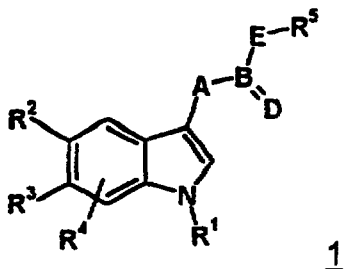


**New hydroxyindoles, their use as inhibitors of
phosphodiesterase 4 and processes for their preparation**

Technical field

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The invention relates to substituted hydroxyindoles of
the general formula 1



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processes for their preparation, pharmaceutical
preparations which contain these compounds, and the
pharmaceutical use of these compounds, which are
inhibitors of phosphodiesterase 4, as active compounds
15 for the treatment of disorders which can be affected by
inhibition of phosphodiesterase 4 activity in
immunocompetent cells (e.g. macrophages and
lymphocytes) by the compounds according to the
invention.

20

Prior art

The activation of cell membrane receptors by
transmitters leads to the activation of the "second
25 messenger" system. Adenylate cyclase synthesizes active
cyclic AMP (cAMP) or cyclic GMP (cGMP) from AMP and
GMP. These lead, for example, to relaxation in smooth
muscle cells or to inhibition of mediator release or
synthesis in inflammatory cells. The breakdown of the
30 "second messenger" cAMP and cGMP is carried out by the
phosphodiesterases (PDE). To date, 7 families of PDE
enzymes (PDE1-7) are known, which differ by their
substrate specificity (cAMP, cGMP or both) and the
dependence on other substrates (e.g. calmodulin). These

isoenzymes have different functions in the body and are prominent to different extents in the individual cell types (Beave JA, Conti M and Heaslip RJ, Multiple cyclic nucleotide phosphodiesterases, Mol. Pharmacol. 1994, 46: 399-405; Hall IP, Isoenzyme selective phosphodiesterase inhibitors; potential clinical uses, Br. J. clin. Pharmacol. 1993, 35: 1-7). As a result of inhibition of the various PDE isoenzyme types, there is an accumulation of cAMP or cGMP in the cells, which can be therapeutically utilized (Torphy TJ, Livi GP, Christensen SB, Novel Phosphodiesterase Inhibitors for the Therapy of Asthma, Drug News and Perspectives 1993, 6: 203-214).

In the cells important for allergic inflammation (lymphocytes, mast cells, eosinophilic granulocytes, macrophages), the prevailing PDE isoenzyme is of type 4 (Torphy, J T. and Undem, B. J., Phosphodiesterase inhibitors: new opportunities for the treatment of asthma, Thorax 1991, 46: 512-523). The inhibition of PDE 4 by suitable inhibitors is therefore considered as an important starting point for the therapy of a large number of allergically induced disorders (Schudt Ch, Dent G, Rabe K, Phosphodiesterase Inhibitors, Academic Press London 1996).

An important property of phosphodiesterase 4 inhibitors is the inhibition of the release of tumour necrosis factor α (TNF α) from inflammatory cells. TNF α is an important pro-inflammatory cytokine, which affects a large number of biological processes. TNF α is released, for example, from activated macrophages, activated T lymphocytes, mast cells, basophils, fibroblasts, endothelial cells and astrocytes in the brain. It has a self-activating effect on neutrophils, eosinophils, fibroblasts and endothelial cells, as a result of which various tissue-destroying mediators are released. In monocytes, macrophages and T lymphocytes, TNF α brings about the increased production of further pro-

inflammatory cytokines such as GM-CSF (granulocyte-macrophage colony-stimulating factor) or interleukin-8. On account of its inflammation-promoting and catabolic action, TNF α plays a central part in a large number of disorders, such as inflammation of the airways, inflammation of the joints, endotoxic shock, tissue rejection, AIDS and numerous other immunological disorders. Inhibitors of phosphodiesterase 4 are thus also suitable for the therapy of disorders of this type which are associated with TNF α .

Chronic obstructive pulmonary diseases (COPD) are widespread in the population and also have great economic importance. Thus COPD diseases cause about 10-15% of all illness costs in the developed countries and about 25% of all cases of death in the USA are to be attributed to this cause (Norman P.: COPD: New developments and therapeutic opportunities, Drug News Perspect. 11 (7), 431-437, 1998), however the patients at the time of death are usually over 55 years old (Nolte D.: Chronische Bronchitis - eine Volkskrankheit multifaktorieller Genese. Atemw.-Lungenkrkh. [Chronic bronchitis - a widespread disease of multifactorial origin]. 20 (5), 260-267, 1994). The WHO estimates that COPD will be the third most frequent cause of death within the next 20 years.

The syndrome of chronic obstructive lung diseases (COPD) summarizes various syndromes of chronic bronchitis with the symptoms coughing and expectoration and progressive and irreversible impairment of lung function (exhalation is particularly affected). The course of the disease is episodic and often complicated by bacterial infections (Rennard S.I.: COPD: Overview of definitions, Epidemiology, and factors influencing its development. Chest, 113 (4) Suppl., 235S-241S, 1998). In the course of the disease, the lung function continuously decreases, the lungs become increasingly emphysematous and the respiratory distress of the

patients is obvious. This disease clearly adversely affects the quality of life of the patients (dyspnoea, low exercise tolerance) and significantly reduces their life expectancy. The main risk factor besides
5 environmental factors is smoking (Kummer F.: Asthma und COPD. Atemw.-Lungenkrkh. 20 (5), 299-302, 1994; Rennard S.I.: COPD: Overview of definitions, Epidemiology, and factors influencing its development. Chest, 113 (4) Suppl., 235S-241S, 1998) and therefore men are clearly
10 more often affected than women. As a result of the change in living habits and the increase in the number of smokers, this picture, however, will change in future.

15 The current therapy aims only at the alleviation of the symptoms, without causally intervening in the progression of the disease. The use of long-acting Beta2 agonists (e.g. salmeterol) possibly in
20 combination with muscarinergic antagonists (e.g. ipratropium) improves the lung function by bronchodilatation and is employed routinely (Norman P.: COPD: New developments and therapeutic opportunities, Drugs News Perspect. 11 (7), 431-437, 1998). A large
25 part in the COPD episodes is played by bacterial infections, which have to be treated with antibiotics (Wilson R.: The role of infection in COPD, Chest, 113 (4) Suppl., 242S-248S, 1998; Grossman R.F.: The value of antibiotics and the outcomes of antibiotic therapy in exacerbations of COPD. Chest, 113 (4) Suppl., 249S-
30 255S, 1998). As yet, the therapy of this disease is unsatisfactory, particularly with respect to the continuous decrease in lung function. New therapeutic approaches which affect inflammatory mediators, proteases or adhesion molecules could be very promising
35 (Barnes P.J.: Chronic obstructive disease: new opportunities for drug development, TiPS 10 (19), 415-423, 1998).

Independently of the bacterial infections complicating the disease, a chronic inflammation which is dominated by neutrophilic granulocytes is found in the bronchi. The mediators and enzymes released by neutrophilic granulocytes, inter alia, have been held responsible for the structural changes observed in the airways (emphysema). The inhibition of the activity of the neutrophilic granulocytes is thus a rational approach to prevent or to slow down progression of COPD (impairment of lung function parameters). An important stimulus for the activation of the granulocytes is the pro-inflammatory cytokine TNF α (tumour necrosis factor). Thus it is known that TNF α stimulates the formation of oxygen radicals by neutrophilic granulocytes (Jersmann, H.P.A.; Rathjen, D.A. and Ferrante A.: Enhancement of LPS-induced neutrophil oxygen radical production by TNF α , Infection and Immunity, 4, 1744-1747, 1998). PDE4 inhibitors can very effectively inhibit the release of TNF α from a large number of cells and thus suppress the activity of the neutrophilic granulocytes. The non-specific PDE inhibitor pentoxifylline is able to inhibit both the formation of oxygen radicals and the phagocytosability of neutrophilic granulocytes (Wenisch, C.; Zedtwitz-Liebenstein, K.; Parschalk, B. and Graninger W.: Effect of pentoxifylline in vitro on neutrophil reactive oxygen production and phagocytic ability assessed by flow cytometry, Clin. Drug. Invest., 13(2):99-104, 1997).

