

Annexe A

Register extract in respect of patent 2010/03601

REPUBLIC OF SOUTH AFRICA

REGISTER OF PATENTS

PATENTS ACT, 1978

Official application No.		Lodging date: Provisional		Acceptance date	
21	01	2010/03601		22	
International classification		Lodging date: Complete		Granted date	
51	A61K;A61P		23	2010/05/04	
International Application No.		International filling Date		Priority Date	
PCT/EP2008/057002		2008/12/21		24/12/2007	
71	Full name(s) of applicant(s)/Patentee(s):				
Global Pharma Innovations GmbH a German company 55304 Stuttgart, Germany					
71	Applicant substituted:			Date registered	
71	Assignee(s):			Date registered	
72	Full name(s) of inventor(s):				
SMITH JORDAN MUELLER ANNA GARCIA CARLOS CHEN LI					
Priority claimed:		Country	Number		Date
		33	EP	31	04030880.4
				32	2007/12/24
54	Title of invention				
MEDICAMENTS FOR THE TREATMENT OR PREVENTION OF FIBRIOTIC DISEASES					
Address of applicant(s)/patentee(s):					
a German company 55304 Stuttgart GERMANY					
74	Address for service				
ALPHA INTELLECTUAL PROPERTY, Suites 1-5, Innovation Hub, 100 Pretoria Road, Lynnwood, Pretoria, 0081, SOUTH AFRICA Reference No.					
61	Patent of addition to No.			Date of any change	
Fresh application based on.			Date of any change		

RENEWAL SHEET

Year	Payment Date	Receipt Number	Amount
8	2015/12/07 00:00:00	044190	85.00
10	2017/12/05 00:00:00	44450	100
11	2018/12/11 00:00:00	46150	120.00
12	2019/12/12 00:00:00	045692	120.00
13	2020/12/05 00:00:00	45530	145.00
14	2021/12/07 00:00:00	00046494	145
15	2022/12/12 00:00:00	046080	164
16	2023/12/02 00:00:00	58643066	164
17	2024/12/02 00:00:00	66210640	181
18	2025/11/30 00:00:00	73108785	181
19			
20			

HISTORY SHEET

Date entry made	Description
2010-05-17	Entry of international patent appplication under PCT
2011-07-17	Application accepted on 16/07/2011.
2011-07-28	Specification amended on 17/01/2011 by ALPHA IP
2016-07-08	Specification amended on 04/02/2016 by ALPHA IP
2017-04-02	Renewal filed on 07/12/2015 by ALPHA IP, for 1 term(s), next renewal due on 21/12/2016.
2017-12-19	Renewal filed on 05/12/2017 by Catch Inc, for 01 term(s), next renewal due on 21/12/2018.
2019-01-06	Renewal filed on 11/12/2018 by Catch Inc, for 01 term(s), next renewal due on 21/12/2019.
2021-03-14	Renewal filed on 12/12/2019 by Catch Inc, for 1 term(s), next renewal due on 21/12/2020.
2017-08-02	Application Granted on 25/09/2011.
2021-12-08	Renewal filed on 05/12/2020 by ALPHA IP, for 01 term(s), next renewal due on 21/12/2021.
2022-02-04	Renewal filed on 07/12/2021 by ALPHA IP, for 1 term(s), next renewal due on 21/12/2022.
2023-01-07	Renewal filed on 12/12/2022 by DN & ASSOCIATES, for 01 term(s), next renewal due on 21/12/2023.
2023-12-02	Renewal filed on 02-12-2020 by DN & ASSOCIATES, for single term, next renewal due on 21-12-2024
2024-12-02	Renewal filed on 02-12-2021 by DN & ASSOCIATES, for single term, next renewal due on 21-12-2025
2025-11-30	Renewal filed on 30-11-2022 by SARAH JONES, for single term, next renewal due on 21-12-2026

Annexe B

Specification of patent 2010/03601, including current claims

SUMMARY OF THE INVENTION

Surprisingly, we found that the compounds of above general formula I are effective in the treatment or prevention of specific fibrotic diseases.

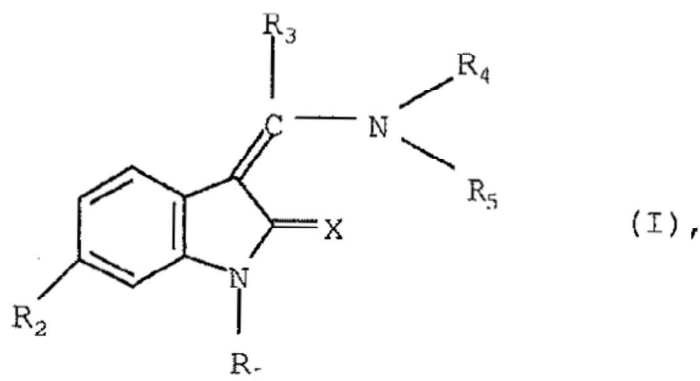
The present invention thus relates to the use of the compounds of above general formula I for the preparation of a medicament for the treatment or prevention of specific fibrotic diseases.

The present invention also relates to a method for the treatment or prevention of specific fibrotic diseases, by administration to a patient in need thereof of a pharmaceutical composition comprising a compound of above general formula I, together with a pharmaceutically suitable carrier. The expression "patient" is meant to comprise the mammalian animal body, preferably the human body.

The present invention further relates to a pharmaceutical composition for the treatment or prevention of specific fibrotic diseases which comprises a compound of above general formula I alone or in combination with one or more further therapeutic agents.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, the compounds of above general formula I are the compounds



in which **[further definition omitted]**, the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

- (b) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone,
- (c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (e) 3-Z-[1-(4-((2,6-dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (f) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (g) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (m) 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (q) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone.

Other compounds that expected to be effective are:

(t) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(u) 3-2-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(v) 3-2-[1-(3-cyano-4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(w) 3-2-[1-(3-methoxy-4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(x) 3-2-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(y) 3-2-[1-(4-(N-(N-(2-dimethylamino-ethyl)-N-methyl-aminomethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone, and

(z) 3-2-[1-(4-(N-(di-(2-hydroxy-ethyl)-amino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone.

Tautomers, stereoisomers or physiologically acceptable salts of these compounds are also contemplated within the scope of the present invention, and may be obtained using the methods described in WO 01/27081, the content of which is herein incorporated by reference.

