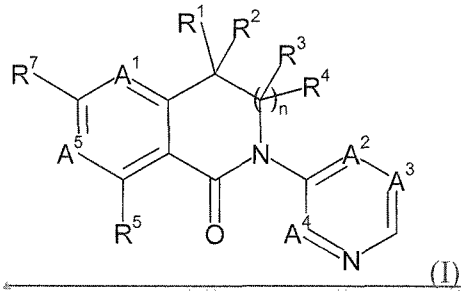
increased PAI-1, and osteopontin mRNA expression, as well as tubulointerstitial fibrosis. Both drugs prevented these renal effects and attenuated cardiac and aortic medial hypertrophy. Following 4 weeks of treatment with FAD286, plasma aldosterone was reduced, whereas spironolactone increased aldosterone 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 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 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 HPA axis and will differentiate different CYP11B2 inhibitors.

Objects of ~~the present invention~~embodiments disclosed herein are the compounds of formula (I) and 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 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.

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



(I)

wherein

R^1, R^2, R^3 and R^4 are independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, halocycloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, halocycloalkylalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted arylalkyl and substituted heteroarylalkyl, wherein substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted arylalkyl and substituted heteroarylalkyl are substituted with R^{12}, $R^{13}$and R^{14};

or R^2 and R^4 together form a double bond, wherein in case R^2 and R^4 together form a double bond, then R^5 is H;

or R^1 and R^2 together with the carbon atom to which they are attached form a substituted cycloalkyl or a substituted heterocycloalkyl, wherein substituted cycloalkyl and substituted heterocycloalkyl are substituted with R^{22}, $R^{23}$and R^{24};

or R^3 and R^4 together with the carbon atom to which they are attached form a substituted cycloalkyl or a substituted heterocycloalkyl, wherein substituted cycloalkyl and substituted heterocycloalkyl are substituted with R^{29}, $R^{30}$and R^{31};

or R^1 and R^3 together with the carbon atom to which they are attached form a substituted cycloalkyl or a substituted heterocycloalkyl, wherein substituted cycloalkyl and substituted heterocycloalkyl are substituted with R^{44}, $R^{45}$and R^{46};

A^1 is CR^8 or N;

A^2 is CR^9 or N;

A^3 is CR^{10} or N;

A^4 is CR^{11} or N;

A^5 is CR^6 or N;

one of R^5, R^6, R^7 and R^8 is selected from halogen, cyano, alkoxy, hydroxyalkoxy, haloalkyl, haloalkoxy and hydroxy and the others are each independently selected from H, halogen, cyano, alkoxy, hydroxyalkoxy, haloalkoxy and hydroxy;

R^9 is H, halogen, hydroxy, cyano, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, halocycloalkyl, alkylcycloalkylalkyl, alkoxycycloalkylalkyl, halocycloalkylalkyl, cycloalkylalkoxy, cycloalkylalkoxyalkyl, cycloalkoxy, cycloalkoxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, alkylcycloalkoxy, alkylcycloalkoxyalkyl, alkoxy, alkoxyalkyl, alkoxycycloalkylalkyl, dialkoxyalkyl, haloalkoxy, haloalkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, haloalkoxyalkoxy, haloalkoxyalkoxyalkyl, substituted arylalkyl, substituted arylhydroxyalkyl, substituted heterocycloalkylalkyl or substituted heteroarylalkyl, wherein substituted arylalkyl, substituted arylhydroxyalkyl, substituted heterocycloalkylalkyl and substituted heteroarylalkyl are substituted with R^{32}, $R^{33}$and R^{34};

R^{10} is $-O_m-(CR^{15}R^{16})_p-(CR^{17}R^{18})_q-(CR^{19}R^{20})_r-R^{21}$;

or R^9 and R^{10} together with the carbon atoms to which they are attached form a substituted cycloalkyl, a substituted heterocycloalkyl, a substituted aryl or a subtituted heteroaryl, wherein substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl and substituted heteroaryl are substituted with R^{35}, $R^{36}$and R^{37};

R^{11} is H;

