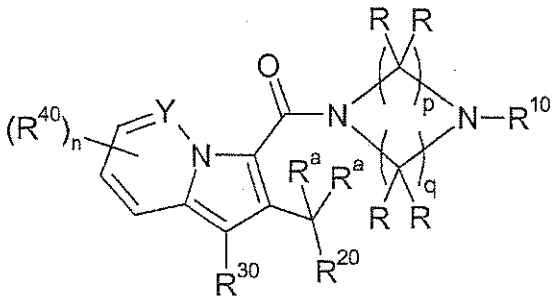
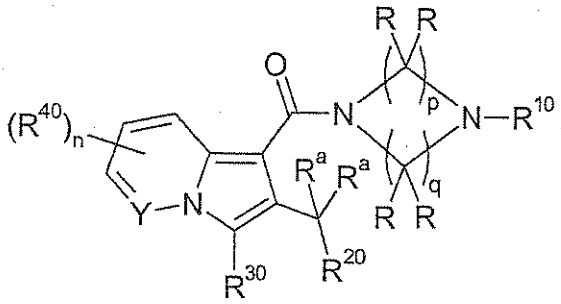
Cyclic (aza)indolizinecarboxamides, their preparation and their use as pharmaceuticals

SUMMARY

In a first aspect, there is provided a compound of the formula Ia or Ib, in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them,



Ia



Ib

wherein

R^a is chosen from hydrogen, fluorine and $(C_1$-$C_4)$-alkyl, wherein the two groups R^a are independent of each other and can be identical or different, or the two groups R^a together are a divalent $(C_2$-$C_5)$-alkyl group;

R is chosen from hydrogen, $(C_1$-$C_6)$-alkyl which is optionally substituted by one or more identical or different substituents R^1, and $(C_3$-$C_7)$-cycloalkyl, wherein all groups R are independent of each other and can be identical or different, or two groups R bonded to the same carbon atom together are a divalent $(C_2$-$C_5)$-alkyl group;

R^1 is chosen from $(C_3$-$C_7)$-cycloalkyl, phenyl, heteroaryl, Het^1, hydroxy, $(C_1$-$C_4)$-alkyl-O-, $(C_1$-$C_4)$-alkyl-$S(O)_m$-, R^2-$N(R^3)$-C(O)-, R^4-O-C(O)- and cyano;

R^2 is chosen from hydrogen, $(C_1$-$C_6)$-alkyl which is optionally substituted by one or more identical or different substituents R^5, and $(C_3$-$C_7)$-cycloalkyl, wherein all groups R^2 are independent of each other and can be identical or different;

R^3, R^4, R^6, R^7 and R^8 are chosen from hydrogen and $(C_1$-$C_4)$-alkyl, wherein all groups R^3, R^4, R^6, R^7 and R^8 are independent of each other and can be identical or different;

R^5 is chosen from hydroxy, $(C_1$-$C_4)$-alkyl-O-, $(C_1$-$C_4)$-alkyl-$S(O)_m$-, R^6-$N(R^7)$-C(O)-, R^8-O-C(O)-, cyano, $(C_3$-$C_7)$-cycloalkyl, phenyl, heteroaryl and Het^1;

R^{10} is chosen from hydrogen, $(C_1$-$C_6)$-alkyl-O-C(O)- and $(C_3$-$C_7)$-cycloalkyl-C_vH_{2v}-O-C(O)-;

R^{20} is chosen from phenyl and heteroaryl which are optionally substituted by one or more identical or different substituents chosen from halogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkyl-O-, $(C_1$-$C_4)$-alkyl-$S(O)_m$- and cyano;

R^{30} is chosen from $(C_5$-$C_7)$-cycloalkyl, $(C_5$-$C_7)$-cycloalkenyl, tetrahydropyranyl, phenyl and heteroaryl, wherein cycloalkyl and cycloalkenyl are optionally substituted by one or more identical or different substituents chosen from fluorine, $(C_1$-$C_4)$-alkyl and hydroxy, and phenyl and heteroaryl are optionally substituted by one or more identical or different substituents chosen from halogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkyl-O- and cyano;

R^{40} is chosen from halogen, $(C_1$-$C_4)$-alkyl, $(C_3$-$C_7)$-cycloalkyl-C_vH_{2v}-, hydroxy, $(C_1$-$C_4)$-alkyl-O-, $(C_1$-$C_4)$-alkyl-$S(O)_m$-, R^{41}-$N(R^{42})$-, Het^2, R^{41}-$N(R^{42})$-C(O)-, Het^2-C(O)-, cyano, R^{41}-$N(R^{42})$-$S(O)_2$- and Het^2-$S(O)_2$-, wherein all substituents R^{40} are independent of each other and can be identical or different;

R^{41} is chosen from hydrogen, $(C_1$-$C_4)$-alkyl and $(C_3$-$C_7)$-cycloalkyl-C_vH_{2v}-, wherein all groups R^{41} are independent of each other and can be identical or different;

