

Current treatments of allergic diseases comprise agents that can block or otherwise interrupt such interactions, e.g. anti-histamines (histamine H1 receptor antagonists), leukotriene receptor antagonists, beta-adrenergic receptor agonists, and corticosteroids. Generally, treatments with anti-histamines and leukotriene antagonists are limited in efficacy, and long-term usage of corticosteroids is often associated with unwanted side effects.

PGD₂ is an agonist known to act on two G-protein-coupled receptors, the PGD₂ receptor DP1 and the recently identified CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) receptor (also referred to as "DP2 receptor").

Elevated PGD₂ levels are considered to cause inflammation as observed in allergic diseases such as allergic rhinitis, allergic asthma, allergic conjunctivitis, atopic dermatitis and the like. Therefore, blocking the interaction of PGD₂ with its receptors is considered a useful therapeutic strategy for the treatment of such diseases.

GB 2388540 discloses the use of ramatroban ((3*R*)-3-(4-fluorobenzene-sulfonamido)-1,2,3,4-tetrahydrocarbazole-9-propionic acid), a TxA₂ receptor (also referred to as "TP receptor") antagonist with additional antagonistic activity on CRTH2, for the prophylaxis and treatment of allergic diseases, such as asthma, allergic rhinitis or allergic conjunctivitis. In T. Ishizuka et al., *Cardiovascular Drug Rev.* **2004**, 22(2), 71-90 effects of ramatroban on late-phase inflammation are described. Furthermore, oral bioavailability of ramatroban and its ability to inhibit prostaglandin D₂-induced eosinophil migration *in vitro* has been reported (*Journal of Pharmacology and Experimental Therapeutics*, **305**(1), p.347-352 (2003)).

Azaindole acetic acid derivatives with CRTH2 antagonistic activity have been disclosed in WO 2010/054113, WO 2010/054114 and B.A. Stearns et al., *Bioorg. Med. Chem. Lett.* 2009, 19, 4647-4651.

WO 2011/117798 and WO 2012/140612 disclose (3-heteroaryl-amino-1,2,3,4-tetrahydro-9H-carbazol-9-yl)-acetic acid and (7-heteroaryl-amino-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)acetic acid derivatives, respectively, which derivatives have CRTH2 antagonistic activity.

Summary

In one aspect, the present disclosure provides a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-*b*]indol-5-yl)acetic acid, characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ: 12.6°, 14.0°, and 21.1°, wherein the X-ray

powder diffraction diagram is measured at about 5%, at about 20%, at about 50%, or at about 95% relative humidity and at a temperature of about 25°C.

In another aspect, the present disclosure provides a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-

5 yl)acetic acid obtainable by:

a) preparation of a solution of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid in THF at 25mg/mL;

b) dispensing 0.2mL of the solution in a 4mL glass vial;

10 c) evaporation of THF by use of an instrument that allows evaporation by combined use of infrared radiation, vortexing and vacuum set at 30°C and 100mbar for 30minutes;

d) addition of 0.02mL of a solvent selected from ethylacetate, acetonitrile, acetone, or isopropanol to the solid residue and allowing to incubate for 3
15 days at ambient temperature in the closed vial; and

e) isolation of the obtained solid residue.

In another aspect, the present disclosure provides a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid as disclosed herein, for use as a medicament.

20 In a further aspect, the present disclosure provides a pharmaceutical composition comprising as active ingredient a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid as disclosed herein, and at least one pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid as disclosed herein, for use in the manufacture of a pharmaceutical
25 composition, wherein said pharmaceutical composition comprises as active ingredient (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid, and at least one pharmaceutically acceptable carrier.

30 In yet another aspect, the present disclosure provides a use of a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid as disclosed herein, or a pharmaceutical composition as disclosed herein, in

the manufacture of a medicament, for the prevention or treatment of diseases selected from the group consisting of chronic and acute allergic/immune diseases/disorders, comprising asthma, allergic asthma, eosinophilic asthma, severe asthma, rhinitis, allergic rhinitis, angioedema, insect venom allergy, drug allergies, allergic sinusitis, allergic nephritis, allergic conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, ulcerative colitis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, rheumatoid arthritis, and nasal polyposis; eosinophil-related diseases comprising small vessel vasculitides like Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyangiitis (and organ-specific subsets of the latter), hypereosinophilic syndromes like eosinophilic pneumonia, eosinophilic esophagitis, reflux esophagitis, eosinophilic endocarditis (Loeffler's endocarditis), eosinophilia-myalgia syndrome, eosinophilic fasciitis, eosinophilic pustular folliculitis (Ofuji's disease), eosinophilic ulcers, angiolymphoid hyperplasia with eosinophilia (ALHE), eosinophilic cellulitis (Wells syndrome), chronic eosinophilic leukemia, DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms), and Still's disease (systemic onset juvenile idiopathic arthritis); basophil-related diseases, comprising basophilic leukemia and basophilic leucocytosis; and cystic fibrosis.

