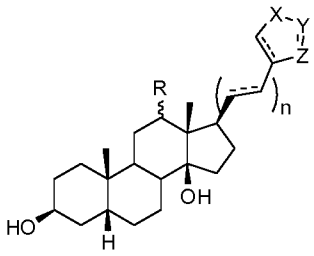
CLAIMS

1. Compounds of formula (I)



wherein X, Y, Z are annular atoms comprised in a five-membered carbocyclic or heterocyclic ring, selected from the group consisting of CH, NH, N, O, S; said carbocyclic or heterocyclic ring being optionally substituted with amino (C_1-C_4) linear or branched alkyl or guanidine or guanidino (C_1-C_4) linear or branched alkyl;

with the proviso that the heterocycle ring is not furyl;

n is 0 or 1;

R is H or OH;

the dotted line represents an optional double bond C=C; the thick line represents a bond in the β configuration; the wavy line represents a bond both in the α and β configuration;

their enantiomeric and/or diastereomeric mixtures, their pharmaceutically acceptable salts, their solvates, hydrates; their metabolite and metabolic precursors.

2. Compounds according to claim 1, wherein heterocycle group in position 17β is selected form the group consisting of imidazolyl, pyrazolyl, thiazolyl, isoxazolyl, the corresponding dihydro- and tetrahydro derivatives, optionally substituted by a amino(C_1-C_4) linear or branched alkyl or guanidine or guanidino (C_1-C_4) linear or branched alkyl.

3. Compounds according to claim 1 or 2, wherein R is beta OH.

4. Compounds according to any one of claims 1-3, wherein the symbol n is 0.

5. Compounds according to any one of claims 1-3, the symbol n is 1 and there is a single or double bond between the androstane skeleton and the 17β-heterocyclyl or carbocyclyl ring.

6. Compounds according to any one of claims 1-5, selected from the group consisting of

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(imidazol-4-yl)androstane;
- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(2-guanidino-thiazol-4-yl)androstane;
- 3β-hydroxy-5β-10β-methyl-12β-hydroxy-13β-methyl-14β-hydroxy-17β-(imidazol-4-yl)androstane;
- 3β-hydroxy-5β-10β-methyl-12β-hydroxy-13β-methyl-14β-hydroxy-17β-(2-guanidino-thiazol-4-yl)androstane.
- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(N-(3-aminopropyl)-imidazol-4-yl)androstane;
- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(pyrazol-3-yl)androstane;
- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-((5-(3-aminopropyl)-isoxazol-3-yl))androstane;
- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-((5-(3-aminopropyl)-isoxazol-3-yl)-ethyl)androstane;
- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(5-(2-aminoethyl)-isoxazol-3-yl)-ethyl)androstane;
- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(5-(2-aminomethyl)-isoxazol-3-yl)-ethenyl)androstane.

7. Compounds according to any one of claims 1-6, wherein the pharmaceutically acceptable salt is selected from chloride, bromide, sulfate, phosphate, nitrate, fumarate, succinate, oxalate, malate, tartrate, maleate, citrate, methanesulfonate, benzoate.

8. A pharmaceutical composition comprising one or more of the compounds of any one of claims 1-7, in combination with at least one pharmaceutically acceptable vehicle and/or excipient.

9. A pharmaceutical composition according to claim 8, formulated for enteral or parenteral administration or inhalation.

10. A pharmaceutical composition according to claim 9, formulated for oral administration.

11. A pharmaceutical composition according to claim 9, formulated for intravenous or intramuscular injection.

12. A pharmaceutical composition according to any one of claims 8-11, further comprising one or more therapeutically active ingredients.

13. A pharmaceutical composition according to claim 12, wherein said further therapeutically active ingredient is selected among therapeutic agents for treating heart failure.

14. A pharmaceutical composition according to claim 13, wherein said further therapeutically active ingredient is selected among ACE inhibitors, AIRBs, diuretics, Ca channel blockers, β blockers, digitalis, NO donors, vasodilators, SERCA2a stimulators, neprilisin (NEP) inhibitors, myosin filament activators, recombinant relaxin-2 mediators, recombinant NP protein, activators of the soluble Guanylate Cyclase (sGC), beta-arrestin ligand of Angiotensin II receptor.

