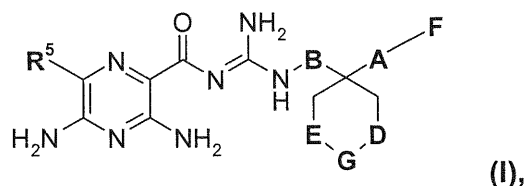


Heterocyclic compounds, medicaments containing said compounds, use thereof and processes for the preparation thereof

1. FIELD OF THE INVENTION

The present invention relates to compounds of general formula (I)



and the tautomers and the salts thereof, particularly the pharmaceutically acceptable salts thereof with inorganic or organic acids and bases, which have valuable pharmacological properties, particularly an inhibitory effect on epithelial sodium channels, the use thereof for the treatment of diseases, particularly diseases of the lungs and airways.

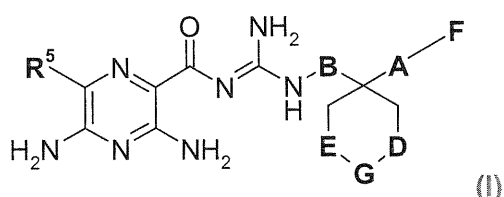
2. BACKGROUND TO THE INVENTION

Amiloride type compounds are known from the prior art as active substances for example for the treatment of diseases of the lungs and airways (*J. Med. Chem.* 49 (2006) 4098-4115). WO 08135557 discloses compounds of similar structure showing ENaC (Epithelial Sodium Channel) inhibitor activity.

The problem of the present invention is to prepare new compounds which may be used therapeutically for the treatment of pathophysiological processes treatable by the blockade of an epithelial sodium channel, particularly for the treatment of the lungs and airways.

2A. SUMMARY

In a first aspect, there is provided a compound of formula (I)



wherein

A denotes a bond or is selected from the group consisting of O, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂-O-, -CH₂-NR^{A1}- and -NR^{A1}-,

wherein

5 **R^{A1}** denotes hydrogen or C₁₋₆-alkyl,

B denotes

-CH₂- or -CH₂CH₂-, or

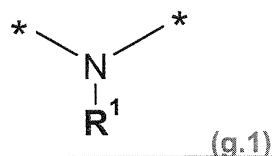
provided that **A** is not O or -NR^{A1}, **B** denotes a bond

D, E denote independently from each other a bond or -CH₂-,

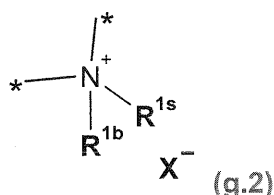
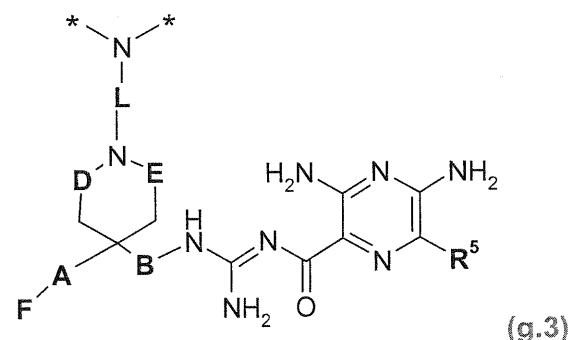
10 **F** denotes optionally substituted aryl,

or optionally substituted heteroaryl,

G denotes a group of formula (g.1), (g.2) or (g.3)



15



wherein

20 **R¹** is selected from the group consisting of

hydrogen, C₁₋₆-alkyl, optionally substituted 5- to 7-membered heterocyclyl-CO-, optionally substituted 5- to 7-membered heterocyclyl-NH-CO-, **R^{1.1}**-SO₂-, **R^{1.2}**-C₂₋₄-alkyl-NH-CO-, H₃C-NH-CO-, **R^{1.2.4}**-O-CO-CH₂-NH-CO-, **R^{1.2}**-C₂₋₄-alkyl-N(C₁₋₄-alkyl)-CO-, H₃C-N(C₁₋₄-alkyl)-CO-, **R^{1.2.4}**-O-CO-CH₂-N(C₁₋₄-alkyl)-CO-, **R^{1.3}**-C₁₋₆-alkyl-CO-, **R^{1.4}**-C₂₋₆-alkyl-, optionally substituted phenyl-CH₂-, **R^{1.4.3}**-O-CO-CH₂-, HO-CO-CH₂- and HOSO₂-CH₂-,