R^{42} is chosen from hydrogen and $(C_1$-$C_4)$-alkyl, wherein all groups R^{42} are independent of each other and can be identical or different;

Y is chosen from N, CH and C($(C_1$-$C_4)$-alkyl);

heteroaryl is an aromatic monocyclic, 5-membered or 6-membered, heterocyclic group which comprises 1, 2 or 3 identical or different ring heteroatoms chosen from N, O and S, wherein one of the ring nitrogen atoms can carry a hydrogen atom or a (C_1-C_4)-alkyl substituent, and wherein the heteroaryl group is bonded via a ring carbon atom;

Het^1 is a saturated, monocyclic, 4-membered to 7-membered heterocyclic group which comprises 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein the group Het^1 is bonded via a ring carbon atom or a ring nitrogen atom, wherein ring nitrogen atoms can carry a hydrogen atom or a substituent chosen from (C_1-C_4)-alkyl, (C_1-C_6)-alkyl-O-C(O)- and (C_3-C_7)-cycloalkyl-C_vH_{2v}-O-C(O)-, wherein ring sulfur atoms can carry one or two oxo groups, and wherein Het^1 is optionally substituted on ring carbon atoms by one or more identical or different substituents chosen from fluorine, (C_1-C_4)-alkyl and oxo;

Het^2 is a saturated, monocyclic, 4-membered to 7-membered heterocyclic group which comprises a ring nitrogen atom via which the group Het^2 is bonded and optionally an additional ring heteroatom chosen from N, O and S, wherein the additional ring nitrogen atom carries a hydrogen atom or a substituent chosen from (C_1-C_4)-alkyl, (C_1-C_6)-alkyl-O-C(O)- and (C_3-C_7)-cycloalkyl-C_vH_{2v}-O-C(O)-, wherein the ring sulfur atom can carry one or two oxo groups, and wherein Het^2 is optionally substituted on ring carbon atoms by one or more identical or different substituents chosen from fluorine, (C_1-C_4)-alkyl and oxo;

m is chosen from 0, 1 and 2, wherein all numbers m are independent of each other and can be identical or different;

n is chosen from 0, 1, 2 and 3;

p and q, which are independent of each other and can be identical or different, are chosen from 2 and 3;

v is chosen from 0, 1 and 2, wherein all numbers v are independent of each other and can be identical or different;

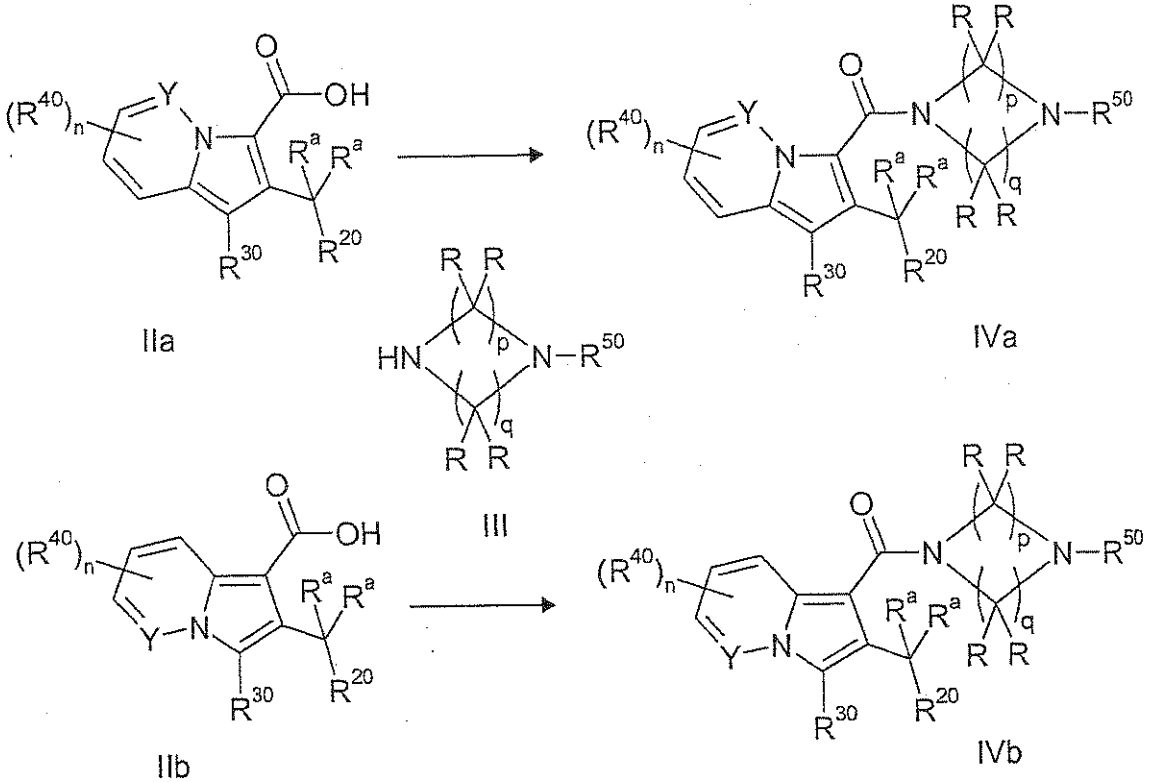
wherein all alkyl groups, independently of each other, are optionally substituted by one or more fluorine atoms;