The metabolites of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate and the prodrugs of this compound or of these metabolites obtained via, for example, chemical or non-chemical derivatization of the entire molecule or of one or more chemical groups on the molecule, are also contemplated compounds within the meaning of the present invention. In this matter, reference is made to WO 04/13099, which describes metabolites and prodrugs of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

The compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are thus suitable for the prevention or treatment of a specific fibrotic disease selected from the group consisting of:

- Fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema;
- Lung fibrosis and pulmonary diseases with a fibrotic component including but not limited to idiopathic pulmonary fibrosis (IPF), giant cell interstitial pneumonia (GIP); sarcoidosis, cystic fibrosis, respiratory distress syndrome (ARDS), granulomatosis, silicosis, drug-induced lung fibrosis (for example, induced by drugs such as bleomycin, bis-chloronitrosourea, cyclophosphamide,

amiodarone, procainamide, penicillamine, gold or nitrofurantoin), asbestosis, systemic scleroderma;

- Fibrosis and remodeling in asthma;
- Fibrosis in rheumatoid arthritis;
- Virally induced hepatic cirrhosis, for example hepatitis C;
- Radiation-induced fibrosis;
- Restenosis, post angioplasty;
- Renal disorders including chronic glomerulonephritis, renal fibrosis in patients receiving cyclosporine and renal fibrosis due to high blood pressure;
- Diseases of the skin with a fibrotic component including but not limited to, scleroderma, sarcoidosis, systemic lupus erythematosus;
- Excessive scarring.

In a preferred embodiment in accordance with the present invention, the compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are especially suitable for the prevention or treatment of idiopathic pulmonary fibrosis.

BIOLOGICAL ACTIVITY

The following experimental results illustrate the present invention without representing a limitation of its scope.

Example: Effect of a representative compound on lung morphology following bleomycin-induced pulmonary fibrosis.

In the following experiment, Example A denotes the compound 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone, which is compound (m) of the list of the preferred compounds.

Materials and Methods Bleomycin sulfate (Bleomycin HEXAL™) was purchased from a local pharmacy.

Bleomycin administration and treatment protocols All experiments were performed in accordance with German guidelines for animal welfare, performed by persons certified to work with animals and approved by the responsible authorities. Male Wistar rats were intratracheally injected with Bleomycin sulfate (body weight in saline) or saline alone (saline control) using a catheter (internal diameter, external diameter) through the nasal passage, following exposure to the anaesthetic Isoflurane for 5

minutes. The following day, the rats were orally treated with compound (m) or saline suspended in Natrosol. Control rats were administered Natrosol (vehicle control).

21 days following bleomycin instillation, the rats were killed with a lethal intraperitoneal injection of Narcoren (Pentobarbital Sodium, Rhone Merieux). The lungs were then removed, blotted dry and half was snap frozen in liquid nitrogen and stored at . The other half was fixed in formalin for subsequent paraffin embedding and histology.

Results Rats treated intratracheally with bleomycin and the vehicle developed severe lung fibrosis. Daily treatment of bleomycin-treated rats with compound (m) showed a consistent, nearly complete reversal of lung fibrosis in this model. Alveoli are intact and little or no fibroblast infiltration or extracellular matrix deposition has occurred. Normal lung structure has been maintained.

For pharmaceutical use the compounds according to the invention are preferably used for warm-blooded vertebrates, particularly humans, in doses of body weight. These compounds may be administered either on their own or in conjunction with other active substances by intravenous, subcutaneous, intramuscular, intraperitoneal or intranasal route, by inhalation, or transdermally, or orally, whilst aerosol formulations are particularly suitable for inhalation.

For administration they are formulated with one or more conventional inert solid, semisolid or liquid carriers e.g. with starch, different types of cellulose, lactose, mannitol, sorbitol, glucose, calcium phosphate, hard fat, fatty alcohols, glycerol, medium chained triglycerides and related esters, polyethylene glycol, refined specialty oils, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, and/or functional excipients, e.g. with polyvinylpyrrolidone, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, sodium starch glycolate, silicon dioxide, polysorbates, poloxamers, gelucires, magnesium stearate, citric acid, tartaric acid, or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, injectable solutions, ampoules, suspensions, solutions, sprays or suppositories.

CLAIMS

1. Use of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenylmethylene]-6methoxycarbonyl-2-indolinone or a tautomer, a diastereomer, an enantiomer, the mixtures thereof or a salt thereof, in the manufacture of a medicament for use in the prevention or treatment of idiopathic pulmonary fibrosis.
2. Use of the monoethanesulfonate salt of the compound 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenylmethylene]-6methoxycarbonyl-2-indolinone, in the manufacture of a medicament for use in the prevention or treatment of idiopathic pulmonary fibrosis.
3. Use in accordance with claim 1 or 2, substantially as herein described and exemplified and/or described with reference to the accompanying figures.

AMENDED SHEET

Annexe C

Form P3 filed in support of the application for patent 2010/03601

Form P.3

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

DECLARATION AND POWER OF ATTORNEY
(Section 30 - Regulations 8, 22(i)(c) and (33))

PATENT APPLICATION NO.		LODGING DATE.		REFERENCE
21	01	2010/03601	22	4 May 2010
FULL NAME(S) OF APPLICANT(S)				
71	GLOBAL PHARMA INNOVATIONS GmLH			
FULL NAME(S) OF INVENTOR(S)				
72	SMITH, Jordan GARCIA, Carlos MUELLER, Anna CHEN, Li			
EARLIEST PRIORITY CLAIMED		COUNTRY EP	NUMBER	DATE
			04 030 770.4	December 24, 2007
NOTE: The country must be indicated by its International Abbreviation - see schedule 4 of the Regulations.		33	31	32
TITEL OF INVENTION				
54	"Medicaments for the treatment or prevention of fibrotic diseases"			

I/We: DR WOLF SCHMIDT

1. I/we am/are the applicant(s) mentioned above;
- ** 2. I/We have been authorised by the applicant(s) to make this declaration and have knowledge of the facts herein stated in the capacity of DIRECTOR of the applicant(s);
- *** 3. the inventor(s) of the abovementioned invention is/are the person(s) named above the applicant(s) has/have acquired the right to apply by virtue of an assignment from the inventor(s);
4. to the best of my/our knowledge and belief, if a patent is granted on the application, there will be no lawful ground for the revocation of the patent;
- **** 5. this is a convention application and the earliest application from which priority is claimed as set out above is the first application in a convention country in respect of the invention claimed in any of the claims; and
6. the directors and qualified staff of the firm of ALPHA IP attorneys, are authorised, jointly and severally, with powers of substitution and revocation, to represent me applicant(s) in this application and to be the address for service of the applicant(s) while the application is pending and after a patent has been granted on the application.

