Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2427814 C 2009/06/02

(11)(21) 2 427 814

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2001/11/02
(87) Date publication PCT/PCT Publication Date: 2002/05/16
(45) Date de délivrance/Issue Date: 2009/06/02
(85) Entrée phase nationale/National Entry: 2003/05/02
(86) N° demande PCT/PCT Application No.: US 2001/045514
(87) N° publication PCT/PCT Publication No.: 2002/038155
(30) Priorité/Priority: 2000/11/07 (US60/246,368)

(51) Cl.Int./Int.Cl. *A61K 31/47* (2006.01),
A61K 31/44 (2006.01)

(72) Inventeur/Inventor:
CHANG, YUJUN, US

(73) Propriétaire/Owner:
MERCK & CO., INC., US

(74) Agent: OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : COMBINAISON D'UN INHIBITEUR DE PDE4 ET D'UN ANTAGONISTE DES LEUCOTRIENES DANS LE TRAITEMENT DE TROUBLES RESPIRATOIRES ET BRONCHIQUES

(54) Title: A COMBINATION OF A PDE4 INHIBITOR AND A LEUKOTRIENE ANTAGONIST IN THE TREATMENT OF BRONCHIAL AND RESPIRATORY DISORDERS

(57) Abrégé/Abstract:
Bronchial and respiratory disorders are treated by the separate, sequential, or simultaneous administration of i) an amount of N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and ii) an amount of a leukotriene antagonist, wherein the sum of the first and second amounts is a therapeutically effective amount.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 May 2002 (16.05.2002)

PCT

(10) International Publication Number
WO 02/38155 A1

(51) International Patent Classification[7]: A61K 31/47, 31/44

(21) International Application Number: PCT/US01/45514

(22) International Filing Date:
2 November 2001 (02.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/246,368 7 November 2000 (07.11.2000) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **CHANG, Yu-jun** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(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, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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.

WO 02/38155 A1

(54) Title: METHOD OF TREATMENT WITH A COMBINATION OF A PDE4 INHIBITOR AND A LEUKOTRIENE ANTAGONIST

(57) Abstract: Bronchial and respiratory disorders are treated by the separate, sequential, or simultaneous administration of i) an amount of N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and ii) an amount of a leukotriene antagonist, wherein the sum of the first and second amounts is a therapeutically effective amount.

A COMBINATION OF A PDE4 INHIBITOR AND A LEUKOTRIENE ANTAGONIST IN THE TREATMENT OF BRONCHIAL AND RESPIRATORY DISORDERS

BACKGROUND OF THE INVENTION

The present invention relates to a method of treatment of bronchial and respiratory disorders with a therapeutic combination of a PDE4 inhibitor and a leukotriene antagonist. In particular, the present invention is directed to a method of treatment of bronchial and respiratory disorders with a therapeutic combination of ROFLUMILAST and SINGULAIR.™

Cyclic nucleotide phosphodiesterase (PDE) inhibitors, particularly inhibitors of type IV (PDE4), are useful in the treatment of bronchial and respiratory disorders such as asthma and chronic obstuction pulminary disease (COPD). N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (ROFLUMILAST, BYK Gulden Lomberg Chemische Fabrik GmbH, Konstanz, Germany) is a PDE4 inhibitor described in U.S. Patent No. 5,712,298.

Leukotriene antagonists, by a route different from PDE4 inhibitors, are also useful in the treatment of bronchial and respiratory disorders such as asthma and COPD. Montelukast, [R-(E)]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio]methyl]cyclopropaneacetic acid, (SINGULAIR, Merck & Co., Inc, Rahway, NJ) is a leukotriene antagonist described in U.S. Patent No. 5,565,473. Other leukotriene antagonists are described in U.S. Patent Nos. 4,649,157, 4,845,083, 5,028,615, and 5,244,899.

