

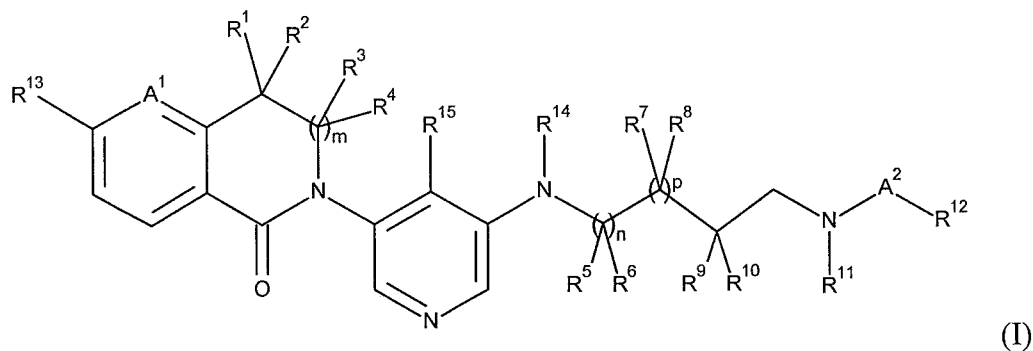
reduced, whereas spironolactone increased aldosterone at 4 and 8 weeks of treatment. Similarly only spironolactone but not FAD286 enhanced angiotensin II and salt-stimulated PAI-1 mRNA expression in the aorta and the heart. In other studies the CYP11B2 inhibitor FAD286 improved blood pressure and cardiovascular function and structure in rats with
5 experimental heart failure. In the same studies FAD286 was shown to improve kidney function and morphology.

Administration of an orally active CYP11B2 inhibitor, LCI699, to patients with primary aldosteronism, lead to the conclusion that it effectively inhibits CYP11B2 in patients with primary aldosteronism resulting in significantly lower circulating aldosterone
10 levels and that it corrected the hypokalemia and mildly decreased blood pressure. The effects on the glucocorticoid axis were consistent with a poor selectivity of the compound and a latent inhibition of cortisol synthesis. Taken together these data support the concept that a CYP11B2 inhibitor can lower inappropriately high aldosterone levels. Achieving good selectivity against CYP11B1 is important to be free of undesired side effects on the
15 HPA axis and will differentiate different CYP11B2 inhibitors.

The compounds of the present disclosure according to formula (I) are potent inhibitors of CYPB11B2 and present an improved selectivity towards CYP11B2 versus CYP11B1 combined with an improved metabolic stability.

Objects of the embodiments disclosed herein are the compounds of formula (I) and
20 their aforementioned salts and esters and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically acceptable salts or esters, the use of the said compounds, salts or esters for the treatment or prophylaxis of illnesses, especially in the treatment or prophylaxis of chronic kidney
25 disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom and the use of the said compounds, salts or esters for the production of medicaments for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.

According to one aspect, there is provided compounds of formula (I)



wherein

R¹, R², R³ and R⁴ are independently selected from H, alkyl and cycloalkyl;

5 or R¹ and R² together form -CH₂-CH₂-;

R⁵ and R⁶ are independently selected from H or alkyl;

A¹ is -CH- or -N-;

A² is -C(O)- or -S(O)₂-;

10 R¹² is heteroaryl or substituted heteroaryl, wherein substituted heteroaryl is substituted with one to three substituent independently selected from alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, cyano and halogen;

R¹³ is halogen, cyano, alkoxy or haloalkoxy;

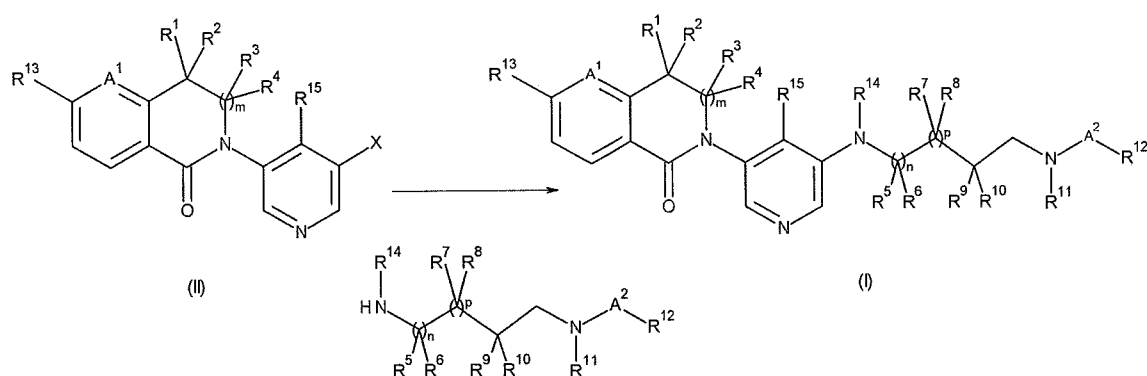
R¹⁵ is H, alkyl, cycloalkyl or halogen;