SIGNED AT Stuttgart, Germany 24 May 2010



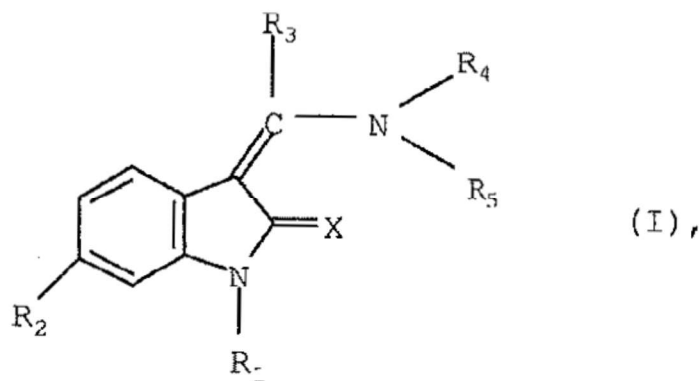
* In the case of applications in the name of a Company, Partnership or Firm, give full names of signatory/signatories, delete paragraph 1, and enter capacity of each signatory in paragraph 2.
** If the applicant is a natural person, delete paragraph 2.
*** If the right to apply is not by virtue of an assignment from the inventor(s), delete "an assignment from the inventor(s)" and give details of acquisition of right.
**** For non-convention applications delete paragraph 5.

Annexe D

Claims of patent application 2010/03601, as filed

CLAIMS

1. Use of the indolinones of general formula



(I), substituted in the 6 position, wherein

[FURTHER DEFINITION OMITTED FROM EXAMINATION PAPER ANNEXE]

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,

for the preparation of a medicament for the prevention or treatment of a fibrotic disease selected from the group consisting of fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease, fibrosis and remodeling of lung tissue in chronic bronchitis, fibrosis and remodeling of lung tissue in emphysema, lung fibrosis and pulmonary diseases with a fibrotic component, fibrosis and remodeling in asthma, fibrosis in rheumatoid arthritis, virally induced hepatic cirrhosis, radiation-induced fibrosis, post angioplasty restenosis, chronic glomerulonephritis, renal fibrosis in patients receiving cyclosporine and renal fibrosis due to high blood pressure, diseases of the skin with a fibrotic component, and excessive scarring.

2. Use in accordance with claim 1 wherein the substituent in the 6 position of the substituted indolinone of general formula I comprises a substituted amido group.
3. Use in accordance with claim 1 wherein the substituted indolinone of general formula I is selected from the group consisting of:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

- (b) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone,
- (c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (e) 3-Z-[1-(4-((2,6-dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (f) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (g) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (m) 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (q) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

4. Use in accordance with claim 1 wherein the substituted indolinone of general formula I is selected from the group consisting of:

(t) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(u) 3-2-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(v) 3-2-[1-(3-cyano-4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(w) 3-2-[1-(3-methoxy-4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(x) 3-2-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(y) 3-2-[1-(4-(N-(N-(2-dimethylamino-ethyl)-N-methyl-aminomethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(z) 3-2-[1-(4-(N-(di-(2-hydroxy-ethyl)-amino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

5. Use in accordance with claim 1 wherein the substituted indolinone of general formula I is selected from 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone or the monoethanesulfonate salt of this compound.
6. Use in accordance with any one of claims 1 to 5 wherein the disease is selected from the group consisting of the lung fibrosis and pulmonary diseases with a fibrotic component selected from idiopathic pulmonary fibrosis, giant cell interstitial pneumonia, sarcoidosis, cystic fibrosis, respiratory distress syndrome, drug-induced lung fibrosis, granulomatosis, silicosis, asbestosis, systemic scleroderma, the virally induced hepatic cirrhosis selected from hepatitis C induced hepatic cirrhosis, and the diseases of the skin with a fibrotic component selected from scleroderma, sarcoidosis and systemic lupus erythematosus.
7. Use in accordance with any one of claims 1 to 6 wherein the disease is idiopathic pulmonary fibrosis.
8. Use in accordance with any one of claims 1 to 7 wherein the treatment is a combined treatment with a further pharmacologically active substance selected

from the group consisting of anticholinergic agents, beta-2 mimetics, steroids, PDE-IV inhibitors, p38 MAP kinase inhibitors, antagonists, LTD4 antagonists, EGFR inhibitors and endothelin-antagonists.

9. A method for the prevention or treatment of a fibrotic disease selected from the group consisting of fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease, fibrosis and remodeling of lung tissue in chronic bronchitis, fibrosis and remodeling of lung tissue in emphysema, lung fibrosis and pulmonary diseases with a fibrotic component, fibrosis and remodeling in asthma, fibrosis in rheumatoid arthritis, virally induced hepatic cirrhosis, radiation-induced fibrosis, post angioplasty restenosis, chronic glomerulonephritis, renal fibrosis in patients receiving cyclosporine and renal fibrosis due to high blood pressure, diseases of the skin with a fibrotic component, and excessive scarring, wherein a substituted indolinone of formula I as defined in any one of claims 1 to 5 is administered to a patient in need thereof, optionally together with one or more pharmaceutically acceptable carriers or excipients.
10. The method in accordance with claim 9, wherein the disease is selected from the group consisting of the lung fibrosis and pulmonary diseases with a fibrotic component selected from idiopathic pulmonary fibrosis, giant cell interstitial pneumonia, sarcoidosis, cystic fibrosis, respiratory distress syndrome, drug-induced lung fibrosis, granulomatosis, silicosis, asbestosis, systemic scleroderma, the virally induced hepatic cirrhosis selected from hepatitis C induced hepatic cirrhosis, and the diseases of the skin with a fibrotic component selected from scleroderma, sarcoidosis and systemic lupus erythematosus.
11. The method in accordance with claim 10 wherein the disease is idiopathic pulmonary fibrosis.

Annexe E

Application on Form P12, for amendment of the application for patent 2010/03601

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

APPLICATION TO AMEND A COMPLETE SPECIFICATION
NOT OPEN TO PUBLIC INSPECTION
(Section 51(1) – Regulation 52(2))

KINDLY DEBIT ACCCJNT NO.