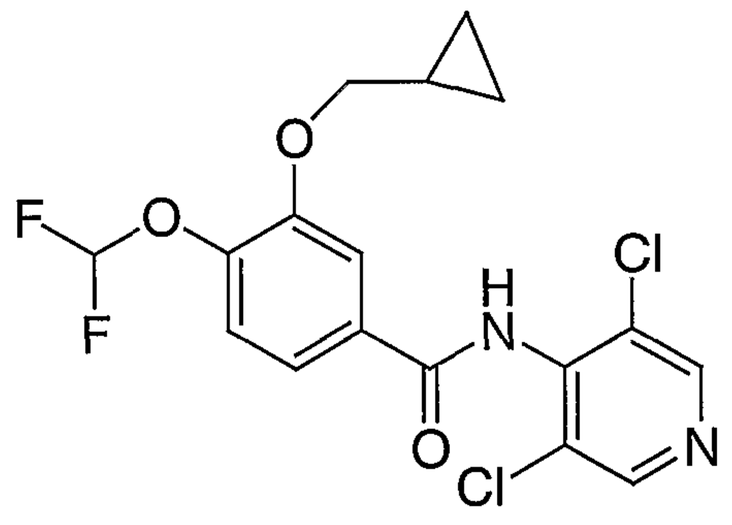
It would be desirable to provide a method that can take advantage of the different therapeutic pathways of a PDE4 inhibitor and of a leukotriene antagonist to more efficaciously treat asthma and COPD.

SUMMARY OF THE INVENTION

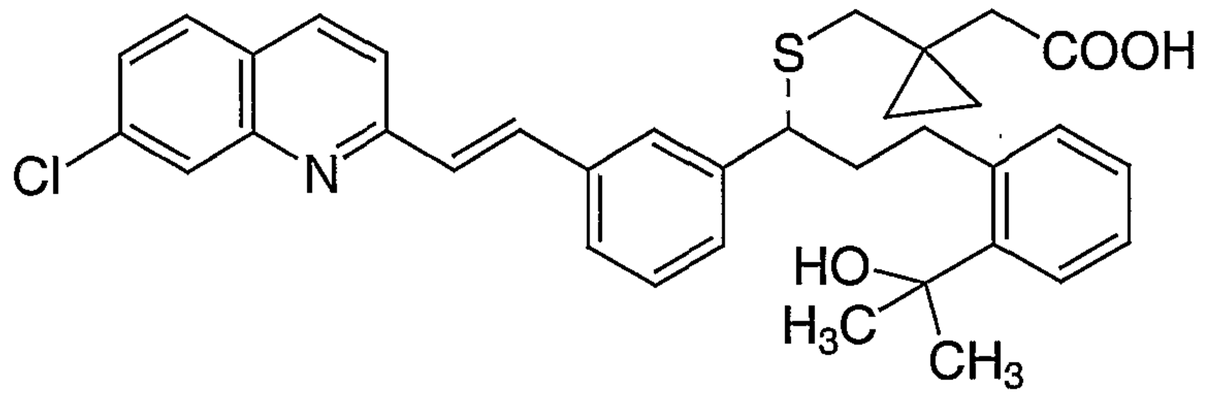
Bronchial and respiratory disorders are treated by the separate, sequential, or simultaneous administration of i) an amount of N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and ii) an amount of a leukotriene antagonist, wherein the sum of the first and second amounts is a therapeutically effective amount.

DETAILED DESCRIPTION OF THE INVENTION

ROFLUMILAST is a PDE4 inhibitor, N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, having the following structure:



SINGULAIR is a leukotriene antagonist, Montelukast, [R-(E)]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio]methyl]cyclopropaneacetic acid, having the following structure:



The present invention treats bronchial and respiratory disorders by adminstering a therapeutically effective amount of a combination of

i) an amount of ROFLUMILAST, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either, and

ii) an amount of a leukotriene antagonist such as SINGULAIR or a pharmaceutically acceptable salt thereof.

Because of the two unique mechanisms of action, the combination has synergistic efficacy providing better relief with fewer and milder side effects. Thus, the present invention provides a method that allows reduced dosages when compared to the individual administration of the drugs individually. The present invention also provides a method that minimizes side effects.

The present invention also provides a pharmaceutical composition comprising:

i) an amount of ROFLUMILAST, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either,

ii) an amount of a leukotriene antagonist such as SINGULAIR or a pharmaceutically acceptable salt thereof, and

iii) a pharmaceutically acceptable carrier.

There is also provided a kit of parts comprising

i) a first pharmaceutical composition comprising an amount of ROFLUMILAST, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either, and a first pharmaceutically acceptable carrier, and

ii) iv) a second pharmaceutical composition comprising an amount of a leukotriene antagonist such as SINGULAIR, or a pharmaceutically acceptable salt thereof, and a second pharmaceutically acceptable carrier for simultaneous or sequential administration.

Accordingly, the present invention is directed to a method of treatment of bronchial and respiratory disorders by adminstering a therapeutically effective amount of a combination of

i) an amount of ROFLUMILAST, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either, and ii) an amount of a leukotriene antagonist such as SINGULAIR or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, there is provided acomposition comprising i) N-(3,5-dichloropyrid-4-yl)cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and ii) a leukotriene antagonist.