m is zero or 1; and

15 R¹⁴ and (i) R⁹ together are -CH₂-, R¹⁰ and R¹¹ together are -CH₂-, n is 1 and p is zero; or (ii) R⁹ together are -CH₂-CH₂-, R¹⁰ and R¹¹ together are -CH₂-, n is 1 and p is 1 and R⁷ and R⁸ are independently selected from H or alkyl; or (iii) R⁷ together are -CH₂-, R⁸ and R¹¹ together are -CH₂-CH₂-, n is 1, p is 1 and R⁹ and R¹⁰ are independently selected from H or alkyl;

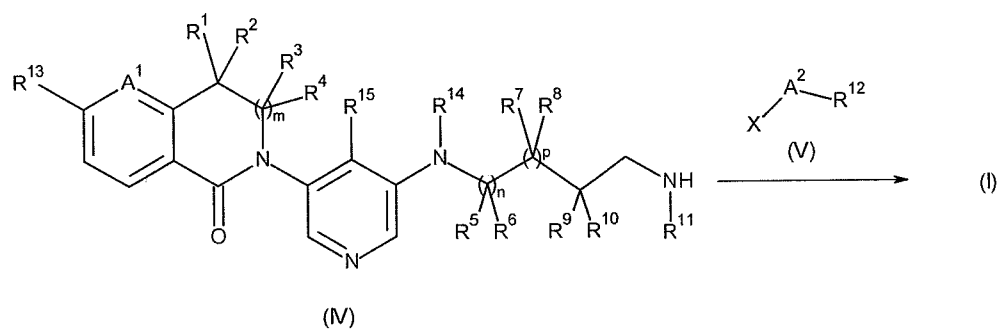
or, a pharmaceutically acceptable salt thereof.

According to another aspect, there is provided a process to prepare a compound as defined herein comprising reacting a compound of formula (II) with a compound of formula (III) to afford compound I wherein $R^1, R^2, R^3,$



5 $R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A^1, A^2$ m, n and p are as described herein and X is halogen or triflate.

According to another aspect, there is provided a process to prepare a compound as defined herein comprising reacting a compound of formula (IV) with a compound of
10 formula (V) to afford a compound of formula (I)



wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A^1, A^2$ m, n and p are as described herein and X is halogen.

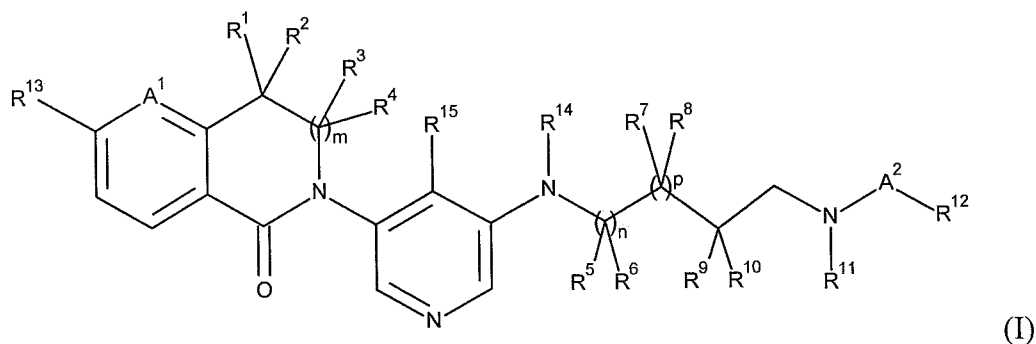
According to another aspect, there is provided a compound as defined herein for use
15 as therapeutically active substance.

According to another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and at least one therapeutically acceptable carrier, diluent or excipient.

According to another aspect, there is provided use of a compound as defined herein
5 in the manufacture of a medicament for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrome.

