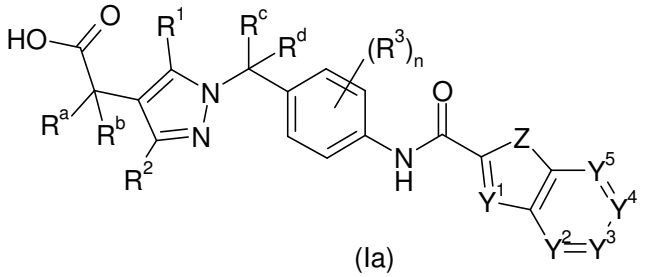
wherein A is an aromatic ring and B is a nitrogen-containing 5-membered hetero ring which may further be substituted, said compounds having hypoglycemic and hypolipidemic activity.

It is an objective of the present invention to provide further compounds having CRTH2 antagonistic activity.

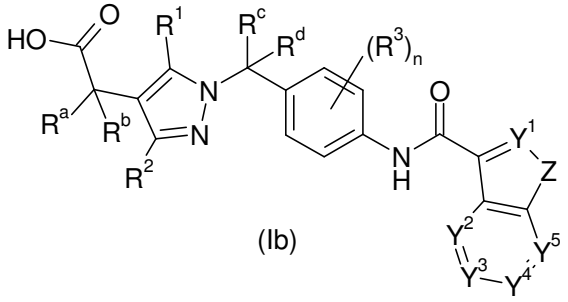
Preferably the compounds of the present invention have enhanced chemical stability, enhanced pharmacokinetic properties (PK) and/or enhanced activity in a whole cell assay.

DETAILED DESCRIPTION

The present disclosure relates to pyrazole compounds of formula (Ia) or (Ib) and pharmaceutically acceptable salts thereof,



(Ia)



(Ib)

wherein

R^a and R^b are independently selected hydrogen, hydroxy, halogen, C_1-C_6-alkyl, C_1-C_6 haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and C_3-C_8-cycloalkyl, or R^a and R^b together with the carbon atom they are bound to form may form a carbonyl group, or R^a and R^b together with the carbon atom they are bound to form a 3- to 8-membered ring, wherein said ring may contain 1 or 2 heteroatoms selected from O, N and S as ring member and wherein the ring members of said ring may optionally be independently

Thus the pyrazole compounds of formula (Ia) or (Ib) according to the present disclosure are suitable for the prevention and/or treatment of diseases related to CRTH2-activity.

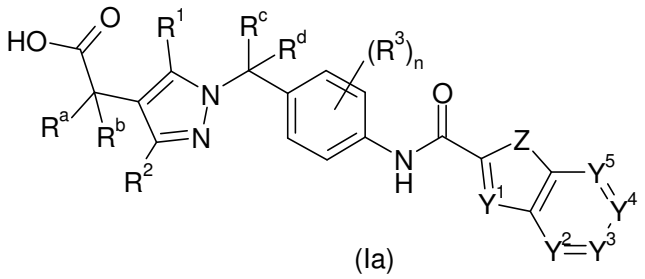
Accordingly the present disclosure further relates to the use of pyrazole compounds of formula (Ia) or (Ib) according to the present disclosure as medicaments.

Furthermore the present disclosure relates to the use of compounds of formula (Ia) or (Ib) for preparing a medicament for the treatment of diseases related to CRTH2-activity. More specifically the present disclosure relates to the use of pyrazole compounds of formula (Ia) or (Ib) for preparing a medicament for the prevention and/or treatment of inflammatory, infectious and immunoregulatory disorders, respiratory or gastrointestinal diseases or complaints, inflammatory diseases of the joints and allergic diseases of the nasopharynx, eyes, and skin.