R^{15}, R^{17} and R^{19} are each independently selected from H, alkyl, cycloalkyl, haloalkyl and halocycloalkyl;

R^{16}, R^{18} and R^{20} are each independently selected from H, hydroxy, halogen and alkyl;

or R^{15} and R^{16} together with the carbon atom to which they are attached form a cycloalkyl;

or R^{17} and R^{18} together with the carbon atom to which they are attached form a cycloalkyl;

or R^{19} and R^{20} together with the carbon atom to which they are attached form a cycloalkyl;

or R^{15} and R^{17} together form $-(CH_2)_v-$;

or R^{15} and R^{19} together form $-(CH_2)_w-$;

or R^{17} and R^{19} together form $-(CH_2)_x-$;

R^{21} is H, halogen, cyano, $-OR^{25}$, $-SR^{25}$, $-S(O)R^{25}$, $-S(O)_2R^{25}$, $-NR^{25}R^{26}$, $-NR^{26}SO_2R^{25}$, $-NR^{26}SO_2NR^{25}R^{27}$, $-NR^{26}C(O)R^{25}$, $-NR^{26}C(O)NR^{25}R^{27}$, $-C(O)R^{28}$, $-C(O)NR^{25}R^{26}$, cycloalkyl, substituted heterocycloalkyl, substituted heteroaryl or substituted aryl, wherein substituted heterocycloalkyl, substituted heteroaryl, substituted heteroarylalkyl and substituted aryl are substituted with R^{38}, $R^{39}$and R^{40};

R^{25} is H, alkyl, hydroxyalkyl, carboxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, halocycloalkyl, alkylcycloalkylalkyl, alkoxycycloalkylalkyl, halocycloalkylalkyl, cycloalkylalkoxyalkyl, cycloalkoxyalkyl, halocycloalkoxyalkyl, alkylcycloalkoxyalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, haloalkoxyalkoxyalkyl, substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted aryl or substituted arylalkyl, wherein substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted aryl and substituted arylalkyl are substituted with R^{41}, $R^{42}$and R^{43};

R^{26} and R^{27} are each independently selected from H, alkyl, cycloalkyl, haloalkyl or halocycloalkyl;

or R^{15} and R^{26} together with the nitrogen atom and carbon atom to which they are attached form a substituted heterocycloalkyl or a substituted heteroaryl, wherein substituted heterocycloalkyl and substituted heteroaryl are substituted with R^{47}, $R^{48}$and R^{49};

or R^{17} and R^{26} together with the nitrogen atom and carbon atom to which they are attached form a substituted heterocycloalkyl or a substituted heteroaryl, wherein substituted heterocycloalkyl and substituted heteroaryl are substituted with R^{47}, $R^{48}$and R^{49};

or R^{19} and R^{26} together with the nitrogen atom and carbon atom to which they are attached form a substituted heterocycloalkyl or a substituted heteroaryl, wherein substituted heterocycloalkyl and substituted heteroaryl are substituted with R^{47}, $R^{48}$and R^{49};

R^{28} is H, hydroxy, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, halocycloalkyl, alkylcycloalkylalkyl, alkoxycycloalkylalkyl, halocycloalkylalkyl, cycloalkylalkoxy, cycloalkylalkoxyalkyl, cycloalkoxy, cycloalkoxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, alkylcycloalkoxy, alkylcycloalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, haloalkoxyalkoxy, haloalkoxyalkoxyalkyl substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted aryl or substituted arylalkyl, wherein substituted substituted heterocycloalkyl, substituted heterocycloalkylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted aryl and substituted arylalkyl are substituted with R^{50}, $R^{51}$and R^{52};