CLAIMS

1. Compounds of formula (I)



wherein

- 5 R¹, R², R³ and R⁴ are independently selected from H, alkyl and cycloalkyl;
or R¹ and R² together form -CH₂-CH₂-;
- R⁵ and R⁶ are independently selected from H or alkyl;
- A¹ is -CH- or -N-;
- A² is -C(O)- or -S(O)₂-;
- 10 R¹² is heteroaryl or substituted heteroaryl, wherein substituted heteroaryl is substituted with one to three substituent independently selected from alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, cyano and halogen;
- R¹³ is halogen, cyano, alkoxy or haloalkoxy;
- R¹⁵ is H, alkyl, cycloalkyl or halogen;
- 15 m is zero or 1; and
- R¹⁴ and (i) R⁹ together are -CH₂-, R¹⁰ and R¹¹ together are -CH₂-, n is 1 and p is zero;
or

(ii) R^9 together are $-CH_2-CH_2-$, R^{10} and R^{11} together are $-CH_2-$, n is 1 and p is 1 and R^7 and R^8 are independently selected from H or alkyl; or

(iii) R^7 together are $-CH_2-$, R^8 and R^{11} together are $-CH_2-CH_2-$, n is 1, p is 1 and R^9 and R^{10} are independently selected from H or alkyl;

5 or, a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R^1 and R^2 are alkyl or R^1 and R^2 together form $-CH_2-CH_2-$.

3. The compound according to claim 1, wherein R^1 and R^2 are alkyl.

4. The compound according to claim 1, wherein R^3 and R^4 are H.

10 5. The compound according to claim 1, wherein R^{13} is halogen.

6. The compound according to claim 1, wherein R^{15} is H.

7. The compound according to claim 1, wherein A^1 is $-CH-$.

8. The compound according to claim 1, wherein A^2 is $-C(O)-$.

15 9. The compound according to claim 1, wherein R^9 and R^{14} together form $-CH_2-$, R^{10} and R^{11} together form $-CH_2-$, n is 1 and p is zero.

10. The compound according to claim 1, wherein R^{12} is a heteroaryl group selected from the group consisting of imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl and pyrimidinyl.

11. The compound according to claim 1, wherein A^1 is $-CH_2-$ and A^2 is $-C(O)-$.

20 12. The compound according to claim 11, wherein R^{12} is a heteroaryl group selected from the group consisting of imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl and pyrimidinyl.

13. The compound according to claim 1, wherein R¹² is pyrazolyl substituted by alkyl or is pyridinyl substituted by alkyl.
14. The compound according to claim 11, wherein R¹² is pyrazolyl substituted by alkyl.
15. The compound according to claim 1 which compound is selected from the group
5 consisting of:

6-Chloro-2-[5-[2-(1-methylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]-3,4-dihydroisoquinolin-1-one;

(3R or 3S)-5-Chloro-3-methyl-2-[4-methyl-5-[2-(1-methylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]isoindolin-1-one;

5 (3S or 3R)-5-Chloro-3-methyl-2-[4-methyl-5-[2-(1-methylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]isoindolin-1-one;

5-Chloro-3,3-dimethyl-2-[5-[7-(1-methylpyrazole-4-carbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-3-pyridyl]isoindolin-1-one;

10 5-Chloro-3,3-dimethyl-2-[5-[7-(4-methylpyridine-3-carbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-3-pyridyl]isoindolin-1-one;

5-Chloro-2-[5-[7-(1-ethylpyrazole-4-carbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-3-pyridyl]-3,3-dimethyl-isoindolin-1-one;

5-Chloro-3,3-dimethyl-2-[5-[2-(1-methylpyrazole-4-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl]-3-pyridyl]isoindolin-1-one;

15 5-Chloro-2-[5-[2-(1-ethylpyrazole-4-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl]-3-pyridyl]-3,3-dimethyl-isoindolin-1-one;

5-Chloro-3,3-dimethyl-2-[5-[2-(4-methylpyridine-3-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl]-3-pyridyl]isoindolin-1-one;

or, a pharmaceutically acceptable salt thereof.