Various PDE 4 inhibitors are already known. As a matter of priority, these are xanthine derivatives, rolipram analogues or nitraquazone derivatives (general survey in: Karlsson J-A, Aldos D, Phosphodiesterase 4 inhibitors for the treatment of asthma, Exp. Opin. Ther. Patents 1997, 7: 989-1003). Until now, it was not possible to use any of these compounds clinically. It had to be established that the known PDE 4 inhibitors also have various side-effects such as nausea and

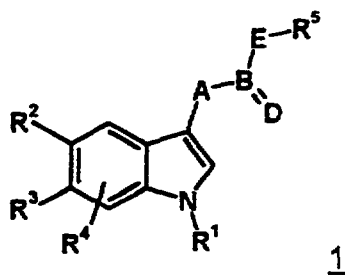
emesis, which it was not possible to suppress adequately until now. The discovery of new PDE 4 inhibitors with better therapeutic breadth is therefore necessary.

5

Although indoles have been playing an important part for many years in the development of new active compounds for various indications, until now hydroxyindoles were completely unknown as inhibitors of
10 PDE 4.

Description of the invention

The invention relates to substituted hydroxyindoles of
15 the general formula 1



in which

20

R¹, R⁵ are

- C₁...₁₂-alkyl, straight-chain or branched-chain, optionally mono- or polysubstituted by -OH, -SH, -NH₂, -NHC₁...₆-alkyl, -N(C₁...₆-alkyl)₂,
25 -NHC₆...₁₄aryl, -N(C₆...₁₄aryl)₂,
-N(C₁...₆alkyl)(C₆...₁₄aryl), -NHCOR⁶, -NO₂, -CN, -F, -Cl, -Br, -I, -O-C₁...₆-alkyl, -O-C₆...₁₄-aryl, -O(CO)R⁶, -S-C₁...₆-alkyl, -S-C₆...₁₄aryl, -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C₁...₆alkyl,
30 -OSO₂C₆...₁₄aryl, -(CS)R⁶, -COOH, -(CO)R⁶, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having



- 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, where the C₆...₁₄aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R⁴,
- 5
- C₁...₁₂-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain,
- 10 optionally mono- or polysubstituted by -OH, -SH, -NH₂, -NHC₁...₆-alkyl, -N(C₁...₆-alkyl)₂, -NHC₆...₁₄aryl, -N(C₆...₁₄aryl)₂, -N(C₁...₆alkyl)(C₆...₁₄aryl), -NHCOR⁶, -NO₂, -CN, -F, -Cl, -Br, -I, -O-C-₁...₆-alkyl, -O-C₆...₁₄-
- 15 aryl, -O(CO)R⁶, -S-C₁...₆-alkyl, -S-C₆...₁₄aryl, -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C₁...₆alkyl, -OSO₂C₆...₁₄aryl, -(CS)R⁶, -COOH, -(CO)R⁶, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring
- 20 members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, where the C₆...₁₄aryl groups and the included carbocyclic and heterocyclic substituents for their part
- 25 can optionally be mono- or polysubstituted by R⁴,
- mono-, bi- or tricyclic saturated or mono- or
- 30 polyunsaturated carbocycles having 3...14 ring members,
- optionally mono- or polysubstituted by -OH, -SH, -NH₂, -NHC₁...₆-alkyl, -N(C₁...₆-alkyl)₂, -NHC₆...₁₄aryl, -N(C₆...₁₄aryl)₂,
- 35 -N(C₁...₆alkyl)(C₆...₁₄aryl), -NHCOR⁶, -NO₂, -CN, -F, -Cl, -Br, -I, -O-C-₁...₆-alkyl, -O-C₆...₁₄-aryl, -O(CO)R⁶, -S-C₁...₆-alkyl, -S-C₆...₁₄aryl, -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C₁...₆alkyl, -OSO₂C₆...₁₄aryl, -(CS)R⁶, -COOH, -(CO)R⁶, mono-,

- bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, where the C₆...₁₄aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R⁴,
- mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, optionally mono- or polysubstituted by -OH, -SH, -NH₂, -NHC₁...₆-alkyl, -N(C₁...₆-alkyl)₂, -NHC₆...₁₄aryl, -N(C₆...₁₄aryl)₂, -N(C₁...₆alkyl)(C₆...₁₄aryl), -NHCOR⁶, -NO₂, -CN, -F, -Cl, -Br, -I, -O-C-₁...₆-alkyl, -O-C₆...₁₄-aryl, -O(CO)R⁶, -S-C₁...₆-alkyl, -S-C₆...₁₄aryl, -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C₁...₆alkyl, -OSO₂C₆...₁₄aryl, -(CS)R⁶, -COOH, -(CO)R⁶, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, where the C₆...₁₄aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R⁴,
- carbo- or heterocyclic saturated or mono- or polyunsaturated spirocycles having 3...10 ring members, where heterocyclic systems contain 1...6 heteroatoms, which are preferably N, O and S,

optionally mono- or polysubstituted by -OH,
 -SH, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂,
 -NHC_{6...14}aryl, -N(C_{6...14}aryl)₂,
 -N(C_{1...6}alkyl)(C_{6...14}aryl), -NHCOR⁶, -NO₂, -CN,
 5 -F, -Cl, -Br, -I, -O-C_{1...6}-alkyl, -O-C_{6...14}-
 aryl, -O(CO)R⁶, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl,
 -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C_{1...6}alkyl,
 -OSO₂C_{6...14}aryl, -(CS)R⁶, -COOH, -(CO)R⁶, mono-,
 bi- or tricyclic saturated or mono- or
 10 polyunsaturated carbocycles having 3...14 ring
 members, mono-, bi- or tricyclic saturated or
 mono- or polyunsaturated heterocycles having
 5...15 ring members and 1...6 heteroatoms,
 which are preferably N, O and S, where the
 15 C_{6...14}aryl groups and the included carbocyclic
 and heterocyclic substituents for their part
 can optionally be mono- or polysubstituted by
 R⁴,

20 where R¹ and R⁵ can be identical or different;

R², R³ can be hydrogen or -OH, where at least one of
 the two substituents must be -OH;

25 R⁴ is

-H, -OH, -SH, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂,
 -NHC_{6...14}aryl, -N(C_{6...14}aryl)₂,
 -N(C_{1...6}alkyl)(C_{6...14}aryl), -NHCOR⁶, -NO₂, -CN, -COOH,
 30 -(CO)R⁶, -(CS)R⁶, -F, -Cl, -Br, -I, -O-C_{1...6}-alkyl,
 -O-C_{6...14}-aryl, -O(CO)R⁶, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl,
 -SOR⁶, -SO₂R⁶.

R⁶ can be

35

-H, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂,
 -NHC_{6...14}aryl, -N(C_{6...14}aryl)₂,
 -N(C_{1...6}alkyl)(C_{6...14}aryl), -O-C_{1...6}-alkyl, -O-C_{6...14}-
 aryl, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl,



-C₁...₁₂-alkyl, straight-chain or branched-chain,
-C₁...₁₂-alkenyl, mono- or polyunsaturated, straight-
chain or branched-chain,
-mono-, bi- or tricyclic saturated or mono- or
5 polyunsaturated carbocycles having 3...14 ring
members,
-mono-, bi- or tricyclic saturated or mono- or
polyunsaturated heterocycles having 5...15 ring
members and 1...6 heteroatoms, which are preferably
10 N, O and S;

A is either a bond, or

-CH₂)_m-, -(CH₂)_m-(CH=CH)_n-(CH₂)_p-, -(CHOZ)_m-, -(C=O)-,
-(C=S)-, -(C=N-Z)-, -O-, -S-, -NZ-,

15 where m, p = 0...3 and n = 0...2 and

Z is

-H, or
-C₁...₁₂-alkyl, straight-chain or branched-chain,
-C₁...₁₂-alkenyl, mono- or polyunsaturated, straight-
20 chain or branched-chain,
-mono-, bi- or tricyclic saturated or mono- or
polyunsaturated carbocycles having 3...14 ring
members,
-mono-, bi- or tricyclic saturated or mono- or
25 polyunsaturated heterocycles having 5...15 ring
members and 1...6 heteroatoms, which are preferably
N, O and S;

B can be either carbon or sulphur, or -(S=O)-;

30

D can be oxygen, sulphur, -CH₂ or N-Z,

where **D** can only be S or CH₂ if **B** is carbon;

E can be a bond, or else

$-(CH_2)_m-$, $-O-$, $-S-$, $-(N-Z)-$, where m and Z have the meaning already described beforehand.

5

The invention furthermore relates to the physiologically tolerable salts of the compounds according to formula 1.