25

$R^{1.5}$ -C₁₋₆-alkyl-CO- and $R^{1.6}$ -C(NH)-,

wherein

$R^{1.1}$ is selected from the group consisting of C₁₋₄-alkyl-,

H₂NC(NH)NH-C₁₋₆-alkyl-, $R^{1.2.1}$ $R^{1.2.2}$ N-C₁₋₄-alkyl-,

5 $R^{1.2.1}$ $R^{1.2.2}$ $R^{1.2.3}$ N⁺-C₁₋₄-alkyl, HOCO-C₁₋₄-alkyl- and

C₁₋₃-alkyl-OCO-C₁₋₄-alkyl-,

$R^{1.2}$ is selected from the group consisting of hydrogen, H₂NC(NH)NH-,

$R^{1.2.1}$ $R^{1.2.2}$ N-, $R^{1.2.1}$ $R^{1.2.2}$ $R^{1.2.3}$ N⁺-, $R^{1.2.3}$ -HN-C(NR^{1.2.3})-NH-, $R^{1.2.4}$ -O-CO-,

$R^{1.2.5}$ -O-CO-NH- and HO-CO-, HOSO₂-,

10 _____ wherein

_____ $R^{1.2.1}$ denotes hydrogen or C₁₋₆-alkyl,

_____ $R^{1.2.2}$ denotes hydrogen or C₁₋₆-alkyl,

or

$R^{1.2.1}$ and $R^{1.2.2}$ together form a 4- to 7- membered heterocyclic ring containing one N-atom,

15 $R^{1.2.3}$ denotes hydrogen or C₁₋₆-alkyl,

$R^{1.2.4}$ denotes hydrogen or C₁₋₆-alkyl,

$R^{1.2.5}$ denotes hydrogen or C₁₋₆-alkyl,

$R^{1.3}$ is selected from the group consisting of hydrogen, C₁₋₆-alkyl, C₁₋₆-alkyl-O-, optionally

20 substituted phenyl, $R^{1.3.1}$ $R^{1.3.2}$ N-, $R^{1.2.1}$ $R^{1.2.2}$ $R^{1.2.3}$ N⁺-,

$R^{1.2.3}$ -HN-C(NR^{1.2.3})-NH-, H₂NC(NH)NH-, $R^{1.2.4}$ -O-CO-, HO-CO- and HOSO₂-,

wherein

_____ $R^{1.3.1}$ denotes hydrogen or C₁₋₆-alkyl,

_____ $R^{1.3.2}$ denotes hydrogen or C₁₋₆-alkyl,

25 _____ or

_____ $R^{1.3.1}$ and $R^{1.3.2}$ together form a 4- to 7- membered heterocyclic ring containing one N-atom,

$R^{1.4}$ is selected from the group consisting of hydrogen, $R^{1.4.1}$ $R^{1.4.2}$ N-,

30 $R^{1.4.1}$ $R^{1.4.2}$ $R^{1.4.3}$ N⁺-, H₂N-C(NH)-NH-, $R^{1.4.3}$ -HN-C(NR^{1.4.4})-NH-, optionally substituted phenyl,

$R^{1.4.3}$ -O-CO-, $R^{1.4.4}$ -O-CO-NH-, HO-CO- and HOSO₂-,

wherein

_____ $R^{1.4.1}$ denotes hydrogen or C₁₋₆-alkyl, .

_____ $R^{1.4.2}$ denotes hydrogen or C₁₋₆-alkyl,

35 $R^{1.4.3}$ denotes hydrogen or C₁₋₆-alkyl.,

$R^{1.4.4}$ denotes hydrogen or C₁₋₆-alkyl.

