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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 April 2004 (22.04.2004)

PCT

(10) International Publication Number
WO 2004/032925 A1

(51) International Patent Classification[7]: A61K 31/44, 31/137, 31/704, 31/335, 31/4745, A61P 35/00

(21) International Application Number: PCT/EP2003/011271

(22) International Filing Date: 10 October 2003 (10.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/417,915 11 October 2002 (11.10.2002) US

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(71) Applicant *(for all designated States except US)*: **ST. JUDES CHILDREN'S RESEARCH HOSPITAL** [US/US]; 332 N. Lauderdale St., Memphis, TN 38103 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOUGHTON, Peter, J.** [US/US]; 158 Harbor Town Boulevard, Memphis, TN 38103 (US). **TRAXLER, Peter** [CH/CH]; Bündtenring 3, CH-4124 Schönenbuch (CH).

(74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

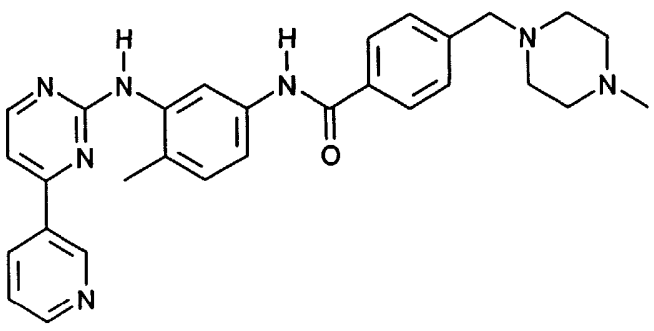
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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:** USE OF IMATINIB (GLIVEC, STI-571) TO INHIBIT BREAST CANCER RESISTANCE PROTEIN (BCRP)-MEDIATED RESISTANCE TO THERAPEUTIC AGENTS



(I)

(57) **Abstract:** The present invention relates to the use of imatinib of the following formula (I) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a cancer that expresses breast cancer resistant protein (BCRP) in a human subject in need of such a treatment.

WO 2004/032925 A1

USE OF IMATINIB (GLIVEC, STI-571) TO INHIBIT BREAST CANCER RESISTANCE PROTEIN (BCRP)-MEDIATED RESISTANCE TO THERAPEUTIC AGENTS

agents.

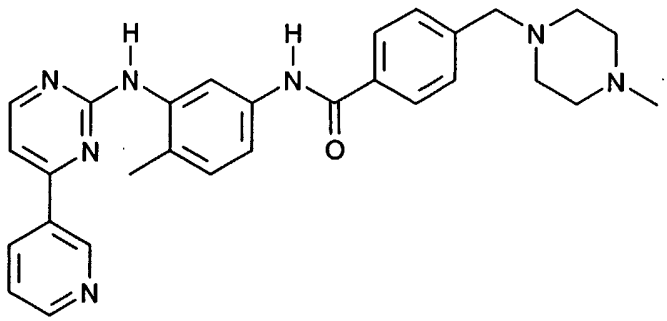
The U.S. Government has a paid-up license in this invention and the right in limited circumstances to require the owner to license others on reasonable terms as provided for by the terms of Grant No. CA23099 awarded by the National Institute of Health.

Summary

This invention relates to a method of utilizing imatinib to inhibit BCRP and BCRP-mediated resistance to therapeutic agents in the treatment of cancer. The invention further relates to a method of treating cancers that demonstrate BCRP-mediated resistance to one or more therapeutic agents wherein imatinib is co-administered with the therapeutic agent.

Background

Imatinib is the generic name [International Non-proprietary Name] for the compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the following formula I



(I),

which has been approved, as its mesylate salt, for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors. Imatinib, its manufacture, its pharmaceutically acceptable salts, e.g. acid addition salts, and its protein kinase inhibiting properties are described in U.S. Patent No. 5,521,184, which is hereby incorporated by reference. In the context of the present patent application, the term "imatinib" is meant to designated 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide in its free form.

It has to be explained that otherwise the wording "imatinib" designates 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide free base in the US only and that "imatinib" for the rest of the world corresponds to 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide mesylate.

The preparation of imatinib and the use thereof, especially as an anti-tumor agent, are described in Example 21 of European patent application EP-A-0 564 409, which is hereby incorporated by reference.

The monomethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide (hereinafter "imatinib mesylate") and a preferred crystal form thereof, e.g. the β-crystal form, are described in PCT patent application WO99/03854, hereby incorporated by reference. Possible pharmaceutical preparations, containing an effective amount of imatinib, e.g. imatinib mesylate, are also described in WO99/03854 and are well known in the prior art.