10 The physiologically tolerable salts are obtained in a customary manner by neutralization of the bases with inorganic or organic acids or by neutralization of the acids with inorganic or organic bases. Possible
15 inorganic acids are, for example, hydrochloric acid, sulphuric acid, phosphoric acid or hydrobromic acid, organic acids are, for example, carboxylic, sulfo or sulphonc acids such as acetic acid, tartaric acid, lactic acid, propionic acid, glycolic acid, malonic acid, maleic acid, fumaric acid, tannic acid, succinic
20 acid, alginic acid, benzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, cinnamic acid, mandelic acid, citric acid, malic acid, salicylic acid, 3-aminosalicylic acid, ascorbic acid, embonic acid, nicotinic acid, isonicotinic acid, oxalic acid, amino
25 acids, methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, ethane-1,2-disulphonic acid, benzenesulphonic acid, 4-methylbenzenesulphonic acid or naphthalene-2-sulphonic acid. Possible inorganic bases are, for example, sodium hydroxide
30 solution, potassium hydroxide solution, ammonia, and possible organic bases are amines, but preferably tertiary amines, such as trimethylamine, triethylamine, pyridine, N,N-dimethylaniline, quinoline, isoquinoline, α -picoline, β -picoline, γ -picoline, quinaldine or
35 pyrimidine.

In addition, physiologically tolerable salts of the compound according to formula 1 can be obtained by

converting derivatives which have tertiary amino groups into the corresponding quaternary ammonium salts in a manner known per se using quaternizing agents. Possible quaternizing agents are, for example, alkyl halides
5 such as methyl iodide, ethyl bromide and n-propyl chloride, but also arylalkyl halides such as benzyl chloride or 2-phenylethyl bromide.

Furthermore, the invention of the compounds of the
10 formula 1 which contain an asymmetric carbon atom relates to the D form, the L form and D,L mixtures and, in the case of a number of asymmetric carbon atoms, the diastereomeric forms. Those compounds of the formula 1 which contain asymmetric carbon atoms and as a rule are
15 obtained as racemates can be separated into the optically active isomers in a manner known per se, for example using an optically active acid. However, it is also possible to employ an optically active starting substance from the start, a corresponding optically
20 active or diastereomeric compound then being obtained as the final product.

Pharmacologically important properties have been found for the compounds according to the invention, which can
25 be utilized therapeutically.

The compounds according to the invention are inhibitors of the release of TNF α .

30 It is therefore a subject of this invention that the compounds according to formula 1 and their salts, and pharmaceutical preparations which contain these compounds or their salts, can be used for the treatment of disorders in which inhibition of TNF α is beneficial.

35 These disorders include, for example, arthritides including arthritis and rheumatoid arthritis and other arthritic disorders such as rheumatoid spondylitis and osteoarthritis. Further application possibilities are

the treatment of patients who are suffering from sepsis, septic shock, gram-negative sepsis, toxic shock syndrome, respiratory distress syndrome, asthma or other chronic pulmonary disorders, bone resorption
5 diseases or transplant rejection reactions or other autoimmune disorders, such as lupus erythematosus, multiple sclerosis, glomerulonephritis and uveitis, insulin-dependent diabetes mellitus and chronic demyelination.

10

Moreover, the compounds according to the invention can also be employed for the therapy of infections such as virus infections and parasite infections, for example for the therapy of malaria, infection-related fever,
15 infection-related myalgia, AIDS and cachexia.

The compounds according to the invention are inhibitors of phosphodiesterase 4.

20 It is therefore a subject of this invention that the compounds according to formula 1 and their salts, and pharmaceutical preparations which contain these compounds or their salts, can be used for the treatment of disorders in which inhibition of phosphodiesterase 4
25 is beneficial.

Thus the compounds according to the invention can be employed as bronchodilators and for asthma prophylaxis. Compounds according to formula 1 are furthermore
30 inhibitors of the accumulation of eosinophils and their activity. Accordingly, the compounds according to the invention can also be employed in disorders in which eosinophils play a part. These disorders include, for example, inflammatory airway disorders such as
35 bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, eczema, allergic angiitis, inflammations mediated by eosinophils such as eosinophilic fasciitis, eosinophilic pneumonia and PIE syndrome (pulmonary infiltration with eosinophilia),

urticaria, ulcerative colitis, Crohn's disease and proliferative skin disorders such as psoriasis or keratosis.

5 It is a subject of this invention that the compounds according to formula 1 and their salts can inhibit both the lipopolysaccharide (LPS)-induced release of TNF α in human blood *in vitro*, and the LPS-induced pulmonary neutrophilic infiltration in ferrets and domestic pigs
10 *in vivo*. All the pharmacologically important properties found confirm that the compounds according to formula 1 and their salts as well as pharmaceutical preparations which contain these compounds or their salts can be used therapeutically for the treatment of chronic
15 obstructive pulmonary diseases.

The compounds according to the invention furthermore have neuroprotective properties and can be used for the therapy of diseases in which neuroprotection is
20 beneficial. Such disorders are, for example, senile dementia (Alzheimer's disease), loss of memory, Parkinson's disease, depression, stroke and intermittent claudication.

25 Further application possibilities of the compounds according to the invention are the prophylaxis and therapy of prostate diseases, such as, for example, benign prostate hyperplasia, pollakiuria, nocturia, and for the treatment of atony of the bladder and of colics
30 caused by kidney stones.

Finally, the compounds according to the invention can also be used for the inhibition of the development of drug dependence on repeated use of analgesics, such as,
35 for example, morphine, and for the reduction of the development of tolerance on repeated use of these analgesics.

For the production of the medicaments, in addition to the customary auxiliaries, carriers and additives, an efficacious dose of the compounds according to the invention or their salts is used.

5

The dose of the active compounds can vary depending on the route of administration, age and weight of the patient, nature and severity of the disorders to be treated and similar factors.

10

The daily dose can be given as an individual dose to be administered once or subdivided into 2 or more daily doses and is, as a rule, 0.001-100 mg.

15 Possible administration forms are oral, parenteral, intravenous, transdermal, topical, inhalational and intranasal preparations.

For administration, possible customary pharmaceutical
20 preparation forms are those such as tablets, coated tablets, capsules, dispersible powders, granules, aqueous solutions, aqueous or oily suspensions, syrup, juices or drops.

25 Solid pharmaceutical forms can contain inert ingredients and carriers, such as, for example, calcium carbonate, calcium phosphate, sodium phosphate, lactose, starch, mannitol, alginates, gelatin, guar gum, magnesium or aluminium stearates, methylcellulose,
30 talc, highly disperse salicylic acids, silicone oil, high molecular weight fatty acids (such as stearic acid), gelatin, agar-agar or vegetable or animal fats and oils, solid high molecular weight polymers (such as polyethylene glycol); preparations suitable for oral
35 administration can, if desired, contain additional flavourings and/or sweeteners.

Liquid pharmaceutical forms can be sterilized and/or optionally contain auxiliaries such as preservatives,

stabilizers, wetting agents, penetrating agents, emulsifiers, spreading agents, solubilizers, salts, sugars or sugar alcohols for regulation of the osmotic pressure or for buffering, and/or viscosity regulators.

5

Additives of this type are, for example, tartrate and citrate buffers, ethanol, complexing agents (such as ethylenediaminetetraacetic acid and its non-toxic salts). For regulation of the viscosity, possible high
10 molecular weight polymers are those such as, for example, liquid polyethylene oxide, microcrystalline celluloses, carboxymethylcelluloses, polyvinylpyrrolidones, dextrans or gelatin. Solid carriers are, for example, starch, lactose, mannitol, methyl-
15 cellulose, talc, highly disperse salicylic acids, high molecular weight fatty acids (such as stearic acid), gelatin, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular weight polymers such as polyethylene glycol.
20 Oily suspensions for parenteral or topical application can be vegetable synthetic or semi-synthetic oils such as, for example, liquid fatty acid esters in each case having 8 to 22 C atoms in the fatty acid chains, for example palmitic, lauric, tridecylic, margaric,
25 stearic, arachidic, myristic, behenic, pentadecanoic, linoleic, elaidic, brassidic, erucic or oleic acid, which are esterified with mono- to trihydric alcohols having 1 to 6 C atoms, such as, for example, methanol, ethanol, propanol, butanol, pentanol or their isomers,
30 glycol or glycerol. Fatty acid esters of this type are, for example, commercially available Miglyols, isopropyl myristate, isopropyl palmitate, isopropyl stearate, PEG 6-capric acid, caprylic/capric acid esters of saturated fatty alcohols, polyoxyethylene glycerol trioleates,
35 ethyl oleate, waxy fatty acid esters such as artificial duck preen gland fat, isopropyl cocoate, oleyl oleate, decyl oleate, ethyl lactate, dibutyl phthalate, diisopropyl adipate, polyol fatty acid esters and others. Also suitable are silicone oils of differing

viscosities or fatty alcohols such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol or oleyl alcohol, fatty acids such as, for example, oleic acid. Furthermore, vegetable oils such as castor oil,
5 almond oil, olive oil, sesame oil, cottonseed oil, groundnut oil or soya bean oil can be used.