15. A pharmaceutical composition according to claim 14, wherein said diuretic, is selected among furosemide, bumetanide, torasemide, metolazone, an aldosterone antagonist, in particular spironolactone and eplerenone; thiazide diuretics, in particular hydrochlorothiazide, metolazone, chlorthalidone.

16. A pharmaceutical composition according to claim 14, wherein said ACE inhibitor is selected among Lisinopril and Ramipril.

17. A pharmaceutical composition according to claim 14, wherein said Angiotensin II receptor blocker is selected among valsartan, candesartan, olmesartan, telmisartan and losartan.

18. A pharmaceutical composition according to claim 14, wherein said Angiotensin receptor/neprilysin inhibitor is sacubitril.

19. A pharmaceutical composition according to claim 14, wherein said Beta-blocker is selected among carvedilol and metoprolol.

20. A pharmaceutical composition according to claim 14, wherein said Vasodilator is selected among Hydralazine, optionally combined with isosorbide dinitrate, nitrates, in particular nitroglycerin or isosorbide nitrate, amlodipine, felodipine, non-dihydropyridines, in particular diltiazem or verapamil.

21. A pharmaceutical composition according to claim 14, wherein said agent for the treatment of heart failure is selected from Digoxin, entresto, omecantiv, serelaxin, ularitide, levosimendan.

22. Compounds of any one of claims 1-7 for use as medicaments.

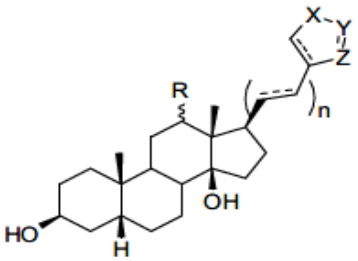
23. Compounds of any one of claims 1-7 for use for treating heart failure.

24. Compounds for use according to claim 23, wherein heart failure is acute or chronic.

25. Compounds for use according any one of claims 23-24 in combination with one or more therapeutically active agents disclosed in any one of claims 13-21.

CLAIMS

1. Compounds of formula (I)



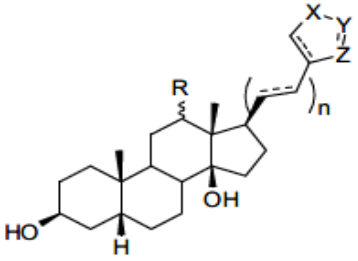
wherein X, Y, Z are annular atoms comprised in a five-membered carbocyclic or heterocyclic ring, selected from the group consisting of CH, NH, N, O, S; said heterocyclic ring selected from the group consisting of imidazolyl, pyrazolyl, thiazolyl, isoxazolyl, and the corresponding dihydro- and tetrahydro derivatives; said carbocyclic or heterocyclic ring being optionally substituted with amino (C_1-C_4) linear or branched alkyl or guanidine or guanidino (C_1-C_4) linear or branched alkyl;

n is 0 or 1;

R is H or OH;

the dotted line represents an optional double bond C=C; the thick line represents a bond in the β configuration; the wavy line represents a bond both in the α and β configuration; or pharmaceutically acceptable salts, solvates, or hydrates thereof.

2. Compounds of formula (I)



wherein X, Y, Z are annular atoms comprised in a five-membered carbocyclic or heterocyclic ring, selected from the group consisting of CH, NH, N, O, S; said carbocyclic or heterocyclic ring being optionally substituted with amino (C_1-C_4) linear or branched alkyl or guanidine or guanidino (C_1-C_4) linear or branched alkyl;

with the proviso that the heterocycle ring is not furyl;

n is 1 and there is a single or double bond between the androstane skeleton and the 17β-heterocyclyl or carbocyclyl ring;

R is H or OH;

the dotted line represents an optional double bond C=C; the thick line represents a bond in the β configuration; the wavy line represents a bond both in the α and β configuration; or

pharmaceutically acceptable salts, solvates, or hydrates thereof.

3. Compounds according to claim 2, wherein heterocycle group in position 17β is selected from the group consisting of imidazolyl, pyrazolyl, thiazolyl, isoxazolyl, the corresponding dihydro- and tetrahydro derivatives, optionally substituted by an amino(C_1-C_4) linear or branched alkyl or guanidine or guanidino (C_1-C_4) linear or branched alkyl.