The present invention is derived from the discovery that imatinib also inhibits breast cancer resistance protein. Breast cancer resistance protein (BCRP) is a member of the ATP-binding cassette (ABC) transporter protein family. Such transporter proteins cause several anticancer drugs to efflux from cancer cells reducing the concentrations of the anticancer agent in these cells and thus reducing or eliminating the desirable anticancer effects of the agent in these resistant cancer cells. BCRP over-expression has been associated with resistance to anticancer agents such as doxorubicin, mitoxanthrone and especially camptothecin analogues and derivatives. In addition, the oral absorption of several therapeutic agents is inhibited by the BCRP ATP pump and inhibition of BCRP with imatinib provides a mechanism to improve the oral absorption of such therapeutic agents.

Detailed Description

In a first aspect, the present invention relates to the use of imatinib, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament, to inhibit breast cancer resistance protein.

One aspect of the present invention is a method of inhibiting breast cancer resistance protein in a cell, which comprises placing the cell in contact with an effective amount of imatinib, or a

pharmaceutically acceptable salt thereof. In accordance with this aspect, the cell is preferably a cancer cell that expresses BCRP.

The present invention further relates to a method of treating cancer that expresses BCRP in a human subject, which comprises administering a therapeutically effective amount of the anticancer agent and an effective BCRP-inhibiting amount of imatinib, or a pharmaceutically acceptable salt thereof, to the subject.

The present invention also relates to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a cancer expressing the breast cancer resistant protein (BCRP).

The present invention further relates to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a cancer over-expressing the breast cancer resistant protein (BCRP).

The present invention also relates to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for preventing or reversing resistance to an anticancer agent in a human subject having a cancer that expresses BCRP.

The cancer to be treated according to the present invention can be, but is not limited to a cancer expressing the BCRP protein, a cancer over-expressing the BCRP protein, a cancer resistant to an anti-cancer agent which anti-cancer agent resistance is mediated by the expression of the BCRP protein, a cancer resistant to an anti-cancer agent which anti-cancer agent resistance is mediated by the over-expression of the BCRP protein, said cancer expressing or over-expressing BCRP can be a colon cancer, a breast cancer, a liver cancer, acute myeloid leukemia (AML), a gastric cancer, an ovarian cancer, a lung cancer, e.g. non-small cell lung cancer, a myeloma, e.g. human multiple myeloma, a fibrosarcoma.

The term "resistant to an anticancer agent" as used herein defines a reduction or loss of therapeutic effectiveness of an anticancer agent in the treatment of a cancer condition. The resistance of a cancer to an anticancer agent can be due to BCRP, e.g. to expression or over-expression of BCRP. Even low expression of BCRP can be responsible for the cancer resistance to an anticancer agent.

By "over-expressing" is meant that the level of expression of the breast cancer resistance protein or of its mRNA is higher, e.g. 1.5, 2, 4, 6, 10, 20 or more times higher, than the corresponding level of the BCRP protein in healthy patient or in corresponding normal tissues not harboring cancer or in cancer not resistant to anticancer agent.

The present invention relates to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to improve the absorption of an orally-administered anticancer agent.

The present invention relates to the use of imatinib of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for improving the absorption of an orally-administered anticancer agent by inhibiting BCRP in a patient having a cancer.

Because BCRP is involved in resistance to certain anticancer agents, another aspect of the present invention relates to a method of preventing or reversing resistance to an anticancer agent in a human subject having a cancer that expresses BCRP, which comprises administering a therapeutically effective amount of the anticancer agent and an effective BCRP-inhibiting amount of imatinib, or a pharmaceutically acceptable salt thereof, to the subject.

According to the present invention, a therapeutically effective amount of the anticancer agent, e.g. anthracycline cytotoxic agents, campothecin-derived topoisomerase I inhibitors, is administered in conjunction with imatinib. Therapeutically effective amounts of anticancer agents are known, or can be determined without undue experimentation, by one of skill in the art.

An effective BCRP inhibiting concentration of imatinib is generally achieved in a human subject by administering 100 mg to 1000 mg, e.g. 200 mg to 800 mg, e.g. 400 mg to 600 mg, of imatinib base daily to the subject. Imatinib is generally administered as a pharmaceutically acceptable salt, particularly as imatinib mesylate.