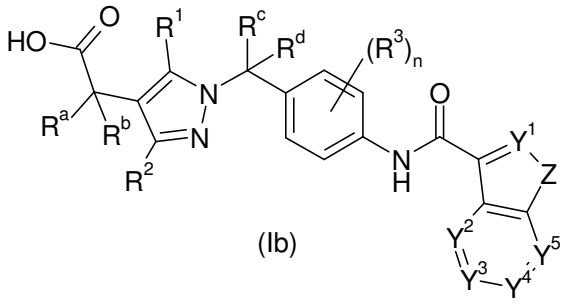
The present disclosure further relates to compounds of formula (Ia) or (Ib) according to the disclosure for treating and/or preveting diseases related to CRTH2-activity More specifically the present disclosure relates to compounds of formula (Ia) or (Ib) for use as a medicament for treating diseases related to CRTH2-activity. More specifically the present disclosure relates to pyrazole compounds of formula (Ia) or (Ib) for use as a medicament for the prevention and/or treatment of inflammatory, infectious and immunoregulatory disorders, respiratory or gastrointestinal diseases or complaints, inflammatory diseases of the joints and allergic diseases of the nasopharynx, eyes, and skin.

Furthermore the present disclosure relates to pharmaceutical formulations, containing one or more of the pyrazole compounds of formula (Ia) or (Ib) according to the present disclosure as sole active substance or in combination with one or more active substances selected from among betamimetics, anticholinergics, corticosteroids, PDE4 inhibitors, LTD4 antagonists, EGFR inhibitors, CCR3 antagonists, CCR5 antagonists, CCR9 antagonists, 5-LO inhibitors, histamine-receptor antagonists, SYK inhibitors and sulphonamides.

According to an aspect there is provided pyrazole compounds of formula (Ia) or (Ib) and pharmaceutically acceptable salts thereof,



(Ia)



(Ib)

wherein

R^a and R^b are independently selected hydrogen, hydroxy, halogen, C_1-C_6-alkyl, C_1-C_6 haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and C_3-C_8-cycloalkyl, or R^a and R^b together with the carbon atom they are bound to form may form a carbonyl group, or R^a and R^b together with the carbon atom they are bound to form a 3- to 8-membered ring, wherein said ring may contain 1 or 2 heteroatoms selected from O, N and S as ring member and wherein the ring members of said ring may optionally be independently substituted by hydroxy, halogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and C_3-C_8-cycloalkyl;

R^c and R^d are independently selected hydrogen, hydroxy, halogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and C_3-C_8-cycloalkyl, or R^c and R^d together with the carbon atom they are bound to form may form a carbonyl group, or R^c and R^d together with the carbon atom they are bound to form a 3- to 8-membered ring, wherein said ring may contain 1 or 2 heteroatoms selected from O, N and S as ring member and wherein the ring members of said ring may optionally be independently substituted by hydroxy, halogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy and C_3-C_8-cycloalkyl;

Y^1, Y^2, Y^3, Y^4 and Y^5 are independently selected from N and CR^y, wherein each R^y is independently selected from H, hydroxy, halogen, cyano, nitro, SF_5, $C(O)NR^fR^g$, C_1-

C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3- C_8-cycloalkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_3-C_8-cycloalkoxy, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylsulfonyl, phenyl, phenoxy, 5- or 6-membered heterocyclyl and 5- or 6-membered heterocyclyloxy, wherein R^f and R^g are independently from each other selected from H, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkenyl and 5- or 6-membered heterocyclyl or R^f and R^g together with the nitrogen atom to which they are bound form a cyclic amine, which may comprise a further heteroatom selected from O, N and S as a ring member;

Z is selected from O, S and NR^z, wherein R^z is H, C_1-C_6-alkyl or benzyl;

R^1 and R^2 are independently from each other selected from H, halogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, -NR^fR^g, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_2-C_6-alkenyl, C_3-C_8-cycloalkenyl, C_3-C_8-cycloalkenyl-C_1-C_6-alkyl, C_3-C_8-cycloalkenyl-C_2-C_6-alkenyl, phenyl, phenyl-C_1-C_6-alkyl, phenyl-C_2-C_6-alkenyl, naphthyl, naphthyl-C_1-C_6-alkyl, naphthyl-C_2-C_6-alkenyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, and heterocyclyl-C_2-C_6-alkenyl, wherein

the C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl moieties in the aforementioned radicals R^1 and R^2 are unsubstituted or carry at least one substituent selected from hydroxy, halogen, cyano, nitro, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkylamino, di C_1-C_6-alkylamino and C_1-C6-alkylsulfonyl and/or

wherein two radicals bound to the same carbon atom of said C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl moieties in the aforementioned radicals R^1 and R^2 together with said carbon atom may form a carbonyl group, and wherein

the C_3-C_8-cycloalkyl, cycloalkenyl, phenyl, naphthyl and heterocyclyl moieties in the aforementioned radicals R^1 and R^2 are unsubstituted or carry at least one substituent selected from hydroxy, halogen, cyano, nitro, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylsulfonyl, phenyl and 5- or 6- membered hetaryl and/or

wherein two radicals bound to the same carbon atom of said C_3-C_8-cycloalkyl, C_3-C_8-cycloalkenyl and heterocyclyl moieties of the radicals R^1 and R^2 together with said carbon atom may form a carbonyl group, and wherein