4. Compounds according to any one of claims 1-3, wherein R is beta OH.

5. Compounds according to claim 1, wherein the symbol n is 0.

6. Compounds according to claim 1, wherein the symbol n is 1 and there is a single or double bond between the androstane skeleton and the 17β-heterocyclyl or carbocyclyl ring.

7. Compounds according to claims 1 or 2, selected from the group consisting of

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β hydroxy-17β-(imidazol-4-yl)androstane;

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(2-guanidino-thiazol-4-yl)androstane;

- 3β-hydroxy-5β-10β-methyl-12β-hydroxy-13β-methyl-14β-hydroxy-17β-(imidazol-4-yl)androstane;

- 3β-hydroxy-5β-10β-methyl-12β-hydroxy-13β-methyl-14β-hydroxy-17β-(2-guanidino-thiazol-4-yl)androstane;

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(N-(3-aminopropyl)-imidazol-4-yl)androstane;

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(pyrazol-3-yl)androstane;

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-((5-(3-aminopropyl)-isoxazol-3-yl))androstane;

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-((5-(3-aminopropyl)-isoxazol-3-yl)-ethyl)androstane;

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(5-(2-aminoethyl)-isoxazol-3-yl)-ethyl)androstane;

- 3β-hydroxy-5β-10β-methyl-13β-methyl-14β-hydroxy-17β-(5-(2-aminomethyl)-isoxazol-3-yl)-ethenyl)androstane.

8. Compounds according to any one of claims 1-7, wherein the pharmaceutically acceptable salt is selected from chloride, bromide, sulfate, phosphate, nitrate, fumarate, succinate, oxalate, malate, tartrate, maleate, citrate, methanesulfonate, benzoate.

9. A pharmaceutical composition comprising one or more of the compounds of any one of claims 1-8, in combination with at least one pharmaceutically acceptable vehicle and/or excipient.

10. A pharmaceutical composition according to claim 9, formulated for enteral or parenteral administration or inhalation.

11. A pharmaceutical composition according to claim 10, formulated for oral administration.

12. A pharmaceutical composition according to claim 10, formulated for intravenous or intramuscular injection.

13. A pharmaceutical composition according to any one of claims 9-12, further comprising one or more therapeutically active ingredients.

14. A pharmaceutical composition according to claim 13, wherein said further therapeutically active ingredient is selected among therapeutic agents for treating heart failure.

15. A pharmaceutical composition according to claim 14, wherein said further therapeutically active ingredient is selected among ACE inhibitors, AIRBs, diuretics, Ca channel blockers, β blockers, digitalis, NO donors, vasodilators, SERCA2a stimulators, neprilisin (NEP) inhibitors, myosin filament activators, recombinant relaxin-2 mediators, recombinant NP protein, activators of the soluble Guanylate Cyclase (sGC), beta-arrestin ligand of Angiotensin II receptor.

16. A pharmaceutical composition according to claim 15, wherein said diuretic, is selected among furosemide, bumetanide, torasemide, metolazone, an aldosterone antagonist, in particular spironolactone and eplerenone; thiazide diuretics, in particular hydrochlorothiazide, metolazone, chlorthalidone.

17. A pharmaceutical composition according to claim 15, wherein said ACE inhibitor is selected among Lisinopril and Ramipril.

18. A pharmaceutical composition according to claim 15, wherein said Angiotensin II receptor blocker is selected among valsartan, candesartan, olmesartan, telmisartan and losartan.

19. A pharmaceutical composition according to claim 15, wherein said Angiotensin receptor/neprilysin inhibitor is sacubitril.

20. A pharmaceutical composition according to claim 15, wherein said Beta-blocker is selected among carvedilol and metoprolol.

21. A pharmaceutical composition according to claim 15, wherein said Vasodilator is selected among Hydralazine, optionally combined with isosorbide dinitrate, nitrates, in particular nitroglycerin or isosorbide nitrate, amlodipine, felodipine, non-dihydropyridines, in particular diltiazem or verapamil.

22. A pharmaceutical composition according to claim 15, wherein said agent for the treatment of heart failure is selected from Digoxin, entresto, omecantiv, serelaxin, ularitide, levosimendan.

23. Compounds of any one of claims 1-8 for use as medicaments.

24. Use of the compounds of any one of claims 1-8 in the preparation of a medicament for treating heart failure.

25. The use according to claim 24 in combination with one or more therapeutically active agents disclosed in any one of claims 14-22.