R70.00

OFFICIAL APPLICATION NO		LODGING DATE		AGENT'S REFERENCE
21	01	2010/03601	23	04 May 2010

FULL NAME(S) OF APPLICANT(S)

71 GLOBAL PHARMA INNOVATIONS GmbH

ADDRESS FOR SERVICE

74 ALPHA INTELLECTUAL PROPERTY

TITLE OF INVENTION

54 MEDICAMENTS FOR THE TREATMENT OR PREVENTION OF FIBRIOTIC DISEASES

The applicant hereby applies to amend the complete specification contained in the above application as shown on the attached relevant pages of that specification.

The reasons for the amendment are as follows:

The amendment serves to delete claims 9-11 in order to take cognizance of Section 25(11) of the Act.

APPLICATION FOR AMENDMENT DATED 17/01/11
AANSOEK OM WYBYSING WEDATIE

18th  DAY OF JANUARY

ALLOWED/REFUSED
GESTOEV/GEWEE

REGISTRAR OF PATENTS
REGISTRATEUR VAN PATENTE

DATED:

16 January 2011

REGISTRAR OF PATENTS DESIGNS,
TRADE MARKS AND COPYRIGHT

1 x Copy showing amendment
2 x Amended sheets

2011-01-17

REGISTRAR OF PATENTS, MODELS,
TRADE MARKS AND COPYRIGHT



Patent Attorney for Applicant(s)

9. ~~A method for the prevention or treatment of a fibrotic disease selected from the group consisting of fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease, fibrosis and remodeling of lung tissue in chronic bronchitis, fibrosis and remodeling of lung tissue in emphysema, lung fibrosis and pulmonary diseases with a fibrotic component, fibrosis and remodeling in asthma, fibrosis in rheumatoid arthritis, virally induced hepatic cirrhosis, radiation-induced fibrosis, post angioplasty restenosis, chronic glomerulonephritis, renal fibrosis in patients receiving cyclosporine and renal fibrosis due to high blood pressure, diseases of the skin with a fibrotic component, and excessive scarring, wherein a substituted indolinone of formula I as defined in any one of claims 1 to 5, is administered to a patient in need thereof, optionally together with one or more pharmaceutically acceptable carriers or excipients.~~

10. ~~The method in accordance with claim 9, wherein the disease is selected from the group consisting of the lung fibrosis and pulmonary diseases with a fibrotic component selected from idiopathic pulmonary fibrosis, giant cell interstitial pneumonia, sarcoidosis, cystic fibrosis, respiratory distress syndrome, drug-induced lung fibrosis, granulomatosis, silicosis, asbestosis, systemic sclerosis, the virally induced hepatic cirrhosis selected from hepatitis C-induced hepatic cirrhosis, and the diseases of the skin with a fibrotic component selected from sclerosis, sarcoidosis and systemic lupus erythematosus.~~

AMENDED SHEET

11. ~~The method in accordance with claim 10 wherein the~~
~~disease is idiopathic pulmonary fibrosis.~~

~~The method in accordance with claim 11 wherein the~~
~~method further comprises the step of administering to the~~
~~subject a second agent selected from the group consisting of~~
~~antifibrotic agents, anti-inflammatory agents, and~~
~~agents that modulate the expression of matrix metalloproteinases.~~
~~The method in accordance with claim 11 wherein the~~
~~second agent is selected from the group consisting of~~
~~antifibrotic agents, anti-inflammatory agents, and~~
~~agents that modulate the expression of matrix metalloproteinases.~~

~~The method in accordance with claim 11 wherein the~~
~~subject is a human.~~
~~The method in accordance with claim 11 wherein the~~
~~subject is a patient with idiopathic pulmonary fibrosis.~~
~~The method in accordance with claim 11 wherein the~~
~~subject is a patient with systemic sclerosis.~~
~~The method in accordance with claim 11 wherein the~~
~~subject is a patient with chronic obstructive pulmonary disease.~~

~~The method in accordance with claim 11 wherein the~~
~~subject is a patient with idiopathic pulmonary fibrosis.~~
~~The method in accordance with claim 11 wherein the~~
~~subject is a patient with systemic sclerosis.~~
~~The method in accordance with claim 11 wherein the~~
~~subject is a patient with chronic obstructive pulmonary disease.~~
~~The method in accordance with claim 11 wherein the~~
~~subject is a patient with idiopathic pulmonary fibrosis.~~

Annexe F

International Preliminary Report on Patentability (separate sheet only) in relation to
parent International Application No. PCT/EP2008/057002

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference P01-1819/WO/1	FOR FURTHER ACTION	See item 4 below
International application No. PCT/EP2008/057002	International filing date (<i>day/month/year</i>) 21 December 2008 (21.12.2005)	Priority date (<i>day/month/year</i>) 24 December 2007 (24.12.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GLOBAL PHARMA INNOVATIONS GMBH		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 7 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	This report contains indications relating to the following items: <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;">☒</td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	Box No. I	Basis of the report	☐	Box No. II	Priority	☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	☐	Box No. IV	Lack of unity of invention	☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	☐	Box No. VI	Certain documents cited	☐	Box No. VII	Certain defects in the international application	☐	Box No. VIII	Certain observations on the international application
☒	Box No. I	Basis of the report																							
☐	Box No. II	Priority																							
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability																							
☐	Box No. IV	Lack of unity of invention																							
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																							
☐	Box No. VI	Certain documents cited																							
☐	Box No. VII	Certain defects in the international application																							
☐	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 26 June 2010 (26.06.2010) Authorized officer David Jones e-mail: pct@wipo.int
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2008/057002

International filing date (day/month/year)
21.12.2008

Priority date (day/month/year)
24.12.2007

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/404 A61K31/44 A61K31/445 A61K31/495 A61P11/00 A61P17/00 A61P17/02 A61P43/00

Applicant
GLOBAL PHARMA INNOVATIONS GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Joseph, David

Telephone No. +49 89 2300-8406



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2008/057002

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application
No.
PCT/EP2008/057002

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 1-13

because:

- ☒ the said international application, or the said claims Nos. 9-11 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-13 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 1-13 are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ no international search report has been established for the whole application or for said claims Nos. 1-13
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application
No.
PCT/EP2008/057002

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-13
Inventive step (IS)	Yes: Claims	
	No: Claims	1-13
Industrial applicability (IA)	Yes: Claims	1-8,12,13
	No: Claims	9-11