R^f and R^g are independently from each other selected from H, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkenyl and heterocyclyl or

R^f and R^g together with the nitrogen atom to which they are bound form a cyclic amine, which may comprise a further heteroatom selected from O, N and S as a ring member;

n is an integer selected from 0, 1, 2 or 3; and

R^3 if present are selected independently from each other from halogen, C_1-C_6-alkoxy and C_1-C_6-haloalkoxy.

According to another aspect, there is provided pyrazole compounds of formula (Ia) or (Ib) described herein for use as medicaments.

According to another aspect, there is provided pyrazole compounds of formula (Ia) or (Ib) described herein for use for the prevention and/or treatment of inflammatory, infectious and immunoregulatory disorders, respiratory or gastrointestinal diseases or complaints, inflammatory diseases of the joints and allergic diseases of the nasopharynx, eyes, and skin.

According to another aspect, there is provided use of pyrazole compounds of formula (Ia) or (Ib) described herein in the manufacture of a medicament for the prevention and/or treatment of inflammatory, infectious and immunoregulatory disorders, respiratory or gastrointestinal diseases or complaints, inflammatory diseases of the joints and allergic diseases of the nasopharynx, eyes, and skin such as rheumatoid arthritis, atherosclerosis, allergic or non-allergic rhinitis or sinusitis, chronic sinusitis or rhinitis, nasal polyposis, chronic rhinosinusitis, acute rhinosinusitis, asthma, pediatric asthma, allergic bronchitis, alveolitis, Farmer's disease, hyperreactive airways, allergic conjunctivitis, bronchitis or pneumonitis caused by infection, e.g. by bacteria or viruses or helminthes or fungi or protozoans or other pathogens, bronchiectasis, adult respiratory distress syndrome, bronchial and pulmonary edema, bronchitis or pneumonitis or interstitial pneumonitis caused by different origins, e.g.

aspiration, inhalation of toxic gases, vapors, bronchitis or pneumonitis or interstitial pneumonitis caused by heart failure, X-rays, radiation, chemotherapy, bronchitis or pneumonitis or interstitial pneumonitis associated with collagenosis, e.g. lupus erythematodes, systemic scleroderma, lung fibrosis, idiopathic pulmonary lung fibrosis (IPF), interstitial lung diseases or interstitial pneumonitis of different origin, including asbestosis, silicosis, m. Boeck or sarcoidosis, granulomatosis, cystic fibrosis or mucoviscidosis, or α1-antitrypsin deficiency, eosinophilic cellulites (e.g., Well's syndrome), eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), eosinophilic fasciitis (e. g., Shulman's syndrome), delayed-type hypersensitivity, non-allergic asthma; exercise induced bronchoconstriction; chronic obstructive pulmonary disease (COPD), acute bronchitis, chronic bronchitis, cough, pulmonary emphysema; systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporin), eosinophilia-myalgia syndrome due to the ingestion of contaminated tryptophane, insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, immune thrombocytopenia (adult ITP, neonatal thrombocytopenia, pediatric ITP), immune hemolytic anemia (auto-immune and drug induced), Evans syndrome (platelet and red cell immune cytopaenias), Rh disease of the newborn, Goodpasture’s syndrome (anti-GBM disease), Celiac, autoimmune cardio-myopathy juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e. g., necrotizing, cutaneous, and hypersensitivity vasculitis); erythema nodosum; eosinophilic myositis, eosinophilic fasciitis, cancers with leukocyte infiltration of the skin or organs.

According to another aspect, there is provided pharmaceutical formulations, containing one or more of the pyrazole compound of formula (Ia) and/or (Ib) described herein.