Possible solvents, gel-forming agents and solubilizers are water or water-miscible solvents. Those suitable
10 are, for example, alcohols such as, for example, ethanol or isopropyl alcohol, benzyl alcohol, 2-octyldodecanol, polyethylene glycols, phthalates, adipates, propylene glycol, glycerol, di- or tripropylene glycol, waxes, methylcellosolve, cellosolve, esters,
15 morpholines, dioxane, dimethyl sulphoxide, dimethylformamide, tetrahydrofuran, cyclohexanone etc.

Film-forming agents which can be used are cellulose ethers which can dissolve or swell both in water and in
20 organic solvents, such as, for example, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose or soluble starches.

Mixed forms between gel- and film-forming agents are
25 also perfectly possible. Those used here are especially ionic macromolecules, such as, for example, sodium carboxymethylcellulose, polyacrylic acid, polymethacrylic acid and its salts, sodium amylopectin semiglycolate, alginic acid or propylene glycol
30 alginate as the sodium salt, gum arabic, xanthan gum, guar gum or carrageenan.

Further formulation auxiliaries which can be employed are: glycerol, paraffin of differing viscosities,
35 triethanolamine, collagen, allantoin, novantisolic acid.

The use of surfactants, emulsifiers or wetting agents can also be necessary for formulation, such as, for

example, of Na lauryl sulphate, fatty alcohol ether
sulphates, di-Na N-lauryl- β -iminodipropionate,
polyethoxylated castor oil or sorbitan monooleate,
sorbitan monostearate, polysorbates (e.g. Tween), cetyl
5 alcohol, lecithin, glycerol monostearate,
polyoxyethylene stearate, alkylphenyl polyglycol
ethers, cetyltrimethylammonium chloride or
mono-/dialkyl polyglycol ether orthophosphoric acid
monoethanolamine salts.

10

Stabilizers such as montmorillonites or colloidal
salicylic acids for the stabilization of emulsions or
for the prevention of the breakdown of the active
substances, such as antioxidants, for example
15 tocopherols or butylhydroxyanisole, or preservatives,
such as p-hydroxybenzoic acid esters, can likewise
optionally be necessary for the preparation of the
desired formulations.

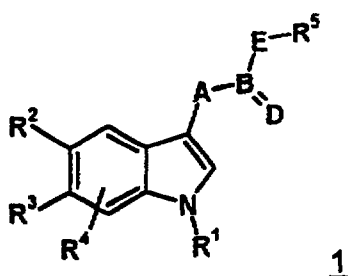
20 Preparations for parenteral administration can be
present in separate dose unit forms such as, for
example, ampoules or vials. Preferably, solutions of
the active compound are used, preferably aqueous
solutions and especially isotonic solutions, but also
25 suspensions. These injection forms can be made
available as finished preparations or only prepared
directly before administration by mixing the active
compound, for example the lyophilizate, if appropriate
with further solid carriers, with the desired solvent
30 or suspending agent.

Intranasal preparations can be present as aqueous or
oily solutions or as aqueous or oily suspensions. They
can also be present as lyophilizates, which are
35 prepared before administration using the suitable
solvent or suspending agent.

The production, dispensation and sealing of the preparations is carried out under the customary antimicrobial and aseptic conditions.

- 5 The invention furthermore relates to processes for the preparation of the compounds according to the invention.

According to the invention, the compounds of the
10 general formula 1



- 15 having the meanings of R^1 , R^2 , R^3 , R^4 , R^5 , A, B, D and E shown beforehand are prepared by converting compounds according to formula 1, for which R^2 or R^3 or R^2 and R^3 = $-O-R^7$, into the compounds according to the invention by removal of R^7 .

- 20 R^7 in this case represents substituents suitable as leaving groups, such as, for example, alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl, acyl, alkoxy-carbonyl, aryloxycarbonyl, aminocarbonyl, N-substituted aminocarbonyl, silyl or sulphonyl groups, and
25 complexing agents, such as, for example, compounds of boric acid, phosphoric acid and covalently or coordinatively bonded metals, such as zinc, aluminium or copper.

- 30 Particularly preferred reactions for the removal of R^7 within the meaning of the preparation process according to the invention are hydrolyses using suitable bases, such as, for example, sodium hydroxide solution,

potassium hydroxide solution or sodium carbonate or potassium carbonate.

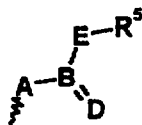
These hydrolyses are preferably used for R^7 = acyl,
5 alkoxy carbonyl, aryloxy carbonyl, aminocarbonyl,
N-substituted aminocarbonyl, silyl or sulphonyl groups
and complexing agents, such as, for example, compounds
of boric acid, phosphoric acid and coordinatively
bonded metals, such as zinc, aluminium or copper.

10

Particularly preferred reactions within the meaning of
the preparation process according to the invention for
the removal of R^7 from the compounds in which R^7 is an
alkyl, cycloalkyl, arylalkyl, aryl or heteroaryl group
15 are ether cleavages, for example by means of
hydrobromic acid, hydrochloric acid, hydriodic acid,
and using activating Lewis acids, such as, for example,
 $AlCl_3$, BF_3 , BBr_3 or $LiCl$, in each case in the absence or
in the presence of additional activators, such as, for
20 example, ethane-1,2-dithiol or benzyl mercaptan and
ether cleavages by means of hydrogen, at elevated
pressure or at normal pressure, in the presence of a
suitable catalyst, such as, for example, palladium or
iridium catalysts.

25

According to the invention, the compounds of the
general formula 1 having the meanings of R^1 , R^2 , R^3 , R^4 ,
 R^5 , A, B, D and E shown beforehand are also prepared by
converting, by means of conversions of the
30 substructure:



by reactions known per se, compounds of the formula 1
according to the invention into other compounds of the
35 formula 1 according to the invention.

Particularly preferred conversion reactions with compounds of the formula 1 according to the invention are, for example, for **A** = -(C=O)-, reductions to give **A** = -(CH-OH)- or **A** = -CH₂- by means of reducing agents
5 known per se, such as, for example, sodium borohydride, or by hydrogenations, which can optionally also be carried out stereoselectively.

Further preferred conversion reactions are the
10 conversion of compounds for which **D** and **E** are oxygen into substances in which only **D** is oxygen, but **E** is -(N-Z)-, where Z has the meaning already explained.

Working examples

15 Exemplary preparation processes for compounds of the formula 1 according to the invention from starting substances of the type described, in which R⁷ is an alkyl, cycloalkyl, arylalkyl, aryl or heteroaryl group:

20

Example 1:

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide (1)

25

1.4 g of N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-methoxyindol-3-yl]-2-oxoacetamide (3 mmol)
are dissolved in 100 ml of dichloromethane. The solution is heated to reflux and treated with a
30 solution of 14 mmol of BBr₃ in 15 ml of dichloromethane with stirring. The reaction mixture is refluxed for 3 hours. After cooling, the solution is intensively stirred for 3 hours at 20°C with 200 ml of an aqueous sodium hydrogencarbonate solution. The product
35 crystallizes out in the course of this. It is isolated, dried at 60°C and recrystallized from 80 ml of ethanol.
Yield: 1.1 g (80% of theory)
Melting point: 213 - 214°C

Example 2:

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide (1)

5
5 g (38 mmol) of anhydrous aluminium chloride are introduced into 50 ml of ethane-1,2,-dithiol. A solution of 4.7 g of N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-methoxyindol-3-yl]-2-oxoacet-
10 amide (10 mmol) in 50 ml of dichloromethane is added at 0°C. The mixture is stirred at 0°C for 4 hours. 50 ml of 10% strength hydrochloric acid are added dropwise at 0 - 10°C with stirring. The crystallizing product is isolated, washed with water and dried at 20°C. A pure
15 product is obtained by recrystallization from ethanol (180 ml).