2. Citations and explanations

see separate sheet

Cited prior art

D1: WO 2004/017948

D2: WO 01/27081

Section III

1. Claims 1-13 were only searched to the extent referred to on form PCT/ISA/210. An opinion is therefore only given on the subject-matter searched (Rule 66.1(e) PCT).
2. Claims 9-11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Section V

3. Having regard to the cited prior art, claims 1-13 do not meet the requirements of Art. 33(2) PCT.
 - 3.1 The use of compounds falling within the scope of Formula (I) are known as medicaments from D1-D2. The subject-matter of claim 13 is therefore not novel.
 - 3.2 Compounds falling within the scope of Formula (I) are also known for the treatment of fibrotic diseases such as glomerulonephritis, asthma, restenosis, psoriasis, hepatic cirrhosis and COPD (cf. present claim 1) from D1-D2. See the passages cited in the ISR. The mechanism by which these compounds act (fibrosis) would appear to be irrelevant in view of the prior art. Both the present application and the prior art seek patent protection for compositions comprising compounds of Formula I for the treatment of the same diseases.
4. Not being novel, claims 1-13 do not meet the requirements of Art. 33(3) PCT.
5. For the assessment of the present claims 9-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Annexe G

WO 2004/017948

International Publication Number: WO 2004/017948 A2

International Application Number: PCT/EP2003/008890

International Filing Date: 11 August 2003 (11.08.2003)

Filing Language: English

Publication Language: English

Priority Data: 102 37 423.6 16 August 2002 (16.08.2002) DE

International Publication Date: 4 March 2004 (04.03.2004)

Applicant (for all designated States except US): Boehringer Ingelheim Pharma GmbH & Co. KG [DE/DE]; 55216 Ingelheim/Rhein (DE).

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TITLE: USE OF LCK INHIBITOR FOR TREATMENT OF IMMUNOLOGIC DISEASES

Use of Lck inhibitors for treatment of immunologic diseases

TECHNICAL FIELD OF THE INVENTION

This invention relates to a method of treating immunologic diseases or pathological conditions involving an immunologic component using a compound selected from compounds (A) to (F) listed below already known as kinase inhibitors for therapy in oncology, and the use of these compounds for the manufacture of a pharmaceutical composition for the treatment of said immunologic diseases or pathological conditions.

BACKGROUND OF THE INVENTION

Compounds (A) to (F) listed below, their preparation as well as the pharmacological activity of these compounds based on inhibition of kinases, e.g. VEGFR-2, suitable for therapy in oncology, are disclosed in WO 02/36564, WO 99/52869, WO 00/18734, WO 00/73297, WO 01/27080, WO 01/27081 and WO 01/32651. The cited documents are herewith incorporated by reference with respect to any aspects disclosed relating to these specific compounds.

Lck, a further tyrosine kinase belonging to the src family of tyrosine kinases not mentioned in the references cited above, is functionally required for T-cell activation through the T-cell antigen receptor (TCR) and possibly T-cell survival. Therefore a Lck inhibitor has a high possible therapeutic potential in the treatment of T-cell mediated diseases, e.g. in the treatment of immunologic diseases. Certain autoimmune diseases such as inflammatory diseases (for example inflammatory bowel disease, rheumatoid arthritis, glomerulonephritis and lung fibrosis, psoriasis, hypersensitivity reactions of the skin, atherosclerosis, restenosis, allergic asthma, multiple sclerosis and type 1 diabetes are believed to be associated with inappropriate T cell activation. In addition the acute rejection of transplanted organs as well as Graft versus Host Disease (GvHD) after allogeneic bone marrow and stem cell transplantation can also be interpreted as consequence of inappropriate T cell activation. Lck inhibitors offer an approach for treatment of the indications mentioned hereinbefore. Agents of this kind would offer therapy for transplant rejection and autoimmune diseases whilst avoiding toxicities associated with the commonly used, less selective immunosuppressants. The leading agent for prevention or treatment of transplant rejection is cyclosporin A which, although effective, is often associated with side-effects such as renal damage and hypertension which results in kidney failure in a substantial number of patients.

It is contemporary practice to treat rheumatoid arthritis initially with symptom relief agents such as NSAIDs, which have no effect on disease progression and are often associated with unwanted side-effects. A rationally based, disease modifying agent, without such deleterious side-effects, would therefore offer significant benefits in the prevention or treatment of transplant rejection or autoimmune conditions such as rheumatoid arthritis.

BRIEF SUMMARY OF THE INVENTION

In view of the work referred to above there is a clear need for compounds being active as Lck inhibitors in order to treat T-cell mediated diseases, e.g. in the treatment of immunologic diseases or pathological conditions involving an immunologic component.

It is therefore an object of the invention to provide a method for treating immunologic diseases or pathological conditions involving an immunologic component comprising administering to a patient in need of such treatment an effective amount of a pharmaceutical composition comprising a compound selected from compounds (A) to (F) already known as agents for therapy in oncology.

A second object of the invention is the use of a compound selected from compounds (A) to (F) for the manufacture of a pharmaceutical composition for the treatment of immunologic diseases or pathological conditions involving an immunologic component.

DETAILED DESCRIPTION OF THE INVENTION

It has now surprisingly been found that compounds

(A) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(methylsulfonylamino)-2-indolinone;

(B) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(ethylsulfonylamino)-2-indolinone;

(C) (Z)-3-(1-(4-(dimethylaminomethyl)-phenylamino)-1-phenyl-methylene)-5-(ethylsulfonylamino)-2-indolinone;

(D) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(phenylsulfonylamino)-2-indolinone;

(E) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(4-amino-phenylsulfonylamino)-2-indolinone;

(F) (Z)-3-(1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-phenylamino)-1-phenyl-methylene)-6-methoxycarbonyl-2-indolinone ; and

the tautomers, the stereoisomers and the physiologically acceptable salts thereof, are effective inhibitors of Lck and therefore are especially suitable and effective in the treatment of immunologic diseases or pathological conditions involving an immunologic component.

Compounds (A) to (E) are described in WO 02/36564, and compound (F) is described in WO 01/27081.

Viewed from a first aspect the present invention provides a method for treating immunologic diseases or pathological conditions involving an immunologic component

comprising administering to a patient in need of such treatment an effective amount of a pharmaceutical composition comprising a compound selected from compounds (A) to (F), the tautomers, the stereoisomers and the physiologically acceptable salts thereof.

The expression "patient" is meant to comprise the human and the non-human mammal patient.