According to another aspect, there is provided pharmaceutical formulations, containing one or more pyrazole compound of formula (Ia) and/or (Ib) described herein in combination with one or more active substances selected from among betamimetics, anticholinergics, corticosteroids, PDE4 inhibitors, LTD4 antagonists, EGFR inhibitors, CCR3 antagonists,

CCR5 antagonists, CCR9 antagonists, 5-LO inhibitors, histamine-receptor antagonists, SYK inhibitors and sulfonamides.

The activity in a whole cell eosinophil shape change assay of the compounds of the disclosure can be determined, for example, according to the following references: (i) Mathiesen JM, Ulven T, Martini L, Gerlach LO, Heinemann A, Kostenis E. Identification of indol derivatives exclusively interfering with a G protein-independent signalling pathway of the prostaglandin D2 receptor CRTH2. Mol Pharmacol. 2005 Aug;68(2):393-402; (ii) Schuligoi R, Schmidt R,

Geisslinger G, Kollroser M, Peskar BA, Heinemann A. PGD2 metabolism in plasma: kinetics and relationship with bioactivity on DP1 and CRTH2 receptors. Biochem Pharmacol. 2007 Jun 30;74(1):107-17; (iii) Royer JF, Schratl P, Carrillo JJ, Jupp R, Barker J, Weyman-Jones C, Beri R, Sargent C, Schmidt JA, Lang-Loidolt D, Heinemann A. A novel antagonist of prostaglandin D2 blocks the locomotion of eosinophils and basophils. Eur J Clin Invest. 2008 Sep;38(9):663-71.

The chemical stability of the compounds of the disclosure can be determined, for example, under the following conditions: (i) 3 days incubation at 60°C in 0.1 N HCl (hydrolytic stability under acidc conditions); (ii) 3 days incubation at 60°C in pH 4.0 buffer solution (hydrolytic stability under weakly acidic conditions); (iii) 3 days incubation at 60°C in pH 7.4 buffer solution (hydrolytic stability at physiological pH); (iv) 3 days incubation at 20°C in 0.3 % hydrogen peroxide (stability against oxidants); (v) 24 h incubation under UV-radiation (lambda = 300 - 800 nm, P = 250 W/m2) in water (stability against light). The kinetics of degradation can, for example, be determined by HPLC analysis.

The pharmacokinetic properties (PK) of the compounds of the disclosure can be determined in pre-clinical animal species, for example, mouse, rat, dog, guinea pig, mini pig, cynomolgus monkey, rhesus monkey. The pharmacokinetic properties of a compound can be described, for example, by the following parameters: Mean residence time, half-life, volume-of-distribution, AUC (area under the curve), clearance, bioavailability after oral administration.

USED TERMS AND DEFINITIONS

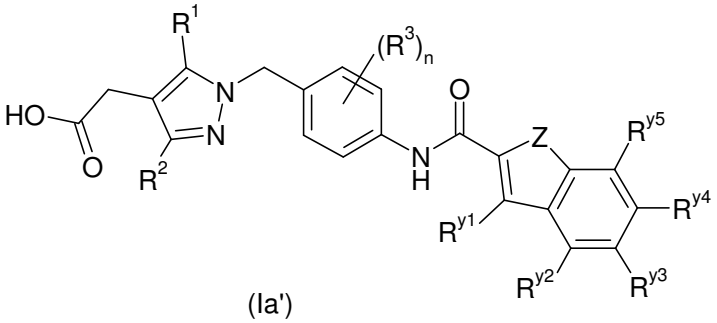
Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals or moieties defined below, the number of carbon atoms is often specified preceding the group. As an example "C_1-C_6-alkyl" means an alkyl group or radical having 1 to 6 carbon atoms.

In general, for groups comprising two or more subgroups, the last named group is the radical attachment point.

16. Pyrazole compounds of formula (Ia) or (Ib) according to any of the preceding claims, wherein R^3 if present are independently selected from halogen.