In another aspect, the present disclosure provides a use of a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid as disclosed herein in the manufacture of a pharmaceutical composition, for the prevention or treatment of diseases selected from the group consisting of chronic and acute allergic/immune diseases/disorders, comprising asthma, allergic asthma, eosinophilic asthma, severe asthma, rhinitis, allergic rhinitis, angioedema, insect venom allergy, drug allergies, allergic sinusitis, allergic nephritis, allergic conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, ulcerative colitis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, rheumatoid arthritis, and nasal polyposis; eosinophil-related diseases comprising small vessel vasculitides like Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyangiitis (and organ-specific subsets of the latter), hypereosinophilic syndromes like eosinophilic pneumonia, eosinophilic esophagitis, reflux esophagitis, eosinophilic endocarditis (Loeffler's endocarditis), eosinophilia-myalgia syndrome, eosinophilic fasciitis, eosinophilic pustular folliculitis (Ofuji's disease), eosinophilic ulcers, angiolymphoid hyperplasia with eosinophilia (ALHE), eosinophilic cellulitis (Wells syndrome), chronic eosinophilic leukemia, DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms), and Still's disease (systemic onset juvenile idiopathic arthritis); basophil-related diseases, comprising basophilic leukemia and basophilic leucocytosis; and cystic fibrosis.

It has surprisingly been found that COMPOUND has significantly improved properties in an *in-vitro* cytotoxicity assay in primary cultured rat hepatocytes. It is thus expected that COMPOUND has an improved toxicity profile *in-vivo*.

- 5 It has now been found that certain crystalline forms of COMPOUND may under certain conditions be found. Said crystalline forms of COMPOUND are novel and may have advantageous properties in view of the potential use of COMPOUND as active pharmaceutical ingredient. Such advantages may include better flow properties; less

essentially shows a gravimetric moisture sorption profile as depicted in Fig. 5, wherein the gravimetric moisture sorption profile is measured at 25°C.

10. A crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid according to any one of claims 1 to 4,
5 obtainable by the processes of claim 5.

11. A crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid according to any one of claims 1 to 10, for use as a medicament.

12. A pharmaceutical composition comprising as active ingredient a crystalline form of (S)-
10 2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid according to any one of claims 1 to 10, and at least one pharmaceutically acceptable carrier.

13. A crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid according to any one of claims 1 to 10, for
15 use in the manufacture of a pharmaceutical composition, wherein said pharmaceutical composition comprises as active ingredient (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid, and at least one pharmaceutically acceptable carrier.

14. Use of a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-
20 6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid according to any one of claims 1 to 10, or a pharmaceutical composition according to claim 12, in the manufacture of a medicament, for the prevention or treatment of diseases selected from the group consisting of chronic and acute allergic/immune diseases/disorders, comprising asthma, allergic asthma, eosinophilic asthma, severe asthma, rhinitis, allergic rhinitis, angioedema, insect
25 venom allergy, drug allergies, allergic sinusitis, allergic nephritis, allergic conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, ulcerative colitis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, rheumatoid arthritis, and nasal polyposis; eosinophil-related diseases comprising small vessel vasculitides like Churg-Strauss syndrome, Wegener's
30 granulomatosis, microscopic polyangiitis (and organ-specific subsets of the latter), hypereosinophilic syndromes like eosinophilic pneumonia, eosinophilic esophagitis, reflux esophagitis, eosinophilic endocarditis (Loeffler's endocarditis), eosinophilia-myalgia syndrome, eosinophilic fasciitis, eosinophilic pustular folliculitis (Ofuji's disease), eosinophilic ulcers, angiolymphoid hyperplasia with eosinophilia (ALHE), eosinophilic cellulitis (Wells syndrome),
35 chronic eosinophilic leukemia, DRESS syndrome (Drug Rash with Eosinophilia and Systemic

Symptoms), and Still's disease (systemic onset juvenile idiopathic arthritis); basophil-related diseases, comprising basophilic leukemia and basophilic leucocytosis; and cystic fibrosis.

15. Use of a crystalline form of (S)-2-(8-((5-chloropyrimidin-2-yl)(methyl)amino)-2-fluoro-6,7,8,9-tetrahydro-5H-pyrido[3,2-b]indol-5-yl)acetic acid according to any one of claims 1 to 10 in the manufacture of a pharmaceutical composition, for the prevention or treatment of diseases selected from the group consisting of chronic and acute allergic/immune diseases/disorders, comprising asthma, allergic asthma, eosinophilic asthma, severe asthma, rhinitis, allergic rhinitis, angioedema, insect venom allergy, drug allergies, allergic sinusitis, allergic nephritis, allergic conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, ulcerative colitis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, rheumatoid arthritis, and nasal polyposis; eosinophil-related diseases comprising small vessel vasculitides like Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyangiitis (and organ-specific subsets of the latter), hypereosinophilic syndromes like eosinophilic pneumonia, eosinophilic esophagitis, reflux esophagitis, eosinophilic endocarditis (Loeffler's endocarditis), eosinophilia-myalgia syndrome, eosinophilic fasciitis, eosinophilic pustular folliculitis (Ofuji's disease), eosinophilic ulcers, angiolymphoid hyperplasia with eosinophilia (ALHE), eosinophilic cellulitis (Wells syndrome), chronic eosinophilic leukemia, DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms), and Still's disease (systemic onset juvenile idiopathic arthritis); basophil-related diseases, comprising basophilic leukemia and basophilic leucocytosis; and cystic fibrosis.