$R^{1.5}$ is selected from the group consisting of hydrogen, C_{1-6} -alkyl-O-,
 $R^{1.5.1} R^{1.5.2} N$ -, $R^{1.5.1} R^{1.5.2} R^{1.5.3} N^+$ -, $H_2N-C(NH)-NH$ -, optionally substituted phenyl, $R^{1.5.3}$ -O-
 CO-, $R^{1.5.4}$ -O-CO-NH-, HO-CO- and $HOSO_2$ -,

wherein

5 $R^{1.5.1}$ denotes hydrogen or C_{1-6} -alkyl, .

$R^{1.5.2}$ denotes hydrogen or C_{1-6} -alkyl,

$R^{1.5.3}$ denotes hydrogen or C_{1-6} -alkyl,

$R^{1.5.4}$ denotes hydrogen or C_{1-6} -alkyl, .

10 $R^{1.6}$ denotes $R^{1.6.1} R^{1.6.2} N$ -,

wherein

$R^{1.6.1}$ denotes hydrogen or C_{1-6} -alkyl;

$R^{1.6.2}$ denotes hydrogen or C_{1-6} -alkyl;

15 R^{1b} is selected from the group consisting of C_{1-4} -alkyl,

$R^{1.4}$ - C_{2-6} -alkyl-, optionally substituted phenyl- CH_2 -, $R^{1.4.3}$ -O-CO- CH_2 - and HO-CO- CH_2 -

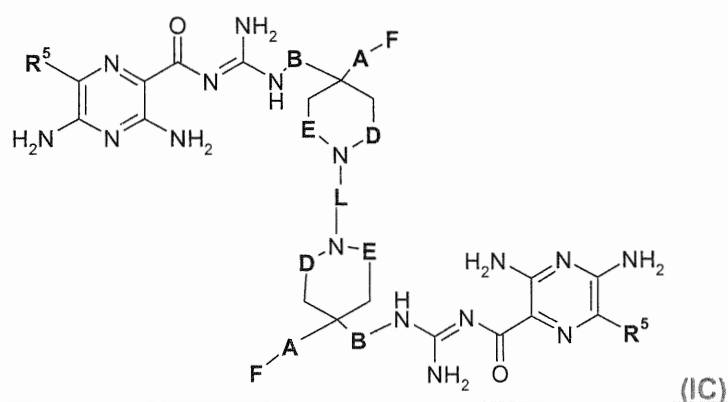
R^{1s} denotes C_{1-6} -alkyl,

20 X^- denotes any anion forming a pharmaceutically acceptable salt,

L denotes a bridging group -CO-NH- C_{2-6} -alkyl-NH-CO-, -COC $_{1-6}$ -alkyl-CO-,
 - C_{2-6} -alkyl-,

forming a compound of formula (IC),

25 whereby the molecular entities of formula (IC) connected by L may be identical or different



R^5 denotes Cl or Br,

30 and the pharmacologically acceptable acid addition salts thereof.

In a second aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof as a medicament.

In a third aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof for the treatment of a disease selected from among respiratory diseases or complaints and allergic diseases of the airways.

In a fourth aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof for the treatment of a disease selected from among chronic bronchitis, acute bronchitis, bronchitis caused by bacterial or viral infection or fungi or helminths, allergic bronchitis, toxic bronchitis, chronic obstructive bronchitis (COPD), asthma (intrinsic or allergic), paediatric asthma, bronchiectasis, allergic alveolitis, allergic or non-allergic rhinitis, chronic sinusitis, cystic fibrosis or mucoviscidosis, alpha-1-antitrypsin deficiency, cough, pulmonary emphysema, interstitial lung diseases, alveolitis, hyperreactive airways, nasal polyps, pulmonary oedema, pneumonitis of different origins.

In a fifth aspect, there is provided a pharmaceutical composition comprising at least one compound as defined above or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In a sixth aspect, there is provided medicament combinations which contain, besides one or more compounds of a compound as defined above, as further active substances, one or more compounds selected from among the categories of further ENaC inhibitors, betamimet-ics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists, MAP-kinase inhibitors, MPR4-Inhibitors, iNOS-Inhibitors, SYK-Inhibitors, corrections of the cystic fibrosis transmembrane regulator (CFTR) and CFTR potentiators or double or triple combinations thereof.

3. DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that the problem mentioned above is solved by compounds of formula (I) and (IC) of the present invention.

The present invention therefore relates to a compound of formula (I)