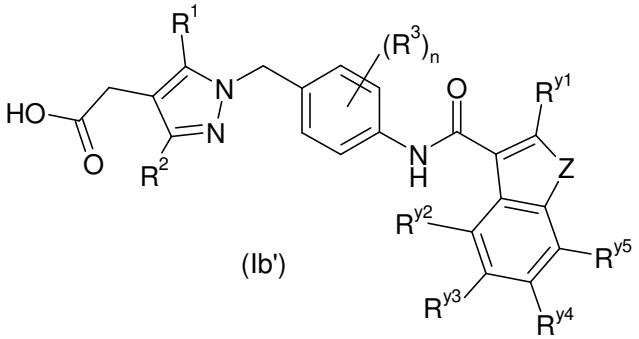
17. Pyrazole compounds of formula (Ia) according to any of the preceding claims, wherein the pyrazole compounds are selected from compounds of formula (Ia'),



(Ia')

wherein Z, R^1, R^2, R^3, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R^{y5} have one of the meanings given in any of the preceding claims and n is 0 or 1.

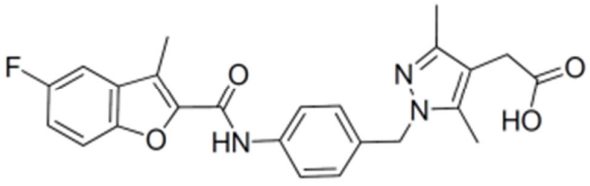
18. Pyrazole compounds of formula (Ib) according to any of claims 1 to 16, wherein the pyrazole compounds are selected from compounds of general formula (Ib'),



(Ib')

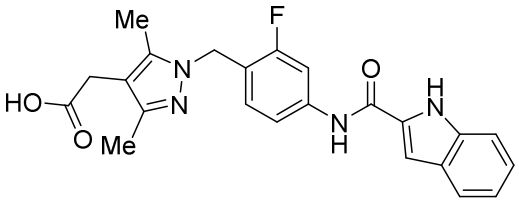
wherein Z, R^1, R^2, R^3, R^{y1}, R^{y2}, R^{y3}, R^{y4} and R^{y5} have one of the meanings given in any of the preceding claims and n is 0 or 1.

19. A pyrazole compound of formula (Compound 4) and pharmaceutically acceptable salts thereof according to claim 1,

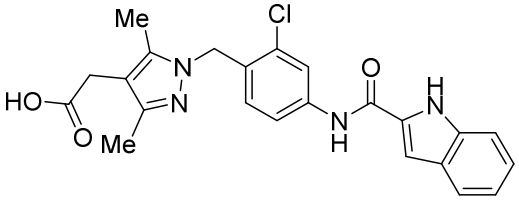


(Compound 4).

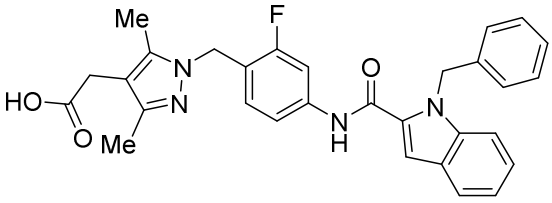
20. A pyrazole compound of formula (Ia) or (Ib) and pharmaceutically acceptable salts thereof according to claim 1, selected from the group consisting of:



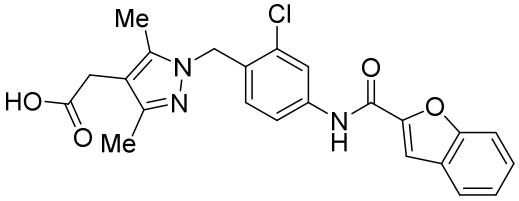
(Compound 1);



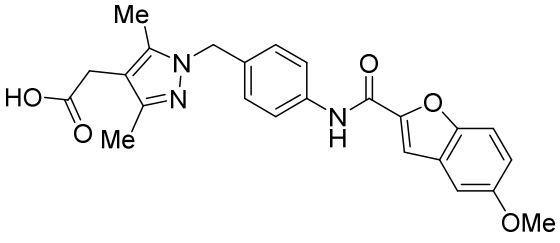
(Compound 2);



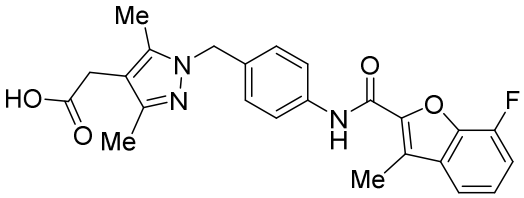
(Compound 3);



(Compound 5);



(Compound 6);



(Compound 7);