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(54) Title **SELECTIVE HISTAMINE H4 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF VESTIBULAR DISORDERS.**

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Patentkrav

1. Selektiv histamin-H4-reseptorantagonist for anvendelse ved behandling og/eller forebygging av minst ett symptom av vestibulære forstyrrelser, hvori den selektive histamin-H4-reseptorantagonisten: har et KiH3:KiH4-forhold over 10:1, og er valgt fra gruppen som består av:

• 1-[(5-klor-1H-benzimidazol-2-yl)karbonyl]-4-metylpiperazin,

• 1-[(5-klor-1H-indol-2-yl)karbonyl]-4-metylpiperazin,

• 4-((3R)-3-aminopyrrolidin-1-yl)-6,7-dihydro-5H-benzo[6,7]syklohepta[1,2-d]pyrimidin-2-ylamin,

• cis-4-(piperazin-1-yl)-5,6,7a,8,9,10,11,11a-oktahydrobenzofuro[2.3-h]kinazolin-2-amin,

• 2-isobutyl-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,

• 2-isobutyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,

• 2-sykloheksylmetyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,

• 2-(4-fluorbenzyl)-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,

• 2-syklopropyl-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,

• 2-tert-butyl-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,

• 2-isopropyl-6-(3-(metylamino)azetidm-1-yl)pyrimidin-4-amin,

• 2-(syklopropylmetyl)-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,

• 6-(3-(metylamino)azetidin-1-yl)-2-(fenoksymetyl)pyrimidin-4-amin,

• 2-syklopropyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,

• 2-tert-butyl-6-((3R)-3-(metylamino)pyrrohdin-1-yl)pyrimidin-4-amin,

- 2-isopropyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- 6-((3R)-3-(metylamino)pyrrolidin-1-yl)-2-(fenoksymetyl)pyrimidin-4-amin,
- 6-(3-aminoazetidin-1-yl)-2-isobutylpyrimidin-4-amin,
- 2-isobutyl-6-(3-metyl-3-(metylamino)azetidin-1-yl) pyrimidin-4-amin,
- 6-((3R)-3-aminopyrrolidin-1-yl)-2-isobutylpyrimidin-4-amin,
- 2-syklobutyl-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,
- 2-syklobutyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- 2-syklopentyl-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,
- 2-syklopentyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- 2-(2,2-dimetylpropyl)-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,
- 2-(2,2-dimetylpropyl)-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- 2-(2-syklopentyletyl)-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- 2-sykloheksylmetyl-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,
- 2-syklopropylmetyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- 2-sykloheksyl-6-(3-(metylamino)azetidin-1-yl)pyrimidin-4-amin,
- 2-sykloheksyl-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- 2-(4-fluorbenzyl)-6-((3R)-3-(metylamino)pyrrolidin-1-yl)pyrimidin-4-amin,
- N^4-(syklopropylmetyl)-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,
- N^4-(syklopropylmetyl)-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamintartrat,
- N^4-isobutyl-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,
- N^4-(2,2-dimetylpropyl)-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin

• N-isobutyl-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-4-amin,

• N-(syklopropylmetyl)-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-4-amin,

• N^4-(2,2-dimetylpropyl)-6-[(4aR*,7aR*)-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,

• N^4-syklopropyl-6-[(4aR*,7aR*)-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin

• N^4-syklobutyl-6-[(4aR*,7aR*)-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-[3-(metylamino)azetidin-1-yl]pyrimidin-2,4-diamin,

• 6-(3-metylamino-azetidin-l-yl)-N^4-(3,3,3-trifluor-propyl)-pyrimidin-2,4-diamin,

• N^4-syklopropylmetyl-6-(3-metylamino-azetidin-1-yl)-pyrimidin-2,4-diamin,

• N^4-(3,3-dimetyl-butyl)-6-(3-metylamino-azetidin-1-yl)-pyrimidin-2,4-diamin,

• N^4-(3-fluor-benzyI)-6-(3-metylamino-azetidin-1-yl)-pyrimidin-2,4-diamin,

• N^4-syklopentylmetyl-6-(3-metylamino-azetidin-1-yl)-pyrimidin-2,4-diamin,

• N^4-isobutyl-6-[3-(metylamino)azetidin-1-yl]pyrimidin-2,4-diamin,

• 6-[3-(metylamino)azetidin-1-yl]-N^4-propyl-pyrimidin-2,4-diamin,

• N^4-(2-metoksybenzyl)-6-[3-(metylamino)azetidin-1-yl]pyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-[(3R)-3-metylpiperazin-1-yl]pyrimidin-2,4-diamin,