The indication "immunologic diseases or pathological conditions involving an immunologic component" should be understood in a non-limiting manner to comprise autoimmune diseases, for instance inflammatory diseases having an autoimmune component such as inflammatory diseases selected from inflammatory bowel disease (e.g. colitis ulcerosa and Morbus Crohn), rheumatoid arthritis, glomerulonephritis and lung fibrosis, furthermore, psoriasis, psoriasis arthritis, hypersensitivity reactions of the skin, atherosclerosis, restenosis, asthma, multiple sclerosis and type 1 diabetes, and indications which need immunosuppressant therapy, for instance prevention or therapy of tissue or organ transplant rejection, e.g. acute or chronic graft-versus-host disease, allograft or xenograft rejection etc. The transplanted organ may be kidney, heart, liver, lung, bone marrow, peripheral blood stem cells, pancreas or islet cells thereof, cornea, small bowel, skin, or heart valve.

Preferred indications which may be treated by the method according to the invention are:

- rheumatoid arthritis,
- inflammatory bowel disease such as colitis ulcerosa and Morbus Crohn,
- psoriasis, psoriasis arthritis,
- prevention or therapy of tissue or organ transplant rejection, acute or chronic graft-versus-host disease, allograft or xenograft rejection,
- allergic asthma, multiple sclerosis and type 1 diabetes.

A further subgroup of indications which may be treated by the method according to the invention and deserves special mention comprises morbus crohn, lung fibrosis, psoriasis arthritis, hypersensitivity reactions of the skin, graft-versus-host disease (acute and chronic), asthma, multiple sclerosis and type 1 diabetes.

A preferred embodiment of the method according to the invention comprises administration of a compound selected from compounds (A), (B), (C), (D), and (F), the tautomers, the stereoisomers and the physiologically acceptable salts thereof.

A further preferred embodiment of the method according to the invention comprises administration of compound (F).

In the method of treatment according to the invention compounds (A) to (F) can be administered orally, parenterally, rectally or, with respect to indications involving treatment of the skin such as psoriasis, psoriasis arthritis or hypersensitivity reactions of the skin, also in topical formulations. Oral administration is preferred.

In oral, rectal or topical administration the compounds may be given, if required in divided doses, in a daily dosage of 0.1 to body weight, preferably 0.5 to body weight, most preferred 1 to body weight.

Parenterally the compounds may be administered in lower doses, for instance in a total daily dosage of 0.01 to body weight, preferably 0.05 to body weight, most preferred 0.1 to body weight.

For administration the compounds may be formulated with one or more conventional inert carriers and/or diluents as known in the art, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, dietetic acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, lozenges, hard or soft capsules, dispersible powders or granules, syrups or elixirs, injectable solutions, ampoules, aqueous or oily suspensions, emulsions, solutions, sprays, creams, ointments, gels, or suppositories. Suitable galenic formulations are disclosed in the documents cited hereinbefore.

Viewed from a third aspect the present invention provides the use of a compound selected from compounds (A) to (F), the tautomers, the stereoisomers and the physiologically acceptable salts thereof, for the manufacture of a pharmaceutical composition for the treatment of a patient suffering from immunologic diseases or pathological conditions involving an immunologic component.

CLAIMS:

1. A method for treating immunologic diseases or pathological conditions involving an immunologic component comprising administering to a patient in need of such treatment an effective amount of a pharmaceutical composition comprising a compound selected from:

(A) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(methylsulfonylamino)-2-indolinone;

(B) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(ethylsulfonylamino)-2-indolinone;

(C) (Z)-3-(1-(4-(dimethylaminomethyl)-phenylamino)-1-phenyl-methylene)-5-(ethylsulfonylamino)-2-indolinone;

(D) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(phenylsulfonylamino)-2-indolinone;

(E) (Z)-3-(1-(4-(piperidin-1-yl-methyl)-phenylamino)-1-phenyl-methylene)-5-(4-amino-phenylsulfonylamino)-2-indolinone; and

(F) (Z)-3-(1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-phenylamino)-1-phenyl-methylene)-6-methoxycarbonyl-2-indolinone; and

the tautomers, the stereoisomers and the physiologically acceptable salts thereof.

2. The method of claim 1, wherein the immunologic disease or pathological condition involving an immunologic component is selected from autoimmune diseases, for instance inflammatory diseases having an autoimmune component such as inflammatory diseases selected from inflammatory bowel disease (e.g. colitis ulcerosa and Morbus Crohn), rheumatoid arthritis, glomerulonephritis and lung fibrosis, furthermore, psoriasis, psoriasis arthritis, hypersensitivity reactions of the skin, atherosclerosis, restenosis, asthma, multiple sclerosis and type 1 diabetes, and indications which need immunosuppressant therapy, for instance prevention or therapy of tissue or organ transplant rejection.
3. The method of claim 2, wherein the immunologic disease or pathological condition involving an immunologic component is selected from morbus crohn, lung fibrosis, psoriasis arthritis, hypersensitivity reactions of the skin, graft-versus-host disease (acute and chronic), asthma, multiple sclerosis and type 1 diabetes.
4. The method according to any of claims 1 to 3, which method comprises administration of a compound selected from (A), (B) and (F) mentioned in claim 1, the tautomers, the stereoisomers and the physiologically acceptable salts thereof.
5. Use of a compound selected from effective compounds (A) to (F) mentioned in claim 1, the tautomers, the stereoisomers and the physiologically acceptable salts

thereof, for the manufacture of a pharmaceutical composition for the treatment of a patient suffering from immunologic diseases or pathological conditions involving an immunologic component.

6. The use of claim 5, wherein the immunologic disease or pathological condition involving an immunologic component is selected from autoimmune diseases, for instance inflammatory diseases having an autoimmune component such as inflammatory diseases selected from inflammatory bowel disease (e.g. colitis ulcerosa and Morbus Crohn), rheumatoid arthritis, glomerulonephritis and lung fibrosis, furthermore, psoriasis, psoriasis arthritis, hypersensitivity reactions of the skin, atherosclerosis, restenosis, asthma, multiple sclerosis and type 1 diabetes, and indications which need immunosuppressant therapy, for instance prevention or therapy of tissue or organ transplant rejection.
7. The use of claim 6, wherein the immunologic disease or pathological condition involving an immunologic component is lung fibrosis.
8. The use of compound (F) mentioned in claim 1, the tautomers, the stereoisomers and the physiologically acceptable salts thereof, according to any of claims 6 to 7.
9. The use according to any of claims 6 to 8 for the manufacture of a pharmaceutical composition adapted for oral, parenteral, rectal or topical administration.

