virus infection, and certain cancers. However, the conditions for which the compounds and methods are useful include any medical condition characterized by an undesirably high level of TGFβ activity. The compounds of the invention have been found to inhibit TGFβ and are thus useful in treating diseases mediated by the activity of this family of factors. The compounds of the invention are of the formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 represents H or OH, or an optionally substituted alkyl, alkoxy, heteroalkyl, amino, acyl, heteroacyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl group;

R^2 represents H or optionally substituted alkyl, heteroalkyl, acyl, heteroacyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;

B represents H or a C1-C8 acyl group that may be substituted or unsubstituted;

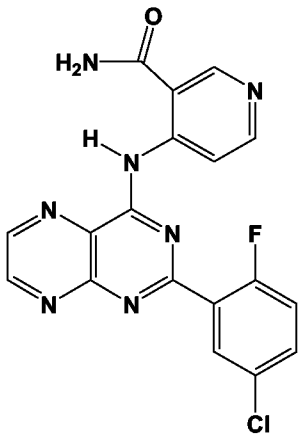
each of W, X, Y and Z is independently C-H, C-J or N, provided that not more than two of W, X, Y and Z represent N;

Ar represents an optionally substituted phenyl ring;

each J independently represents halo, OH, SH, or optionally substituted alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, acyl, heteroacyl, or heteroaryl, or NR^1R^2, NO_2, CN, CF_3, COOR, $CONR_2$, or SO_2R, wherein each R is independently H or an optionally substituted alkyl, alkenyl, alkynyl, acyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroacyl or heteroaryl group,

R^1 and R^2 of any NR^1R^2 can cyclize to form a 3-8 membered ring that can be saturated, unsaturated, or aromatic, and that contains 1-3 heteroatoms selected from N, O and S as ring members, and is optionally substituted; and

n is 0-3;



provided the compound is not 4-[2-(5-chloro-2-fluorophenyl)-pteridin-4-ylamino]-nicotinamide:

The invention is also directed to pharmaceutical compositions containing one or more compounds of formula (I) or their pharmaceutically acceptable salts, or prodrug forms thereof, as active ingredients and to methods of treating conditions characterized by an excessive level of TGFβ activity, particularly fibroproliferative conditions, using compounds of formula (I) or compositions containing such compounds.

Modes of Carrying Out the Invention

The compounds of formula (I) are useful in treating conditions which are characterized by an excessive level of TGFβ activity. As used herein, "TGFβ" refers to the superfamily which includes TGFβ1, TGFβ2, and TGFβ3 as well as other members of the family known or which become known in the art such as inhibin, bone morphogenic protein, and the like. One or more of these family members may be more active than desired in the conditions which the compounds of the invention are designed to ameliorate or prevent.

Conditions "characterized by an excessive level of TGFβ activity" include those wherein TGFβ synthesis is stimulated so that TGFβ is present in enhanced amount, and those wherein TGFβ latent protein is undesirably activated or converted to active TGFβ protein, and those wherein TGFβ receptors are upregulated, and those wherein the TGFβ protein shows enhanced binding to cells or extracellular matrix in the location of the disease. Thus, in each case, "excessive level of TGFβ activity" refers to any condition wherein the activity of TGFβ is undesirably high, regardless of the cause and regardless of whether the actual amount or activity of TGFβ present is within a 'normal' range.

Compounds of the present invention moreover show antiviral activity against the hepatitis C virus.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.