Yield: 3.1 g (67% of theory)

Melting point: 212 - 214°C

20 Exemplary preparation process for compounds of the formula 1 according to the invention from starting substances of the type described, in which R⁷ is an acyl, alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, N-substituted aminocarbonyl, silyl or sulphonyl group:

25

Example 3:

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide Na salt (2)

30

5 g of N-(3,5-dichloropyridin-4-yl)-2-[5-acetoxy-1-(4-fluorobenzyl)-indol-3-yl]-2-oxoacetamide (10 mmol) are stirred at 40 - 50°C for 1 hour in 50 ml of dilute sodium hydroxide solution. The solution is neutralized
35 with hydrochloric acid (10% strength) while cooling with ice and concentrated to dryness. The residue is dissolved in 80 ml of acetone. Insoluble constituents are removed. The clear solution is treated with a solution of 0.4 g of NaOH in 3 ml of water and stirred

at 20°C for 2 hours. The crystallized product is isolated, washed with acetone and dried at 60°C.

Yield: 2.44 g (51% of theory)

Melting point: 265°C

5

Exemplary preparation process for compounds of the formula 1 according to the invention from other compounds of the formula 1 according to the invention:

10 Example 4:

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-hydroxyacetamide (3)

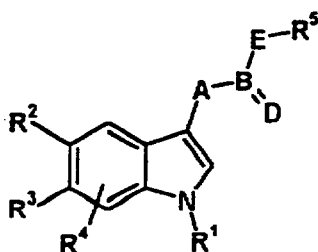
15 1 g of N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide (1; 2 mmol) are suspended in 75 ml of methanol. After addition of a solution of 0.2 g of sodium borohydride in 3 ml of dilute sodium hydroxide solution, the reaction mixture
20 is stirred at 20°C for 6 hours. After the solvent has been removed by distillation, the residue is recrystallized from 40 ml of ethanol.

Yield: 0.5 g (50% of theory)

Melting point: 205 - 207°C

25

Using the exemplary variants indicated, numerous further compounds of the formula 1 can be prepared, of which the following are given by way of example:



30

Cpd.	R ¹	R ²	R ³	R ⁴	R ⁵	A	B	D	E	Melting point [°C]
1	4-Fluorobenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	215
2	4-Fluorobenzyl	-O ⁻ Na ⁺	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	265
3	4-Fluorobenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(CHOH)-	C	O	-(N-H)-	205-207
4	2,6-Difluorobenzyl	-OH	-H	-H	4-Pyridyl	-(C=O)-	C	O	-(N-H)-	327-329
5	2,6-Difluorobenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	266-268
6	3-Nitrobenzyl	-O ⁻ Na ⁺	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	235-238 dec.
7	n-Propyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	280-282
8	Isopropyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	245-247
9	Cyclopentylmethyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	246-248
10	4-Fluorobenzyl	-OH	-H	-H	2,6-Dichlorophenyl	-(C=O)-	C	O	-(N-H)-	216-218
11	4-Fluorobenzyl	-OH	-H	-H	2,6-Dichloro-4-trifluoromethylphenyl	-(C=O)-	C	O	-(N-H)-	199-201
12	4-Fluorobenzyl	-OH	-H	-H	2,6-Dichloro-4-trifluoromethoxyphenyl	-(C=O)-	C	O	-(N-H)-	176-178
13	4-Fluorobenzyl	-H	-OH	-H	3,5-Dichloro-4-pyridyl	-(C=O)-	C	O	-(N-H)-	212-213
14	4-Methoxybenzyl	-OH	-H	-H	3,5-Dichloro-4-pyridyl	-	C	O	-(N-H)-	239-241

The compounds according to the invention are strong inhibitors of phosphodiesterase 4 and TNF α release. Their therapeutic potential is confirmed *in vivo*, for example, by the inhibition of the asthmatic late-phase
5 reaction (eosinophilia) in guinea-pigs and by the influencing of the allergen-induced vascular permeability in actively-sensitized brown Norway rats.

Inhibition of phosphodiesterase

10

The PDE 4 activity is determined in enzyme preparations of human polymorphonuclear lymphocytes (PMNLs), the PDE 2, 3 and 5 activity with PDE from human platelets. Human blood was anticoagulated with citrate. The
15 thrombocyte-rich plasma in the supernatant is separated from the erythrocytes and leucocytes by centrifugation at 700 $\times$ g for 20 minutes at RT. The platelets are lysed by ultrasound and employed in the PDE 3 and PDE 5 assay. For the determination of the PDE 2 activity, the
20 cytosolic platelet fraction is purified on an anion exchange column by means of NaCl gradients and the PDE 2 peak is recovered for the assay. The PMNLs for the PDE 4 determination are isolated by a following dextran sedimentation and subsequent gradient
25 centrifugation using Ficoll-Paque. After a second washing of the cells, the erythrocytes still contained are lysed in the course of 6 minutes at 4°C by the addition of 10 ml of hypotonic buffer (155 mM NH₄Cl, 10 mM NaHCO₃, 0.1 mM EDTA, pH 7.4). The still intact
30 PMNLs are washed with PBS a further two times and lysed by means of ultrasound. The supernatant of a one-hour centrifugation at 4°C at 48,000 $\times$ g contains the cytosolic fraction of the PDE 4 and is employed for the PDE 4 measurements.

35

The phosphodiesterase activity is determined with some modifications according to the method described by Thompson et al. (Thompson, W.J.; Appleman, M.M., Assay of cyclic nucleotide phosphodiesterase and resolution

of multiple molecular forms of the enzyme, Adv. Cycl. Nucl. Res. 1979, 10, 69-92).

The reaction mixtures contain 50 mM tris HCl (pH 7.4),
5 5 mM MgCl₂, the inhibitors in variable concentrations,
the corresponding enzyme preparation and also the
further components necessary for the detection of the
individual isoenzymes (see below). The reaction is
started by the addition of the substrate 0.5 μ M [³H]-
10 cAMP or [³H]-cGMP (about 6000 CPM/test). The final
volume is 100 μ l. Test substances are prepared as stock
solutions in DMSO. The DMSO concentration in the
reaction mixture is 1% v/v. At this DMSO concentration,
the PDE activity is not affected. After the start of
15 the reaction by means of substrate addition, the
samples are incubated at 37°C for 30 minutes. The
reaction is stopped by heating the test tubes for
2 minutes at 110°C. The samples remain in the ice for a
further 10 minutes. After the addition of 30 μ l of 5'-
20 nucleotidase (1 mg/ml, of a snake venom suspension from
Crotalus adamanteus) incubation is carried out for
10 minutes at 37°C. The samples are stopped on ice,
400 μ l each of a mixture of Dowex-water-ethanol (1+1+1)
are added, and the samples are well mixed and again
25 incubated on ice for 15 minutes. The reaction vessels
are centrifuged at 3000 $\times$ g for 20 minutes. 200 μ l
aliquots of the supernatant are transferred directly to
scintillation vessels. After the addition of 3 ml of
scintillator, the samples are measured in a beta
30 counter.

[³H]-cAMP is used as a substrate for the determination
of the PDE 4, 3 and 2 activity, [³H]-cGMP for the
determination of the PDE 5 activity. The non-specific
35 enzyme activities in each case are determined in the
presence of 100 μ M rolipram in the case of PDE 4 and in
the presence of 100 μ M IBMX in the determination of
PDE 3 and 5 and subtracted from the test values. The
incubation batches of the PDE 3 assay contain 10 μ M

rolipram in order to inhibit possible contamination by the PDE 4. The PDE 2 is tested using an SPA assay from Amersham. The assay is carried out in the presence of the activator of PDE 2 (5 μ M cGMP).

5

IC₅₀ values in the range from 10^{-9} to 10^{-5} M were calculated for the compounds according to the invention in relation to the inhibition of phosphodiesterase 4. The selectivity to the PDE types 2, 3 and 5 is factor
10 100 to 10,000.

Inhibition of TNF α release from cells of nasal polyps

The experimental arrangement essentially corresponds to
15 the method described by Campbell, A.M. and Bousquet J (Anti-allergic activity of H₁-blockers, Int. Arch. Allergy Immunol., 1993, 101, 308-310). The starting material is nasal polyps (operation material) of patients who have been subjected to surgical treatment.