Whether the cancer expresses BCRP is determined by methods known in the art, such as those described in Kawabata *et al., Biochemical and Biophysical Research Communications*, **280**, 1216-1223 (2001) and Erlichman *et al., Cancer Research*, **61**, 379-748 (2001), both publications incorporated hereby by reference.

Generally, anticancer agents that are affected by BCRP-mediated resistance include the anthracycline cytotoxic agents and campothecin-derived topoisomerase I inhibitors. The anthracycline cytotoxic agents that are known to be affected by BCRP-mediated resistance include mitoxanthrone and doxorubicin. The camptothecin-derived topoisomerase I inhibitors include analogues and derivatives of camptothecin and homocampthecin, such as, topotecan, irinotecan also referred as CTP-11, and its metabolite 7-ethyl-10-hydroxycamptothecin also referred as SN-38, 9-amino-campthThecin, 9-nitrocamptothecin, lurtotecan, diflomotecan, BAY38-3441, silatecans, such as 7-(2-trimethylsilyl)ethylcamptothecin also referred as BNP1350 and 10-hydroxy-7-t-butyldimethylsilylcamptothecin also referred as DB67, and various polymer-conjugated camptothecin derivatives, such as CT2016, DE310, T-0128 and PROTHECAN. Topotecan, irinotecan, mitoxanthrone and doxorubicin are particularly useful as the anticancer agent used according to the present invention.

The anthracycline cytotoxic agents and the campothecin-derived topoisomerase I inhibitors can be administered, e.g. in the form as they are marketed. Irinotecan can be administered , e.g. in the form as it is marketed, e.g. under the trademark CAMPTOSTAR™. Topotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark HYCAMTIN™.

In one embodiment, the present invention pertains to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to improve the absorption of an orally-administered anticancer agent selected from the group comprising the anthracycline cytotoxic agents and the campothecin-derived topoisomerase I inhibitors.

In another embodiment, the present invention pertains to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to improve the absorption of an orally-administered anticancer agent selected from the group comprising mitoxanthrone, doxorubicin, topotecan, irinotecan also referred as CTP-11, 7-ethyl-10-hydroxycamptothecin also referred as SN-38, 9-amino-campthThecin, 9-nitrocamptothecin, lurtotecan, diflomotecan, BAY38-3441, silatecans, such as 7-(2-trimethylsilyl)ethylcamptothecin also referred as BNP1350 and 10-hydroxy-7-t-butyldimethylsilylcamptothecin also referred as DB67, CT2016, DE310, T-0128 and PROTHECAN.

The present invention pertains to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to improve the absorption of an orally-administered anticancer

agent selected from the group comprising mitoxanthrone, doxorubicin, topotecan, irinotecan and SN-38.

In another embodiment, the present invention pertains to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to prevent or reverse resistance to an orally-administered anticancer agent selected from the group comprising the anthracycline cytotoxic agents and the campothecin-derived topoisomerase I inhibitors, in a cancer that expresses BCRP in a human subject having said cancer.

In another embodiment, the present invention pertains to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to prevent or reverse resistance to an orally-administered anticancer agent selected from the group comprising mitoxanthrone, doxorubicin, topotecan, irinotecan also referred as CTP-11, 7-ethyl-10-hydroxycamptothecin also referred as SN-38, 9-amino-campthothecin, 9-nitrocamptothecin, lurtotecan, diflomotecan, BAY38-3441, silatecans, such as 7-(2-trimethylsilyl)ethylcamptothecin also referred as BNP1350 and 10-hydroxy-7-t-butyldimethylsilylcamptothecin also referred as DB67, CT2016, DE310, T-0128 and PROTHECAN.

The present invention pertains to the use of imatinib or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to prevent or reverse resistance to an orally-administered anticancer agent selected from the group comprising mitoxanthrone, doxorubicin, topotecan, irinotecan and SN-38.

Because BCRP is expressed in normal human intestinal villi, the BCRP ATP pump also has an adverse effect on the oral bioavailability of the anticancer agents and its inhibition improves the oral bioavailability of the agent.

Another aspect of this invention relates to a method of improving the absorption of an orally-administered anticancer agent, which comprises administering the anticancer agent and an effective BCRP-inhibiting amount of imatinib, or a pharmaceutically acceptable salt thereof, to the subject.