In still another aspect of the invention, there is provided a pharmaceutical kit for treatment of bronchial and respiratory disorders comprising: i) a first amount of N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; ii) a second amount of a leukotriene antagonist, wherein the sum of the first and second

amounts is a therapeutically effective amount, and iii) written instructions for the administration of i) or ii).

In yet another aspect of the invention, there is provided use of i) a first amount of N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and ii) a second amount of a leukotriene antagonist, wherein the sum of the first and second amounts is a therapeutically effective amount, in the manufacture of a medicament for treatment of bronchial and respiratory disorders.

The pharmaceutically acceptable salt of the [R-(E))-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio) methyl]cyclopropaneacetic acid herein, may be, for example, the monosodium salt.

The pharmaceutical compositions of the present invention are preferably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e. g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e. g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of each active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2,5,10,25,50 or 100 mg, of each active ingredient. The tablets or pills of the novel composition can be coated or

otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former.

The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

For the treatment of bronchial and respiratory disorders, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, and especially about 0.01 to 5 mg/kg of body weight per day of each active ingredient. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.

The synergistic effect of the combination of the present invention can be shown, for example, by comparing the combined dosage of the combination with dosages of the same amount of each of the active ingredients separately on subjects using assays such as the Asthmatic Rat Assay, PAF-Induced Hyperalgesia Assay, the Pulmonary Mechanics in Trained Conscious Squirrel Monkeys, and the Prevention of Induced Bronchoconstriction in Allergic Sheep, as described in U. S. Patent Nos. 4,845,083 and 5,565,473.

CLAIMS:

1. A composition comprising i) N-(3,5-dichloropyrid-4-yl)cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and ii) a leukotriene antagonist.

2. The composition according to claim 1, wherein said leukotriene antagonist is [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-[2(1hydroxy-1-methylethyl)-phenyl]propyl]thio]methyl]cyclopropaneacetic acid or a pharmaceutically acceptable salt thereof.

3. The composition according to claim 2, wherein said leukotriene antagonist is [R-(E))-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio)methyl]cyclopropaneacetic acid, monosodium salt.

4. The composition according to claim 1, 2 or 3, further comprising a pharmaceutically acceptable carrier.

5. The composition according to any one of claims 1 to 4, for use in treatment of bronchial and respiratory disorders.

6. The composition according to claim 5, wherein said disorders are selected from asthma and chronic obstruction pulmonary disease (COPD).

7. A pharmaceutical kit for treatment of bronchial and respiratory disorders comprising:
i) a first amount of N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound;
ii) a second amount of a leukotriene antagonist,
wherein the sum of the first and second amounts is a therapeutically effective amount, and
iii) written instructions for the administration of i) or ii).

8. The pharmaceutical kit of claim 7, wherein said first and second amounts are for separate administration.

9. The pharmaceutical kit of claim 7, wherein said first and second amounts are for sequential administration.

10. The pharmaceutical kit of claim 7, wherein said first and second amounts are for simultaneous administration.

11. The pharmaceutical kit of any one of claims 7 to 10, wherein said leukotriene antagonist is [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio]methyl]cyclopropaneacetic acid or a pharmaceutically acceptable salt thereof.

12. The pharmaceutical kit of claim 11, wherein said leukotriene antagonist is [R-(E))-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio)methyl]cyclopropaneacetic acid, monosodium salt.

13. The pharmaceutical kit of any one of claims 7 to 11, wherein said disorders are selected from asthma and chronic obstruction pulmonary disease (COPD).

14. Use of i) a first amount of N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and
ii) a second amount of a leukotriene antagonist,
wherein the sum of the first and second amounts is a therapeutically effective amount, in the manufacture of a medicament for treatment of bronchial and respiratory disorders.

15. Use of claim 14, wherein said medicament comprises a first pharmaceutical composition comprising i) and a pharmaceutically acceptable carrier; and a second pharmaceutical composition comprising ii) and a pharmaceutically acceptable carrier, for separate, simultaneous or sequential administration.

16. Use of claim 14 or 15, wherein said leukotriene antagonist is [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio]methyl]cyclopropaneacetic acid or a pharmaceutically acceptable salt thereof.

17. Use of claim 16, wherein said leukotriene antagonist is [R-(E))-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio)methyl]cyclopropaneacetic acid, monosodium salt.

18. Use of any one of claims 14 to 17, wherein said disorders are selected from asthma and chronic obstruction pulmonary disease (COPD).