20

The tissue is washed with RPMI 1640 and then broken down at 37°C for 2 h using protease (2.0 mg/ml), collagenase (1.5 mg/ml), hyaluronidase (0.75 mg/ml) and DNase (0.05 mg/ml) (1 g of tissue to 4 ml of RPMI 1640
25 with enzymes). The cells obtained, a mixture of epithelial cells, monocytes, macrophages, lymphocytes, fibroblasts and granulocytes, are filtered and washed by repeated centrifugation in nutrient solution, passively sensitized by addition of human IgE and the
30 cell suspension is adjusted to a concentration of 2 million cells/ml in RPMI 1640 (supplemented with antibiotics, 10% foetal calf serum, 2 mM glutamine and 25 mM Hepes). This suspension is distributed in 6-well cell culture plates (1 ml/well). The cells are
35 preincubated for 30 min with the test substances in various final concentrations and then stimulated to TNF α release by addition of anti-IgE (7.2 μ g/ml). The maximum release into the nutrient medium takes place after about 18 hours. In this period, the cells are

incubated at 37°C and 5% CO₂. The nutrient medium (supernatant) is recovered by centrifugation (5 min, 4000 rpm) and stored at -70°C until cytokine determination. The determination of TNFα in the
5 supernatant is carried out using so-called sandwich ELISAs (basic material Pharmingen), in which concentrations of the cytokine in the range from 30-1000 pg/ml can be detected.

10 Cells not stimulated with anti-IgE barely produce TNFα, stimulated cells, however, secrete large amounts of TNFα, which can be decreased in a dose-dependant manner, for example, by PDE 4 inhibitors. The IC₅₀ (concentration at 50% inhibition) is calculated from
15 the percentage inhibition (TNFα release of the cells stimulated with anti-IgE = 100%) of the tested substances at various concentrations.

For the compounds according to the invention, IC₅₀
20 values in the range of 10⁻⁷ to 10⁻⁵ M were determined.

Inhibition of the late-phase eosinophilia 24 h after
inhalational ovalbumin challenge of actively sensitized
guinea-pigs

25

The inhibition of the pulmonary eosinophil infiltration by the substances is investigated in an *in vivo* test on male Dunkin-Hartley guinea-pigs (200-250 g) actively sensitized against ovalbumin (OVA). The sensitization
30 is carried out by means of two intraperitoneal injections of a suspension of 20 µg of OVA together with 20 mg of aluminium hydroxide as an adjuvant in 0.5 ml of physiological saline solution per animal on two successive days. 14 days after the second
35 injection, the animals are pretreated with mepyramine maleate (10 mg/kg i.p.) in order to protect them from anaphylactic death. 30 minutes later, the animals are exposed for 30 sec in a plastic box to an OVA aerosol (0.5 mg/ml) which is generated by a nebulizer driven

with compressed air (19.6 kPa) (allergen challenge). Control animals are nebulized with physiological saline solution. 24 hours after the challenge, the animals are anaesthetized with an overdose of ethylurethane (1.5 g/kg of body weight i.p.) and a bronchoalveolar lavage (BAL) is carried out using 2 x 5 ml of physiological saline solution. The BAL fluid is collected, centrifuged at 300 rpm for 10 min and the cell pellet is then resuspended in 1 ml of physiological saline solution. The eosinophils in the BAL are counted using an automatic cell differentiation apparatus (Bayer Diagnostics Technicon H1). 2 control groups (nebulization with physiological saline solution and nebulization with OVA solution) are included in each test.

The percentage inhibition of eosinophilia of the test group treated with substance is calculated according to the following formula:

20

$$\% \text{ inhibition} = 100 - \frac{100 \cdot (B - C)}{(A - C)}$$

A = Eosinophils in the control group with OVA challenge and vehicle

25 B = Eosinophils in the group with OVA challenge treated with substance

C = Eosinophils in the control group with 0.9% strength NaCl challenge and vehicle

30 The test substances are administered intraperitoneally or orally as a suspension in 10% polyethylene glycol 300 and 0.5% strength 5-hydroxyethylcellulose 2 hours before the allergen challenge. The control groups are treated with the vehicle according to the administration form of the test substance.

35

The compounds according to the invention inhibit late-phase eosinophilia by 30% to 80% after intraperitoneal

administration of 10 mg/kg and by 40% to 70% after oral administration of 30 mg/kg.

The compounds according to the invention are thus particularly suitable for the production of medicaments
5 for the treatment of disorders which are connected with the action of eosinophils.

Effect of allergen-induced vascular permeability on
actively sensitized brown Norway rats

10

Male brown Norway rats weighing 280-300 g are actively sensitized on 2 successive days by intraperitoneal injection of a suspension of 1 mg of ovalbumin together with 100 mg of aluminium hydroxide in 1 ml/animal.
15 Three weeks after sensitization, the rats are anaesthetized with sodium thiopental and fixed in the supine position. For perfusion of the nasal cavity, a polyethylene catheter was advanced into the trachea in a backwards direction as far as the internal opening of
20 the choanas, so that it was possible for the solution to trickle out through the nasal cavities. A short tracheal catheter was tied into the trachea in an orthograde manner in order to make respiration possible. For perfusion, phosphate-buffered saline
25 solution (PBS) was continuously pumped through the nasal cavity (0.5 ml/min) using a roller pump and collected by means of a fraction collector. Evans Blue was used as a plasma marker and injected intravenously (1 ml/animal each of a 1% strength solution in PBS)
30 through a catheter in the jugular vein.

Substance administration was carried out topically. During this administration, the test substance was added to the perfusion medium (PBS). The nasal mucous
35 membrane was perfused for 30 min with PDE 4 inhibitor-containing solution. Evans Blue was then injected immediately before the start of the perfusion with ovalbumin-containing solution (challenge). After the start of the ovalbumin challenge (10 mg/ml of ovalbumin

dissolved in PBS) 15 min fractions were collected every 15 min in the fraction collector over a period of 60 min. The Evans Blue concentration in the perfusates was measured with a Digiscan photometer at a wavelength of 620 nm. The blank values were automatically subtracted in the course of this. The course of action over 60 min was calculated using an AUC program. The substance action of the preparation group was calculated against vehicle controls in %.

10

For the compounds according to the invention, IC_{50} values in the range from 10^{-8} to 10^{-5} M were determined.

The utility of the compounds according to the invention as in formula I for the therapy of chronic obstructive pulmonary diseases is confirmed by the inhibition of LPS-induced $TNF\alpha$ release in human blood and by the inhibition of LPS-induced pulmonary neutrophil infiltration in ferrets and domestic pigs.

20

The stimulation of isolated leucocytes to cytokine release can take place in various ways. Lipopolysaccharides (LPSs) are a stimulus suitable for the investigation of $TNF\alpha$ release. LPS is a constituent of the bacterial cell walls and is released by killing the bacteria (antibiotics or immune system). LPS particularly stimulates the activity of the phagocytizing leucocytes (tissue macrophages, granulocytes, monocytes) and causes the infiltration of leucocytes from the blood stream into the affected tissue. A cytokine important for these mechanisms is $TNF\alpha$, which is secreted in large amounts by the affected cells (the monocytes and macrophages are the main source) and initiates and maintains inflammation alongside other mediators.

35

LPS-induced TNF α release in human blood diluted 1:5

For the investigation of the effect on TNF α release, blood was obtained from various donors (inhibition of
5 coagulation by means of citrate) and diluted 1:5 with RPMI 1640 cell culture medium. The test substances were added to the samples in various concentrations before the LPS challenge. The stimulation of the leucocytes was carried out 30 min later using lipopolysaccharides
10 (LPS) from *Salmonella abortus equi* in a final concentration of 10 $\mu\text{g/ml}$. After incubation of the test batches for 24 hours at 37°C and under 5% CO₂ in an incubator, the diluted blood was centrifuged and the TNF α concentration in the cell-free supernatant was
15 measured by means of ELISA.

IC₅₀ values in the range from 10⁻⁷ to 10⁻⁵ M were determined for the compounds according to the invention. An IC₅₀ value of 0.8 $\mu\text{mol/l}$, for example, was determined for the compound as in working example 1. In
20 comparison with this, an IC₅₀ value of 7.0 $\mu\text{mol/l}$ was determined with the reference standard SB 207499.