Example1: Imatinib mesylate is a potent inhibitor of BCRP and reverses topotecan resistance *in vitro.*

Imatinib is assayed for its ability to selectively reverse BCRP-mediated resistance. Saos2 human osteosarcoma cells with no detectable expression of BCRP or P-glycoprotein are engineered to express similar levels of BCRP (Saos2BCRP#4), or non-functional mutant with a mutation in the Walker ATP binding motif (Saos2BCRPMut#10). Saos2 cells transfected with pcDNA3 vector are used as an additional control. The IC_{50} concentrations of topotecan are 9 nM, 16 nM and 167 nM for Saos2Mut#10, Saos2pcDNA and Saos2BCRP#4 respectively. Imatinib selectively sensitized Saos2BCRP#4 cells, almost completely reversing topotecan resistance at a concentration of 1μM. To define the concentration of imatinib required to reverse topotecan resistance by 50%, Saos2BCRP#4 cells are exposed to topotecan for 5 days in the presence of increasing concentrations of imatinib (10-1000 nM). 50% reversal of BCRP resistance is obtained at around 170 nM. Imatinib is an potent inhibitor of BCRP-mediated resistance to topotecan. As BCRP may inhibit the absorption of orally administered topotecan and irinotecan.

Table 1 discloses the effect of imatinib on the IC_{50} for topotecan in three human cancer cell lines. The data demonstrates a synergistic effect between topotecan and imatinib and complete reversal of BCRP-mediated resistance to topotecan in the BCRP expressing SaosBCRP#4 cell line.

	Saos2 pcDNA#3#2	Saos2 BCRP#4	Saos2 BCRPMUT#10
topotecan alone	20 nM	254 nM	9 nM
1μM imatinib + topotecan	23 nM	35 nM	18 nM
3 μM imatinib + topetecan	20 nM	24 nM	9.9 nM
5 μM Imatinib + topotecan	23 nM	22 nM	15 nM
imatinib alone	7.3 mM	9.6 mM	9.5 nM

Table 1: The effect of imatinib on the IC_{50} for topotecan in three human cancer cell lines: a vector control Saos2pcDNA#3#2, a cell line expressing functional BCRP Saos2BCRP#4, and a cell line equivalently expressing a non-functional mutant BCRP, Saos2BCRPMUT#10. Results show the concentration of topotecan causing 50% growth inhibition in the absence (0) or presence of imatinib at the concentrations shown.

Example 2: Reversal of BCRP-mediated resistance to SN-38 by imatinib

	IC_{50} nM		
Imatinib in µM	Saos2BCRP#4	Saos2pcDNA#3#2	Saos2MUT#10
0	> 100	2.9	1.7
0.1	82	2.7	1.7
0.3	29	2.7	1.6
1.0	14	3.3	1.7
3.0	7	3.7	1.6

Table 2: Reversal of BCRP-mediated resistance to SN-38 by imatinib. BCRP#4 are Saos2 cells expressing functional BCRP, pcDNA are Saos2 cells with a control vector, MUT#10 are Saos2 cells expressing non-functional BCRP. Results show the concentration of SN-38 causing 50% growth inhibition in the absence (0) or presence of imatinib at the concentrations shown.

Example 3: Effect of imatinib on irinotecan Pharmacokinetics in Mice

The experiment is performed on non-tumored mice after a single oral administration of imatinib of 50 mg/kg and a single oral administration of irinotecan (IRN) of 10 mg/kg.

	Without imatinib	With imatinib
IRN Cl (L/h/m2)	16.7±3.3	11.2±4.0
Ka (hr-1)	1.65±0.3	1.6±0.2
F	0.09±0.02	0.23±0.02
SN-38 (ng/hr/ml)	263	775

Table 3: Effect of imatinib on irinotecan Pharmacokinetics in Mice. Mice are dosed orally with CPT-11 alone or immediately after a single oral dose of Imatinib (50 mg/kg). Plasma levels of irinotecan (IRN) and SN-38, the active metabolite, are determined.

Those results suggest that administration of imatinib enhances oral bioavailability of irinotecan and increases exposure to SN-38 by 3 fold. Ci: rate of clearance; Ka: absorption rate; F: calculated bioavailability (relative to intravenous dosing).

Example 4: Capsules with 4-[(4-methyl-1-piperazin-1-ylmethyl)-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide mesylate, β-crystal form.