• N^4-etyl-6-(4-metylpiperazin-1-yl)pyrimidin-2,4-diamin,

• N^4-(syklopropylmetyl)-6-(4-metylpiperazin-1-yl)pyrimidin-2,4-diamin,

• 6-[3-(metylamino)azetidin-1-yl]-N^4-(2-metylbutyl)pyrimidin-2,4-diamin,

• N^4-(2,5-difluorbenzyl)-6-[3-(metylamino)azetidin-1-yl]pyrimidin-2,4-diamin,

• N^4-(2,3-difluorbenzyl)-6-[3-(metylamino)azetidin-1-yl]pyrimidin-2,4-diamin,

• N^4-butyl-6-[3-(metylamino)azetidin-1-yl]pyrimidin-2,4-diamin,

• 6-[(3R)-3-(metylamino)pyrrolidin-1-yl]-N^4-(2-metylsyklopropyl)pyrimidin-2,4-diamin,

• N^4-isobutyl-6-(4-metyl-1,4-diazepan-1-yl)pyrimidin-2,4-diamin,

• N^4-(syklopropylmetyl)-6-(3-pyrrolidin-1-yl-azetidin-1-yl)pyrimidin-2,4-diamin,

• N^4-bisyklo[1.1.1]pent-1-yl-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,

• 6-[3-metyl-3-(metylamino)azetidin-1-yl]-N^4-propylpyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-(heksahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-(3-pyrrolidin-1-yl-azetidin-1-yl)pyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-[3-(isopropylamino)azetidin-1-yl]pyrimidin-2,4-diamin,

• N^4-(tert-butyl)-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,

• 6-[(3R)-3-(metylamino)pyrrolidin-1-yl]-N^4-(1-metylsyklopropyl)pyrimidin-2,4-diamin,

• N^4-(tert-butyl)-6-[(4aS*,7aS*)-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-piperazin-1-ylpyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-[3-(metylamino)azetidin-1-yl]pyrimidin-2,4-diaminhydroklorid,

• N^4-(2,2-dimetylpropyl)-6-[(3aR*,7aS*)-oktahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidin-2,4-diamin,

• 6-piperazin-1-yl-N^4-propylpyrimidin-2,4-diamin,

• N^4-(syklopropylmetyl)-6-[4aR,7aR]-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,

• N^4-(2,2-dimetylpropyl)-6-[(4aS,7aS)-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,

• N^4-(syklopropylmetyl)-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,

• N^4-isopropyl-6-[(4aS,7aS)-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,

• 4-[3-(metylamino)azetidin-1-yl]-6-(4-metylpiperidin-1-yl)pyrimidin-2-amin,

• N^4-(syklopentylmetyl)-6-[(3R)-3-(metylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,

• N^4-syklobutyl-6-[(4aS,7aS)-oktahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,

• 6-[(3R)-3-(metylamino)pyrrolidin-1-yl]-N4-propylpyrimidin-2,4-diamin, og

• N^4-etyl-6-(4-metyl-1,4-diazepan-1-yl)pyrimidin-2,4-diamin.

2. Den selektive histamin-H4-reseptorantagonisten for anvendelse ifølge krav **1**, hvori det minst ene symptomet på vestibulære forstyrrelser er valgt fra gruppen som består av vertigo, svimmelhet, ubalanse, og kvalme.

3. Den selektive histamin-H4-reseptorantagonisten for anvendelse ifølge krav **1** eller **2**, hvori vertigo er en godartet paroksysmal vertigo eller familiær episodisk vertigo.

4. Den selektive histamin-H4-reseptorantagonisten for anvendelse ifølge et hvilket som helst av kravene **1** til **3**, hvori den vestibulære forstyrrelsen er valgt fra vestibularisnevritt, spell av Ménières sykdom, endolymfatisk hydrops, perilymfatisk fistel, hodeskade med vestibulære forstyrrelser, labyrintisk blødning, kronisk eller akutt labyrintisk infeksjon, serøs labyrinthitis, barotraumatisme med vestibulære forstyrrelser, vestibulære syndromer etter autoimmun sykdom i det indre øret, vestibulær migrene, vestibulære syndromer etter kirurgisk behandling i mellomøret, endolymfatisk sekk eller pontocerebellare vinkelsvulster, kanalopatier i det indre øret, kronisk Ménières sykdom, vestibularisschwannom, presbyvestibuli, og vestibular ataksi.

5. Den selektive histamin-H4-reseptorantagonisten for anvendelse ifølge et hvilket som helst av kravene **1** til **4,** for administrering gjennom trommehinnen eller for systemisk administrering.

6. Farmasøytisk sammensetning omfattende en selektiv histamin-H4-reseptorantagonist ifølge et hvilket som helst av kravene **1** til **5,** for anvendelse ved behandling og/eller forebygging av minst ett symptom av vestibulære forstyrrelser.