Inhibition of lipopolysaccharide (LPS)-induced neutrophilia in ferrets

25 The inhibition of the pulmonary neutrophil infiltration by the substance is investigated in an *in vivo* test on male ferrets (0.6 - 2 kg). The experimental animals are anaesthetized with pentobarbital sodium (40 mg/kg of
30 body weight i.p.), placed individually into a closed nebulization box of capacity 5 l and exposed to an ultrasonically nebulized aerosol of 0.01% strength LPS (lipopolysaccharide) solution (additionally 0.1% hydroxylamine in PBS) for 10 minutes. The aerosol is
35 generated by a nebulizer driven with compressed air (0.2 Mpa). Control animals are treated with an aerosol of physiological saline solution. The animals are observed during the entire process and removed from the nebulization box after admission of fresh air. On

inhalation, nebulized LPS immediately induces inflammation of the airways, which is characterized by a massive infiltration of neutrophilic granulocytes into the lungs of the experimental animals. The
5 neutrophilia achieves its maximum 4 to 6 hours after LPS exposure. In order to be able to measure the number of infiltrated neutrophilic granulocytes, the animals are anaesthetized with an overdose of ethylurethane (1.5 g/kg of body weight i.p.) 6 hours after LPS
10 provocation and a bronchioalveolar [sic] lavage (BAL) is carried out using 2 x 10 ml of physiological saline solution. The number of cells in the pooled original BAL fluid (100 µl) are determined using the Technicon H1E automatic cell-counting apparatus (Bayer
15 Diagnostic) and the different leucocytes per µl are differentiated. In each test, 2 control groups (nebulization with physiological saline solution or with LPS solution) are included. Substances having anti-inflammatory activity, particularly those which
20 affect TNF α release or the function of the neutrophilic granulocytes, inhibit the infiltration of leucocytes. The inhibition of infiltration is determined by the comparison of the number of infiltrated neutrophils in untreated experimental animals (with and without LPS
25 provocation).

ID₅₀ values in the range from 1 to 20 mg/kg i.p. were determined for the compounds according to the invention. The compound as in working example 1 was
30 administered, for example, in the doses 1, 3 and 10 mg/kg i.p. 2 hours before LPS provocation to up to 3 experimental animals per dose. The neutrophilia in the BAL was inhibited in a dose-dependent manner (18%, 64% and 78%). The ID₅₀ is 2.4 mg/kg i.p.
35 The administration of the selected PDE 4 inhibitor RPR-73401 (reference substance) caused an inhibition of neutrophilia of 49% in the dose 1 mg/kg i.p.

For intrapulmonary administration, the trachea of the animals is opened up under anaesthesia (40 mg/kg i.p. of pentobarbital sodium, 3% strength, 1.3 ml/kg), a 7 cm-long PVC catheter is tied in and the test substances are administered intrapulmonarily in powder form (mixed with lactose to 20 mg/kg) by means of a syringe 2 hours before LPS provocation.

The intrapulmonary administration of the compound as in working example 1 in the doses 1, 3 and 10 mg/kg inhibits LPS-induced neutrophilia in a dose-dependent manner (43%, 65% and 100%). The ID₅₀ is 1.65 mg/kg i.palm.

LPS-induced neutrophilia in the domestic pig

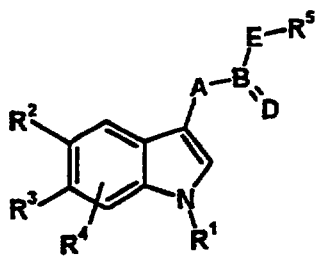
Pulmonary neutrophilia can be induced in the domestic pig in a manner similar to that in the ferret. The animals are anaesthetized (pentobarbital 10 mg/kg i.v.) and intubated. Using a bronchoscope, a partial bronchoalveolar lavage is carried out in order to determine the proportion of neutrophilic granulocytes under physiological conditions. The test substance is then administered and the animals inhale an ultrasonically nebulized aerosol of 0.03% strength LPS (lipopolysaccharide) solution (additionally 0.1% hydroxylamine in PBS) through the tracheal tube for 20 min. The inhaled LPS induces a reactive inflammation of the airways and neutrophilic granulocytes infiltrate on a huge scale. The neutrophilia achieves its maximum 4 to 6 hours after LPS exposure. After 6 hours, the bronchioalveolar [sic] lavage is repeated and the increase in the neutrophil count is determined arithmetically.

The pig animal species is particularly suitable for these investigations, since there are large anatomical and physiological similarities to man.

For the compounds according to the invention, inhibitions of LPS-induced neutrophilia of 20% to 65%

were determined on intrapulmonary administration of 10 mg/animal.

The intrapulmonary administration of the compound as in working example 1 in the dose 10 mg/animal (about
5 0.75 mg/kg) inhibited LPS-induced pulmonary neutrophilia by 51%.

Patent Claims1. Hydroxyindoles of the formula 1

This Sheet Has Been Replaced

5

in which

R^1 , R^5 are

- 10 - $C_{1...12}$ -alkyl, straight-chain or branched-chain,
 optionally mono- or polysubstituted by -OH,
 -SH, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂,
 -NHC_{6...14}aryl, -N(C_{6...14}aryl)₂,
 -N(C_{1...6}alkyl)(C_{6...14}aryl), -NHCOR⁶, -NO₂, -CN,
 15 -F, -Cl, -Br, -I, -O-C_{1...6}-alkyl, -O-C_{6...14}-
 aryl, -O(CO)R⁶, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl,
 -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C_{1...6}alkyl,
 -OSO₂C_{6...14}aryl, -(CS)R⁶, -COOH, -(CO)R⁶,
 20 mono-, bi- or tricyclic saturated or mono- or
 polyunsaturated carbocycles having 3...14
 ring members, mono-, bi- or tricyclic
 saturated or mono- or polyunsaturated
 heterocycles having 5...15 ring members and
 25 1...6 heteroatoms, which are preferably N, O
 and S, where the C_{6...14}aryl groups and the
 included carbocyclic and heterocyclic
 substituents for their part can optionally be
 mono- or polysubstituted by R⁴,
- 30 - $C_{1...12}$ -alkenyl, mono- or polyunsaturated,
 straight-chain or branched-chain,



- optionally mono- or polysubstituted by -OH, -SH, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂, -NHC_{6...14}aryl, -N(C_{6...14}aryl)₂, -N(C_{1...6}alkyl)(C_{6...14}aryl), -NHCOR⁶, -NO₂, -CN, -F, -Cl, -Br, -I, -O-C_{1...6}-alkyl, -O-C_{6...14}-aryl, -O(CO)R⁶, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl, -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C_{1...6}alkyl, -OSO₂C_{6...14}aryl, -(CS)R⁶, -COOH, -(CO)R⁶, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, where the C_{6...14}aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R⁴,
- mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, optionally mono- or polysubstituted by -OH, -SH, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂, -NHC_{6...14}aryl, -N(C_{6...14}aryl)₂, -N(C_{1...6}alkyl)(C_{6...14}aryl), -NHCOR⁶, -NO₂, -CN, -F, -Cl, -Br, -I, -O-C_{1...6}-alkyl, -O-C_{6...14}-aryl, -O(CO)R⁶, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl, -SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C_{1...6}alkyl, -OSO₂C_{6...14}aryl, -(CS)R⁶, -COOH, -(CO)R⁶, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, where the C_{6...14}aryl groups and the included carbocyclic and heterocyclic



substituents for their part can optionally be mono- or polysubstituted by R^4 ,

- 5 - mono-, bi- or tricyclic saturated or mono- or
polyunsaturated heterocycles having 5...15 ring
members and 1...6 heteroatoms, which are
preferably N, O and S,
optionally mono- or polysubstituted by -OH,
-SH, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂,
10 -NHC_{6...14}aryl, -N(C_{6...14}aryl)₂,
-N(C_{1...6}alkyl)(C_{6...14}aryl), -NHCOR⁶, -NO₂, -CN,
-F, -Cl, -Br, -I, -O-C_{1...6}-alkyl, -O-C_{6...14}-
aryl, -O(CO)R⁶, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl,
-SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C_{1...6}alkyl,
15 -OSO₂C_{6...14}aryl, -(CS)R⁶, -COOH, -(CO)R⁶,
mono-, bi- or tricyclic saturated or mono- or
polyunsaturated carbocycles having 3...14
ring members, mono-, bi- or tricyclic
saturated or mono- or polyunsaturated
20 heterocycles having 5...15 ring members and
1...6 heteroatoms, which are preferably N, O
and S, where the C_{6...14}aryl groups and the
included carbocyclic and heterocyclic
substituents for their part can optionally be
25 mono- or polysubstituted by R^4 ,
- 30 - carbo- or heterocyclic saturated or mono- or
polyunsaturated spirocycles having 3...10 ring
members, where heterocyclic systems contain
1...6 heteroatoms, which are preferably N, O and
S,
optionally mono- or polysubstituted by -OH,
-SH, -NH₂, -NHC_{1...6}-alkyl, -N(C_{1...6}-alkyl)₂,
-NHC_{6...14}aryl, -N(C_{6...14}aryl)₂,
35 -N(C_{1...6}alkyl)(C_{6...14}aryl), -NHCOR⁶, -NO₂, -CN,
-F, -Cl, -Br, -I, -O-C_{1...6}-alkyl, -O-C_{6...14}-
aryl, -O(CO)R⁶, -S-C_{1...6}-alkyl, -S-C_{6...14}aryl,
-SOR⁶, -SO₃H, -SO₂R⁶, -OSO₂C_{1...6}alkyl,
-OSO₂C_{6...14}aryl, -(CS)R⁶, -COOH, -(CO)R⁶,





mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring members and 1...6 heteroatoms, which are preferably N, O and S, where the C₆...₁₄aryl groups and the included carbocyclic and heterocyclic substituents for their part can optionally be mono- or polysubstituted by R⁴,

where R¹ and R⁵ can be identical or different;