Capsules containing 119.5 mg of imatinib mesylate corresponding to 100 mg of imatinib free base as active substance are prepared in the following composition:

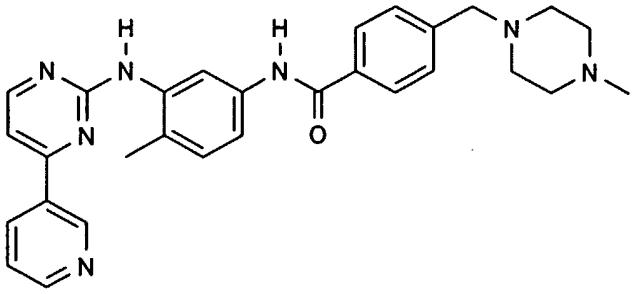
Composition

Imatinib mesylate	119.5 mg
Cellulose MK GR	92 mg
Crospovidone XL	15 mg
Aerosil 200	2 mg
Magnesium stearate	1.5 mg
	230 mg

The capsules are prepared by mixing the components and filling the mixture into hard gelatin capsules, size 1.

Claims:

1. Use of imatinib of the formula I



(I)

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of cancer expressing breast cancer resistance protein (BCRP).

2. Use of imatinib of the formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a cancer over-expressing breast cancer resistance protein (BCRP).

3. Use of imatinib of the formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting breast cancer resistance protein (BCRP).

4. Use of imatinib of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to prevent or reverse resistance to an anticancer agent of a cancer that expresses BCRP in a human subject having said cancer.

5. Use of imatinib of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for improving the absorption of an orally-administered anticancer agent.

6. Use of imatinib of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for improving the absorption of an orally-administered anticancer agent by inhibiting BCRP in a patient having a cancer.

7. Use according to claim 4, 5 or 6 wherein the anticancer agent is an anthracycline cytotoxic agent or a campothecin-derived topoisomerase I inhibitor.

8. Use according to claim 7 wherein the anticancer agent is selected from the group comprising mitoxanthrone, doxorubicin, topotecan, irinotecan also referred as CTP-11, 7-ethyl-10-hydroxycamptothecin also referred as SN-38, 9-amino-campthThecin, 9-nitrocamptothecin, lurtotecan, diflomotecan, BAY38-3441, 7-(2-trimethylsilyl)ethylcamptothecin also referred as BNP1350, 10-hydroxy-7-t-butyldimethylsilylcamptothecin also referred as DB67, CT2016, DE310, T-0128 and PROTHECAN.

9. Use according to claim 8 wherein the anticancer agent is selected from the group comprising of topotecan, irinotecan, SN-38, mitoxanthrone and doxorubicin.

10. Use according to any one of claims 1 to 6 wherein imatinib is in the form of the mesylate salt.

11. Method of treating a cancer that expresses BCRP in a human subject, which comprises administering a therapeutically effective amount of an anticancer agent and an effective BCRP-inhibiting amount of imatinib or a pharmaceutically acceptable salt thereof.

12. Use according any one of claims 1 to 4 and 6 wherein the cancer is selected from the group comprising colon cancer, breast cancer, liver cancer, ovarian cancer, fibrosarcoma, myeloma, acute myeloid leukemia (AML), gastric cancer and non-small cell lung cancer

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/EP 03/11271

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/137 A61K31/704 A61K31/335 A61K31/4745
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FAGIN J A: "Perspective: Lessons learned from molecular genetic studies of thyroid cancer: Insights into pathogenesis and tumor-specific therapeutic targets" ENDOCRINOLOGY, BALTIMORE, MD, US, vol. 143, no. 6, June 2002 (2002-06), pages 2025-2028, XP002251224 ISSN: 0013-7227 page 2026, right-hand column, paragraph 2 --- -/--	1,11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2004	26/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	LEVITZKI A: "Tyrosine kinases as targets for cancer therapy" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, September 2002 (2002-09), pages S11-S18, XP004402495 ISSN: 0959-8049 page S14, right-hand column figure 3 ---	1,2,11
X	SELLE B ET AL: "ABL-specific tyrosine kinase inhibitor imatinib as salvage therapy in a child with Philadelphia chromosome-positive acute mixed lineage leukemia (AMLL)" LEUKEMIA (BASINGSTOKE), vol. 16, no. 7, July 2002 (2002-07), pages 1393-1395, XP002268892 ISSN: 0887-6924 page 1394, right-hand column, last paragraph ---	1,2,11
X	CAPDEVILLE R ET AL: "Imatinib: the first 3 years" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, September 2002 (2002-09), pages S77-S82, XP004402504 ISSN: 0959-8049	1,2,10, 11
Y	page S79, right-hand column, paragraph 2 page D80, left-hand column, paragraph 2 ---	1-11
X	KANO Y ET AL: "IN VITRO CYTOTOXIC EFFECTS OF A TYROSINE KINASE INHIBITOR STI571 IN COMBINATION WITH COMMONLY USED ANTILEUKEMIC AGENTS" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 97, no. 7, 1 April 2001 (2001-04-01), pages 1999-2007, XP001035243 ISSN: 0006-4971	1,2,10, 11
Y	page 1999, abstract ---	1-11
X	TOPALY J ET AL: "SYNERGISTIC ACTIVITY OF STI571 WITH CHEMOTHERAPEUTIC DRUGS AND IRRADIATION" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 96, no. 11, PART 1, 1 December 2000 (2000-12-01), page 736A XP009010656 ISSN: 0006-4971 abstract ---	1-3,10, 11