wherein all cycloalkyl groups, independently of each other, are optionally substituted by one or more identical or different substituents chosen from fluorine and $(C_1$-$C_4)$-alkyl, unless specified otherwise;

wherein all phenyl and heteroaryl groups present in R^1 and R^5, independently of each other, are optionally substituted by one or more identical or different substituents chosen from halogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkyl-O-, $(C_1$-$C_4)$-alkyl-$S(O)_2$- and cyano.

In a second aspect, there is provided a process for the preparation of a compound of the formula Ia or Ib or its salt or a solvate thereof as defined herein, comprising reacting a

compound of the formula IIa or IIb with a compound of the formula III to give a compound of the formula IVa or IVb,



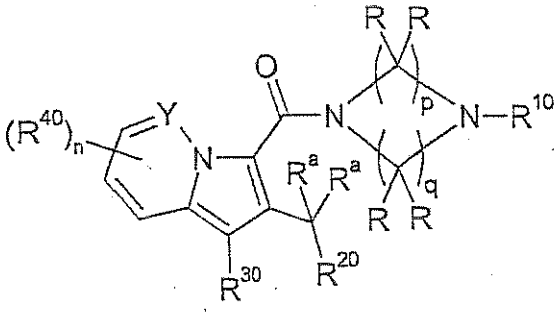
wherein R, R^a, R^{20}, R^{30}, R^{40}, Y, n , p and q are defined herein and additionally functional groups can be present in protected form or in the form of a precursor group, and R^{50} is defined as R^{10} as defined herein with the exception of hydrogen, or R^{50} is a protective group, and removing the protective group R^{50} in case of the preparation of a compound of the formula Ia or Ib in which R^{10} is hydrogen.

In a third aspect, there is provided a pharmaceutical composition, which comprises at least one compound of the formula Ia or Ib as defined herein or a physiologically acceptable salt thereof or a physiologically acceptable solvate of any of them and a pharmaceutically acceptable carrier.

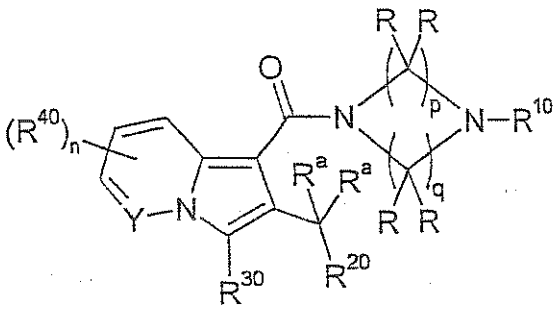
In a fourth aspect, there is provided the use of a compound of the formula Ia or Ib as defined herein or a physiologically acceptable salt thereof or a physiologically acceptable solvate of any of them for the manufacture of a medicament for the treatment of hypertension, heart failure, cardiac infarction, angina pectoris, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, vascular hypertrophy, left ventricular dysfunction, restenosis, renal fibrosis, renal ischemia, renal failure, kidney insufficiency, nephropathy, retinopathy, ischemic or obstructive peripheral circulation disorder, glaucoma or end-organ damage.

DETAILED DESCRIPTION

The present invention relates to cyclic indolizinecarboxamides and azaindolizinecarboxamides of the formulae Ia and Ib,



Ia



Ib

wherein R, R^a, R^{10}, R^{20}, R^{30}, R^{40}, Y, n, p and q have the meanings indicated below, which are valuable pharmaceutical active compounds. Specifically, they inhibit the enzyme renin and modulate the activity of the renin-angiotensin system, and are useful for the treatment of diseases such as hypertension, for example. The invention furthermore relates to processes for the preparation of the compounds of the formulae Ia and Ib, their use and pharmaceutical compositions comprising them.

The renin-angiotensin system (RAS; also designated as renin-angiotensin aldosterone system, RAAS) is a key regulator of cardiovascular functions as well as for the balance of electrolytes and for maintaining body fluid volume, and a determinant of blood pressure (cf., for example, E. Lonn, Can. J. Cardiol. 20 (Suppl. B) (2004), 83B; I. A. Reid, Am. J. Physiol.: Advances in Physiology Education 20 (1998), S236). It acts via the effects of angiotensin II, an octapeptide hormone, which binds to angiotensin receptors. The formation of angiotensin II involves two main steps. In the first step, renin (EC 3.4.23.15; formerly EC 3.4.99.19 and EC 3.4.4.15), a 340 amino acid aspartyl proteinase, cleaves angiotensinogen to form the