R², R³ can be hydrogen or -OH, where at least one of the two substituents must be -OH;

R⁴ is

-H, -OH, -SH, -NH₂, -NHC₁...₆-alkyl, -N(C₁...₆-alkyl)₂, -NHC₆...₁₄aryl, -N(C₆...₁₄aryl)₂, -N(C₁...₆alkyl)(C₆...₁₄aryl), -NHCOR⁶, -NO₂, -CN, -COOH, -(CO)R⁶, -(CS)R⁶, -F, -Cl, -Br, -I, -O-C₁...₆-alkyl, -O-C₆...₁₄-aryl, -O(CO)R⁶, -S-C₁...₆-alkyl, -S-C₆...₁₄aryl, -SOR⁶, -SO₂R⁶.

R⁶ can be

-H, -NH₂, -NHC₁...₆-alkyl, -N(C₁...₆-alkyl)₂, -NHC₆...₁₄aryl, -N(C₆...₁₄aryl)₂, -N(C₁...₆alkyl)(C₆...₁₄aryl), -O-C₁...₆-alkyl, -O-C₆...₁₄-aryl, -S-C₁...₆-alkyl, -S-C₆...₁₄aryl, -C₁...₁₂-alkyl, straight-chain or branched-chain, -C₁...₁₂-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, -mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles having 3...14 ring members, -mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles having 5...15 ring





- 40 -

members and 1...6 heteroatoms, which are preferably N, O and S;

A is either a bond, or

5 $-\text{CH}_2)_m-$, $-(\text{CH}_2)_m-(\text{CH}=\text{CH})_n-(\text{CH}_2)_p-$, $-(\text{CHOZ})_m-$,
 $-(\text{C}=\text{O})-$, $-(\text{C}=\text{S})-$, $-(\text{C}=\text{N}-\text{Z})-$, $-\text{O}-$, $-\text{S}-$, $-\text{NZ}-$,

where $m, p = 0...3$ and $n = 0...2$ and

Z is

$-\text{H}$, or
10 $-\text{C}_{1...12}$ -alkyl, straight-chain or branched-chain,
 $-\text{C}_{1...12}$ -alkenyl, mono- or polyunsaturated,
 straight-chain or branched-chain,
 -mono-, bi- or tricyclic saturated or mono- or
 polyunsaturated carbocycles having 3...14 ring
15 members,
 -mono-, bi- or tricyclic saturated or mono- or
 polyunsaturated heterocycles having 5...15 ring
 members and 1...6 heteroatoms, which are
 preferably N, O and S;

20

B can either be carbon or sulphur, or $-(\text{S}=\text{O})-$;

D can be oxygen, sulphur, CH_2 or $\text{N}-\text{Z}$,

where **D** can only be S or CH_2 if **B** is carbon;

25

E can be a bond, or else

$-(\text{CH}_2)_m-$, $-\text{O}-$, $-\text{S}-$, $-(\text{N}-\text{Z})-$, where m and **Z** have
 the meaning already described beforehand.

30 2. Physiologically tolerable salts of the compounds
 as shown in formula 1 according to Claim 1,



* C L N S *

characterized by neutralization of the bases with inorganic or organic acids or by neutralization of the acids with inorganic or organic bases or by quaternization of tertiary amines to give quaternary ammonium salts.

3. Compounds as shown in formula 1 according to Claims 1 and 2 having an asymmetric carbon atom in the D form, the L form and D,L mixtures, and, in the case of a number of asymmetric carbon atoms, the diastereomeric forms.

4. Of the compounds as shown in formula 1 according to Claims 1 to 3, particularly one of the following compounds:

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide Na salt;

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-hydroxyacetamide;

N-(pyridin-4-yl)-2-[1-(2,6-difluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-[1-(2,6-difluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

N-(3,5-dichloropyridin-4-yl)-2-[1-(3-nitrobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide Na salt;

N-(3,5-dichloropyridin-4-yl)-2-(1-propyl-5-hydroxyindol-3-yl)-2-oxoacetamide;



N-(3,5-dichloropyridin-4-yl)-2-(1-isopropyl-5-hydroxyindol-3-yl)-2-oxoacetamide;

5 N-(3,5-dichloropyridin-4-yl)-2-(1-cyclopentyl-methyl-5-hydroxyindol-3-yl)-2-oxoacetamide;

N-(2,6-dichlorophenyl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

10 N-(2,6-dichloro-4-trifluoromethylphenyl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

N-(2,6-dichloro-4-trifluoromethoxyphenyl)-2-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]-2-oxoacetamide;

15

N-(3,5-dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-6-hydroxyindol-3-yl]-2-oxoacetamide;

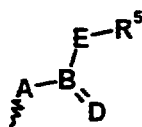
20 N-(3,5-dichloropyridin-4-yl)-5-hydroxy-1-(4-methoxybenzyl)indole-3-carboxamide.

5. Process for the preparation of compounds as shown in formula 1 according to Claims 1 to 4, characterized in that compounds as shown in
25 formula 1, for which R^2 or R^3 or R^2 and $R^3 = -O-R^7$, are converted into the compounds according to the invention by removal of R^7 , where R^7 in this case is a substituent suitable as a leaving group.

30 6. Preparation of compounds as shown in formula 1 by the process according to Claim 5, particularly preferably from compounds of the formula 1 for which R^7 is alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl, acyl, alkoxycarbonyl, aryloxy carbonyl,
35 aminocarbonyl, N-substituted aminocarbonyl, silyl or sulphonyl groups, and complexing agents, such as, for example, compounds of boric acid, phosphoric acid and covalently or coordinatively bonded metals, such as zinc, aluminium or copper.



7. Process for the preparation of compounds as shown in formula 1 according to Claims 1 to 4, characterized in that compounds of the general formula 1 are converted by means of conversions of the sub-structure:



into other compounds of the formula 1 according to the invention.

8. Use of the compounds as shown in formula 1 according to Claims 1 to 4 as therapeutic active compounds for the production of medicaments for the treatment of disorders in which the inhibition of TNF α is therapeutically beneficial.

9. Use of the compounds as shown in formula 1 according to Claims 1 to 4 as therapeutic active compounds for the production of medicaments for the treatment of disorders in which the inhibition of phosphodiesterase 4 is therapeutically beneficial.

10. Particularly preferred use of the compounds as shown in formula 1 according to Claims 1 to 4 as therapeutic active compounds for the production of medicaments for the treatment of disorders which are connected with the action of eosinophils.

11. Particularly preferred use of the compounds as shown in formula 1 according to Claims 1 to 4 as therapeutic active compounds for the production of medicaments for the treatment of chronic obstructive pulmonary diseases (COPD).



12. Medicaments comprising one or more compounds according to Claims 1 to 4 in addition to customary physiologically tolerable carriers and/or diluents or auxiliaries.
- 5
13. Process for the production of a medicament according to Claim 12, characterized in that one or more compounds according to Claims 1 to 4 are processed to give pharmaceutical preparations or brought into a therapeutically administrable form using customary pharmaceutical carriers and/or diluents or other auxiliaries.
- 10
14. Use of compounds of the general formula 1 according to Claims 1 to 4 and/or pharmaceutical preparations according to Claims 12 and 13 on their own or in combination with one another or in combination with carriers and/or diluents or other auxiliaries.
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