-/--

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PC1/EP 03/11271

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 564 409 A (CIBA GEIGY AG) 6 October 1993 (1993-10-06) page 5, line 36 - line 38	4
Y	US 5 521 184 A (ZIMMERMANN JUERG) 28 May 1996 (1996-05-28) column 7, line 44 - line 45 column 8, line 6 - line 7 column 9, line 1 - line 4	4

INTERNATIONAL SEARCH REPORT

onal application No.
CT/EP 03/11271

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Present claims 4 - 6 and 11 relate to a compound defined by reference to a desirable characteristic or property, namely "anticancer agent". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the following compounds: mitoxanthrone, doxorubicin, topotecan, irinotecan, 7-ethyl-10-hydroxycamptothecin, 9-amino-camptothecin, 9-nitrocamptothecin, lurtotecan, diflomotecan, BAY38-3441, BNP1350, DB67, CT2016, DE310, T-0128 and prothecan (page 5 of the description).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/EP 03/11271

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0564409 A	06-10-1993	AT 188964 T	15-02-2000
		AU 3569493 A	07-10-1993
		BR 1100739 A3	06-06-2000
		CA 2093203 A1	04-10-1993
		CN 1077713 A ,B	27-10-1993
		CY 2229 A	18-04-2003
		CZ 9300560 A3	16-02-1994
		DE 59309931 D1	24-02-2000
		DK 564409 T3	19-06-2000
		EP 0564409 A1	06-10-1993
		ES 2142857 T3	01-05-2000
		FI 931458 A	04-10-1993
		GR 3032927 T3	31-07-2000
		HU 64050 A2	29-11-1993
		IL 105264 A	11-04-1999
		JP 2706682 B2	28-01-1998
		JP 6087834 A	29-03-1994
		KR 261366 B1	01-08-2000
		LU 90908 A9	30-04-2003
		MX 9301929 A1	29-07-1994
		NO 931283 A	04-10-1993
		NZ 247299 A	26-07-1995
		PT 564409 T	30-06-2000
		RU 2125992 C1	10-02-1999
		SG 43859 A1	14-11-1997
		SK 28093 A3	06-04-1994
		US 5521184 A	28-05-1996
		ZA 9302397 A	04-10-1993
US 5521184 A	28-05-1996	AT 188964 T	15-02-2000
		AU 3569493 A	07-10-1993
		BR 1100739 A3	06-06-2000
		CA 2093203 A1	04-10-1993
		CN 1077713 A ,B	27-10-1993
		CY 2229 A	18-04-2003
		CZ 9300560 A3	16-02-1994
		DE 59309931 D1	24-02-2000
		DK 564409 T3	19-06-2000
		EP 0564409 A1	06-10-1993
		ES 2142857 T3	01-05-2000
		FI 931458 A	04-10-1993
		GR 3032927 T3	31-07-2000
		HU 64050 A2	29-11-1993
		IL 105264 A	11-04-1999
		JP 2706682 B2	28-01-1998
		JP 6087834 A	29-03-1994
		KR 261366 B1	01-08-2000
		LU 90908 A9	30-04-2003
		MX 9301929 A1	29-07-1994
		NO 931283 A	04-10-1993
		NZ 247299 A	26-07-1995
		PT 564409 T	30-06-2000
		RU 2125992 C1	10-02-1999
		SG 43859 A1	14-11-1997
		SK 28093 A3	06-04-1994
		ZA 9302397 A	04-10-1993
		AU 693804 B2	09-07-1998
		AU 7697594 A	01-05-1995

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/EP 03/11271

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5521184 A		CA 2148477 A1	13-04-1995
		WO 9509852 A1	13-04-1995
		EP 0672040 A1	20-09-1995
		JP 8504834 T	28-05-1996
		US 5543520 A	06-08-1996