Annexe H

Expert opinion regarding the disclosure of the specification of patent 2010/03601 and
WO 2004/017948

EXPERT OPINION

1. I have been asked to comment on scientific technical issues arising in relation to the specifications of patent 2010/03601 ("the patent in issue") and International Patent Publication no. WO 2004/017948 ("the 2004 publication").
2. I understand that you are most concerned with the compound known as "Nintedanib" and its use in the treatment of idiopathic pulmonary fibrosis.

NINTEDANIB

3. Nintedanib is identified in both specifications as follows:
 - 3.1 In the 2004 publication as "compound (F)" identified on page 2; and
 - 3.2 In the patent in issue as "compound (m)" on page 3.

BACKGROUND ON LUNG FIBROSIS AND IDIOPATHIC PULMONARY FIBROSIS

4. In general terms, "fibrosis" is a term used to describe tissue that is overgrown, hardened and/or scarred as a result of chronic inflammation. Fibrosis is essentially an immunological response – the most visible example being scarring on the skin following injury.
5. Fibrosis occurring in the lungs is referred to as "lung fibrosis" or "pulmonary fibrosis", with the adjective "pulmonary" referring to something that relates to or affects the lungs. Lung fibrosis is a condition characterised by thickening and scarring of the tissue in the lungs. This makes it difficult for oxygen to pass into the bloodstream, resulting in symptoms of shortness of breath, chest discomfort, coughing, and fatigue; as well as weight loss, aching muscles and joints, and clubbing of the tips of fingers and toes.
6. There are different types of lung fibrosis, which are, for the most part, classified according to their cause. To illustrate this, I point to the passage at pages 4-5 of the specification of the patent in issue, referring to:

"Lung fibrosis and pulmonary diseases with a fibrotic component including but not limited to idiopathic pulmonary fibrosis (IPF), giant cell interstitial pneumonia (GIP), sarcoidosis, cystic fibrosis, respiratory distress syndrome (ARDS), granulomatosis, silicosis, drug-induced lung fibrosis (for example, induced by drugs such as bleomycin, bis-chloronitrosourea, cyclophosphamide, amiodarone, procainamide, penicillamine, gold or nitrofurantoin), silicosis, asbestosis, systemic scleroderma."

7. In the above-quoted paragraph, diseases identified as "lung fibrosis" are:
 - idiopathic pulmonary fibrosis ("IPF");
 - drug-induced lung fibrosis (with bleomycin, bis-chloronitrosourea, cyclophosphamide, amiodarone, procainamide, penicillamine, gold and nitrofurantoin being known to induce pulmonary fibrosis in some cases); and
 - silicosis and asbestosis, which are forms of lung fibrosis induced by exposure, respectively, to silicon and asbestos particles.

8. The term "idiopathic" denotes a condition which arises spontaneously or for which the cause is unknown; and IPF is thus distinguished from other forms of lung fibrosis by the fact that its cause is unknown.
9. In the case of lung fibrosis that is induced by an external stimulus, the most obvious treatment response is to address the cause by removing the stimulus; and, in many cases, further progression of the ensuing lung fibrosis will thereby be prevented.
10. This is obviously not possible in cases of lung fibrosis where the cause is not known to be caused by an external stimulus; and in such cases, the need for treatment is particularly acute.

THE 2004 PUBLICATION

11. Before discussing the patent in issue further, I have been asked to consider the import of International Publication WO 2004/017948 ("**the 2004 publication**") insofar as it pertains to the treatment of lung fibrosis.
12. The abstract of the 2004 publication states,

"The invention relates to a method of treating immunologic diseases or pathological conditions involving an immunologic component using Lck inhibitors already known as kinase inhibitors for therapy in oncology, optionally in combination with one or other drugs ..., pharmaceutical composition comprising said Lck inhibitor together with said other drugs, and the use of Lck inhibitors for the manufacture of a pharmaceutical composition for the treatment of immunologic diseases or pathological conditions involving an immunologic component" (own ellipsis).
13. The designation "Lck" refers to lymphocyte-specific protein kinase, a protein that is found inside specialised cells of the immune system called lymphocytes. The Lck is a member of the Src kinase family, and is associated with the activation of T-cell receptor signalling.
14. On pages 1 to 2, the 2004 publication discusses the potential use of Lck inhibitors in therapy, including for the treatment of lung fibrosis. At page 1, line 31 to page 2, line 3, the specification states:

"Certain autoimmune diseases such as inflammatory diseases (for example ... lung fibrosis ... are believed to be associated with inappropriate T cell activation" (own ellipsis).
15. One of the compounds discussed in the 2004 publication is compound (F) identified on page 2, which is Nintedanib.
16. In the section entitled "DETAILED DESCRIPTION OF THE INVENTION", starting on page 2, the specification states:
 - 16.1 *"The indication 'immunologic diseases or pathological conditions involving an immunologic component' should be understood in a non-limiting manner to comprise ... autoimmune diseases, for instance inflammatory diseases having an autoimmune*

component such as inflammatory diseases selected from [a list including] lung fibrosis";

- 16.2 *"A further subgroup of indications which may be treated by the method according to the invention and deserves special mention comprises ... lung fibrosis";*
- 16.3 *"A preferred embodiment of the method according to the invention comprises administration of a compound selected from compounds ... (F), ... the tautomers, the stereoisomers and the physiologically acceptable salts thereof, optionally in combination with one or more other drugs ..."; and*
- 16.4 *"A further preferred embodiment of the method according to the invention comprises administration of a compound selected from the compounds (A), (B) and (F), the tautomers, the stereoisomers and the physiologically acceptable salts thereof, especially preferred is administration of the compound (F)".*
17. Additionally, at page 4, the specification sets out proposed routes of administration and dosages and formulations for the compounds of the invention.
18. Reading claim 8 together with the claims on which it is dependent, claim 8 claims the use of Nintedanib in the treatment of lung fibrosis.
19. In light of the above-mentioned passages in the 2004 publication, I make the following observations:
- 19.1 The 2004 publication discloses the use on Nintedanib for treating lung fibrosis;
- 19.2 Although the general term "lung fibrosis" is used in the 2004 publication, the discussion of lung fibrosis is framed in the context of a more general discussion of autoimmune diseases, with lung fibrosis being identified as one of these autoimmune diseases;
- 19.3 While I do not necessarily agree that IPF fits into the model of autoimmune diseases, it is clear that any form of lung fibrosis that is known to be induced by a particular external stimulus would not be considered to be an "autoimmune disease". I therefore understand the reference to "lung fibrosis" in the 2004 publication to be directed at IPF in particular.

