NOVEL HYDROXY-6-HETEROARYLPHENANTHRIDINES AND THEIR USE AS PDE4 INHIBITORS

Field of application of the invention

The invention relates to novel hydroxy-6-heteroarylphenanthridine derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

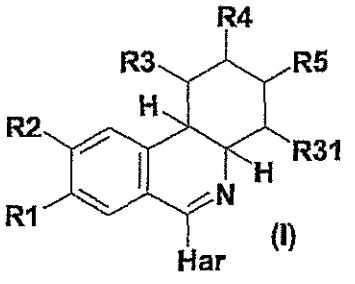
Known technical background

The International Patent applications WO99/57118 and WO02/05616 describe 6-phenylphenanthridines as PDE4 inhibitors.
In the International Patent application WO99/05112 substituted 6-alkylphenanthridines are described as bronchial therapeutics.
In the European Patent application EP 0490823 dihydroisoquinoline derivatives are described which are said to be useful in the treatment of asthma.
The International Patent application WO00/42019 discloses 6-arylphenanthridines as PDE4 inhibitors.
The International Patent application WO02/06270 discloses 6-heteroarylphenanthridines as PDE4 inhibitors.
The International Patent application WO97/35854 discloses phenanthridines substituted in the 6-position as PDE4 inhibitors.
The International Patent applications WO2004/019944 and WO2004/019945 disclose hydroxy-substituted 6-phenylphenanthridines as PDE4 inhibitors.

Description of the invention

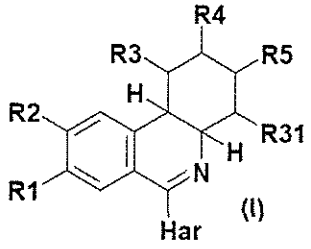
It has now been found that the novel 2- or 3-hydroxy-6-heteroarylphenanthridines described in greater detail below differ from the previously known compounds by unanticipated and sophisticated structural alterations and have surprising and particularly advantageous properties.

The invention thus relates in a first aspect (aspect A) to compounds of formula I,



Claims

1. A compound of formula I



in which

R1 is methoxy,

R2 is methoxy, ethoxy, difluoromethoxy or 2,2-difluoroethoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen,

R5 is hydrogen,

Har is substituted by R6 and R7, and is pyridinyl, in which

R6 is oxo, and

R7 is methyl,

or an enantiomer, a salt, a N-oxide or a salt of an enantiomer of this compound.

2. A compound of formula I according to claim 1 in which

R1 is methoxy,

R2 is methoxy, ethoxy, difluoromethoxy or 2,2-difluoroethoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen,

R5 is hydrogen,

Har is 1-methyl-1H-pyridin-2-one-5-yl,

or an enantiomer, a salt, a N-oxide or a salt of an enantiomer of this compound.

3. A compound of formula I according to claim 1 in which

R1 is methoxy,

R2 is ethoxy, difluoromethoxy or 2,2-difluoroethoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen,

R5 is hydrogen,

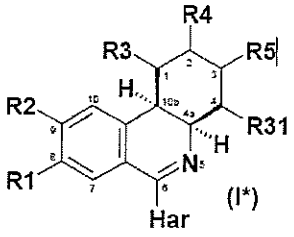
Har is 1-methyl-1H-pyridin-2-one-5-yl,

or an enantiomer, a salt or a salt of an enantiomer of this compound.

4. A compound of formula I according to claim 1 which is 5-((2R,4aR,10bR)-9-Ethoxy-2-hydroxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-6-yl)-1-methyl-1H-pyridin-2-one or a salt of this compound.

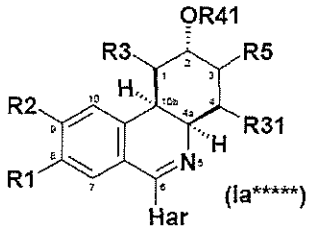
5. A compound of formula I according to claim 1 which is 5-((2R,4aR,10bR)-9-Ethoxy-2-hydroxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-6-yl)-1-methyl-1H-pyridin-2-one.

6. A compound of formula I according to any one of claims 1 to 3, which has with respect to the positions 4a and 10b the configuration shown in formula I*



or a salt, a N-oxide or a salt of a N-oxide of this compound.

7. A compound of formula I according to any one of claims 1 to 3, which has with respect to the positions 2, 4a and 10b the configuration shown in formula Ia*****



or a salt, a N-oxide or a salt of a N-oxide of this compound.

8. The compound of formula I or a salt of this compound as claimed in claim 4 for use in the treatment of diseases.

9. The compound of formula I as claimed in claim 5 for use in the treatment of diseases.

10. A pharmaceutical composition comprising one or more compound(s) of formula I or an enantiomer, a salt, a N-oxide or a salt of an enantiomer or a N-oxide of this (these) compound(s) according to any one of claims 1 to 3 together with customary pharmaceutical excipients and/or vehicles.

11. A pharmaceutical composition comprising the compound of formula I or a salt of this compound as claimed in claim 4 together with customary pharmaceutical excipients and/or vehicles.

12. A pharmaceutical composition comprising the compound of formula I as claimed in claim 5 together with customary pharmaceutical excipients and/or vehicles.

13. A pharmaceutical composition comprising one or more compound(s) of formula I or a salt, a N-oxide or a salt of a N-oxide of this (these) compound(s) as claimed in any one of claims 6 or 7 together with customary pharmaceutical excipients and/or vehicles.

14. Use of a compound of formula I or an enantiomer, a salt, a N-Oxide or a salt of an enantiomer or N-oxide of this compound as claimed in any one of claims 1 to 3 for the production of pharmaceutical compositions for the treatment of bronchial asthma, COPD, psoriasis, atopic eczema or diabetes mellitus.

15. Use of a compound of formula I or a salt of this compound as claimed in claim 4 for the production of pharmaceutical compositions for the treatment of bronchial asthma, COPD, psoriasis or atopic eczema.

16. Use of a compound of formula I or a salt of this compound as claimed in claim 4 for the production of pharmaceutical compositions for the treatment of diabetes mellitus.

17. Use of the compound of formula I as claimed in claim 5 for the production of pharmaceutical compositions for the treatment of bronchial asthma, COPD, psoriasis or atopic eczema.

18. Use of the compound of formula I as claimed in claim 5 for the production of pharmaceutical compositions for the treatment of diabetes mellitus.

19. Use of a compound of formula I or a salt of a N-oxide of this compound as claimed in any one of claims 6 or 7 for the production of pharmaceutical compositions for the treatment of bronchial asthma, COPD, psoriasis, atopic eczema or diabetes mellitus.

20. A compound of formula I or an enantiomer, a salt, a N-oxide or a salt of an enantiomer or N-oxide of this compound as claimed in any one of claims 1 to 3 for use in the treatment of bronchial asthma, COPD, psoriasis, atopic eczema or diabetes mellitus.

21. The compound of formula I or a salt of this compound as claimed in claim 4 for use in the treatment of bronchial asthma, COPD, psoriasis or atopic eczema.

22. The compound of formula I or a salt of this compound as claimed in claim 4 for use in the treatment of diabetes mellitus.

23. The compound of formula I as claimed in claim 5 for use in the treatment of bronchial asthma, COPD, psoriasis or atopic eczema.

24. The compound of formula I as claimed in claim 5 for use in the treatment of diabetes mellitus.

25. A compound of formula I or a salt, a N-oxide or a salt of a N-oxide of this compound as claimed in any one of claims 6 or 7 for use in the treatment of bronchial asthma, COPD, psoriasis, atopic eczema or diabetes mellitus.