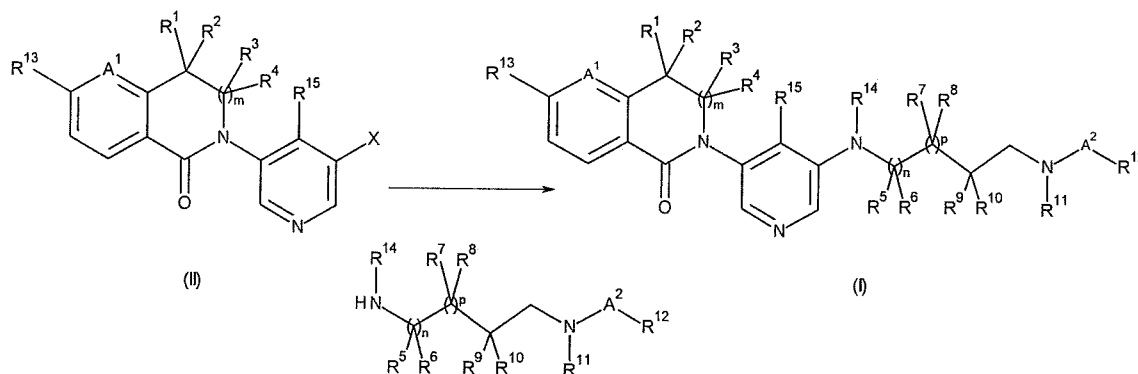
20 16. The compound according to any one of claims 1 to 13, selected from

5-Chloro-3,3-dimethyl-2-[5-[2-(1-methylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]isoindolin-1-one;

5-Chloro-2-[5-[2-(1-ethylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]-3,3-dimethyl-isoindolin-1-one;

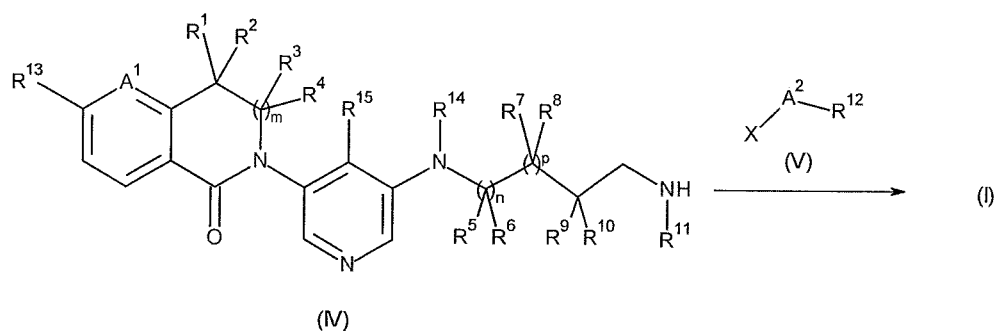
- 5-Chloro-3,3-dimethyl-2-[5-[2-(4-methylpyridine-3-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]isoindolin-1-one;
- 2-[5-[2-(1-Ethylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]-3,3-dimethyl-1-oxo-isoindoline-5-carbonitrile;
- 5 2-Methoxy-7,7-dimethyl-6-[5-[2-(1-methylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]pyrrolo[3,4-b]pyridin-5-one;
- 5'-Chloro-2'-[5-[2-(1-methylpyrazole-4-carbonyl)-2,6-diazaspiro[3.3]heptan-6-yl]-3-pyridyl]spiro[cyclopropane-1,3'-isoindoline]-1'-one;
- 5-Chloro-3,3-dimethyl-2-[5-[7-(1-methylpyrazole-4-carbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-3-pyridyl]isoindolin-1-one;
- 10 5-Chloro-2-[5-[7-(1-ethylpyrazole-4-carbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-3-pyridyl]-3,3-dimethyl-isoindolin-1-one;
- 5-Chloro-3,3-dimethyl-2-[5-[2-(1-methylpyrazole-4-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl]-3-pyridyl]isoindolin-1-one;
- 15 or, a pharmaceutically acceptable salt thereof.
17. A process to prepare a compound according to claim 1 comprising

reacting a compound of formula (II) with a compound of formula (III) to afford compound I wherein R^1 , R^2 , R^3 ,



- 20 R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , A^1 , A^2 m, n and p are as described in claim 1 and X is halogen or triflate.

18. A process to prepare a compound according to claim 1 comprising reacting a compound of formula (IV) with a compound of formula (V) to afford a compound of formula (I)



5 wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A^1, A^2$ m, n and p are as described in claim 1 and X is halogen.

19. A compound according to claim 1 for use as therapeutically active substance.
20. A pharmaceutical composition comprising a compound according to claim 1 and at least one therapeutically acceptable carrier, diluent or excipient.
- 10 21. The use of a compound according to claim 1 in the manufacture of a medicament for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.