THE PATENT IN ISSUE:

20. According to the abstract,

"The present invention relates to the use of indolinones of general formula (I) substituted in the 6 position, wherein R1 to R5 and X are defined as in claim 1, the isomers and the salts thereof, particularly the physiologically acceptable salts thereof, as a medicament for the prevention or treatment of specific fibrotic diseases".

21. The "indolinones" referred to are a group of chemical compounds. While I have not calculated the number of compounds falling within formula I, it is clear that many thousands

of compounds fall within the general definition, and 17 individual compounds are individually identified in the specification as being "particularly preferred".

22. The list of compounds that are identified as "particularly preferred" includes Nintedanib (as compound (m) on page 3).

23. The body of the specification mentions idiopathic pulmonary fibrosis only 3 times, as follows:

23.1 In the BACKGROUND on page 1, stating,

"Fibrosis often severely compromises the normal function (s) of the organ and many fibrotic diseases are, in fact, life-threatening or severely disfiguring, such as idiopathic pulmonary fibrosis (IPF), liver cirrhosis, scleroderma, or renal fibrosis. Treatment options for these diseases are often limited to organ transplantation, a risky and expensive procedure."

23.2 In a general description of the invention on pages 4 - 5, where it is stated:

"The compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are thus suitable for the prevention or treatment of a specific fibrotic disease selected from the group consisting of:

Fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema;

Lung fibrosis and pulmonary diseases with a fibrotic component including but not limited to idiopathic pulmonary fibrosis (IPF), giant cell interstitial pneumonia (GIP), sarcoidosis, cystic fibrosis, respiratory distress syndrome (ARDS), granulomatosis, silicosis, drug-induced lung fibrosis (for example, induced by drugs such as bleomycin, bis-chloronitrosourea, cyclophosphamide, amiodarone, procainamide, penicillamine, gold or nitrofurantoin), silicosis, asbestosis, systemic scleroderma;

Fibrosis and remodeling in asthma;

Fibrosis in rheumatoid arthritis;

Virally induced hepatic cirrhosis, for example hepatitis C;

Radiation-induced fibrosis;

Restenosis, post angioplasty;

Renal disorders including chronic glomerulonephritis, renal fibrosis in patients receiving cyclosporine and renal fibrosis due to high blood pressure;

Diseases of the skin with a fibrotic component including but not limited to, scleroderma, sarcoidosis, systemic lupus erythematosus;

Excessive scarring"; and

23.3 On page 5, following the previous passage, where it is stated:

"In a preferred embodiment in accordance with the present invention, the compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are especially suitable for the prevention or treatment of idiopathic pulmonary fibrosis."

24. The two references in the specification to IPF in relation to the invention thus both involve the use of the entire class of *"compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof"*. Neither of these references identifies a preference for Nintedanib over any other compounds of formula I for the treatment of IPF.
25. The only discussion in the body of the specification in which Nintedanib is considered distinctly from the general group of compounds of formula I, is found in the Example, starting on page 5, which describes an experiment in which rats were treated with bleomycin to induce pulmonary fibrosis; and Nintedanib was shown to inhibit the development of pulmonary fibrosis in the subject rats.
26. Bleomycin is a chemotherapy drug used to treat various cancers; and which is known to increase the likelihood of developing pulmonary fibrosis. Animal models using bleomycin-induced pulmonary fibrosis are sometimes used to emulate human IPF, as bleomycin-induced IPF displays certain similarities to IPF.
27. However, despite similarities, drug-induced pulmonary fibrosis is not IPF as such; and, indeed, the specification itself distinguishes between IPF and bleomycin-induced pulmonary fibrosis in the list of pulmonary diseases with a fibrotic component on page 4, identifying these diseases as,

"including but not limited to idiopathic pulmonary fibrosis (IPF), giant cell interstitial pneumonia (GIP), sarcoidosis, cystic fibrosis, respiratory distress syndrome (ARDS), granulomatosis, silicosis, drug-induced lung fibrosis (for example, induced by drugs such as bleomycin, bis-chloronitrosourea, cyclophosphamide, amiodarone, procainamide, penicillamine, gold or nitrofurantoin) , silicosis, asbestosis, systemic sclerosis" (my emphasis).

28. The conclusions drawn in the specification from the Example are that:

"Daily treatment of bleomycin-treated rats with 50 mg/kg of compound (m) showed a consistent, nearly complete reversal of lung fibrosis in this model" (page 6).
29. Given that, other than the bleomycin-rat studies, no treatment examples are provided to exemplify the use of the compounds of general formula I for any of the fibrotic diseases identified in the specification, it appears that the Example is intended to demonstrate the usefulness of Nintedanib (as *"a representative compound"*, page 5) for all the identified fibrotic diseases.
30. The specification does not suggest that the bleomycin-rat experiment of the Example is provided to exemplify use of Nintedanib specifically in treatment of IPF. Rather, the only basis on which the bleomycin-rat experiment of the Example may be understood to support the use of Nintedanib in the treatment of IPF, is on the basis of generalising and extending

its application to IPF as one of the other pulmonary diseases with a fibrotic component listed in the specification.

COMMENT ON PROSECUTION AND AMENDMENTS

31. While the register sheet reflects 2 amendments to the specification, only the amendment on Form P12, dated 17 January 2011, is included in the file as provided by the CIPC. Nevertheless, by comparing the claims as filed, the red copy of the 2011 amendment, and the claims as they currently stand, it can be established that:

31.1 The claims originally filed with the application included:

31.1.1 Claim 1 to the use of compounds of formula I broadly in the manufacture of medicaments for the treatment of several conditions, including “lung fibrosis and pulmonary diseases with a fibrotic component”; and

31.1.2 Claims 9 to 11 to methods of treatment; and

31.2 While the 2011 amendment deleted the method of treatment claims, it did not limit claim 1 to address the novelty objections raised in the PCT Written Opinion; and

31.3 To the extent that the scope of the claims has been limited to Nintedanib and its use in treatment of IPF, this amendment can only have been made in the amendment of 4 February 2016.