R^{12}, R^{13}, R^{14}, R^{22}, R^{23}, R^{24}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51} and R^{52} are each independently selected from H, halogen, hydroxy, amino, nitro, cyano, oxo, alkyl, alkylcarbonyl, alkylsulfonyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, halocycloalkyl, alkylcycloalkylalkyl, alkylcarbonylamino, alkylsulfonyl, alkylsulfonylamino, alkoxycycloalkylalkyl, halocycloalkylalkyl, cycloalkylalkoxy, cycloalkylalkoxyalkyl, cycloalkoxy, cycloalkoxyalkyl, halocycloalkoxy,

halocycloalkoxyalkyl, alkylcycloalkoxy, alkylcycloalkoxyalkyl, alkoxy, alkoxycarbonyl, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, haloalkoxyalkoxy, haloalkoxyalkoxyalkyl, chloropyridinylcarbonyl and heterocycloalkyl;

n is zero or 1;

m zero or 1;

p, q and r are independently selected from zero and 1;

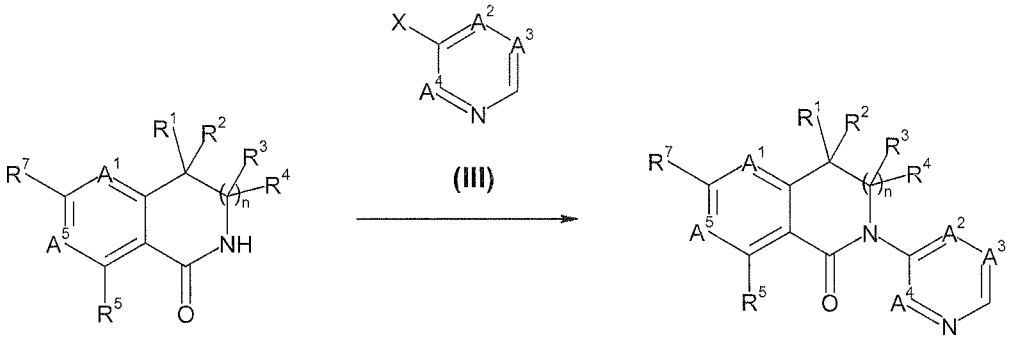
v and x are independently selected from 1, 2, 3 or 4;

w is zero, 1, 2 or 3;

with the proviso that no more than two of A^2, A^3 and A^4 are N;

and pharmaceutically acceptable salts thereof.

In another aspect, there is provided a process to prepare a compound as defined herein comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III);



wherein R^1, R^2, R^3, R^4, R^5, R^6, A^1, A^2, A^3, A^4, A^5 and n are as defined herein and wherein X is halogen or triflate.

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

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided a compound as defined herein for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.

In another aspect, there is provided use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.

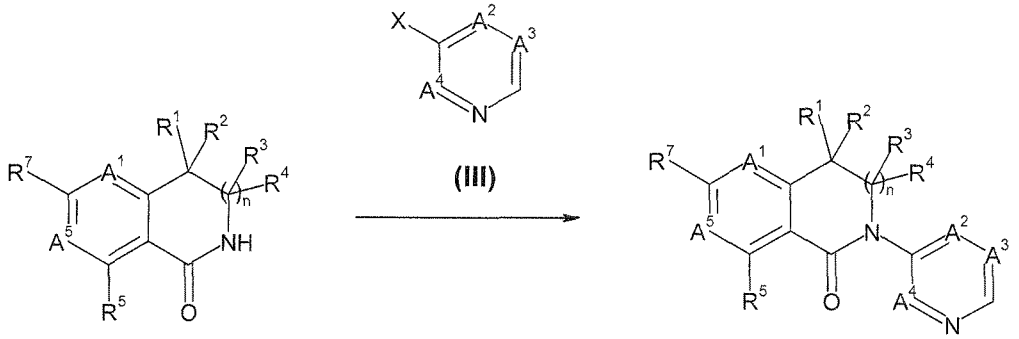
In another aspect, there is provided a compound as defined herein, when manufactured according to a process as defined herein.

The term "alkoxy" denotes a group of the formula -O-R', wherein R' is an alkyl group. Examples of alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. Particular alkoxy group include methoxy.

2-(1'-Acetyl-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-5-yl)-5-chloro-3,3-dimethyl-2,3-dihydro-isoindol-1-one;

and pharmaceutically acceptable salts thereof.

27. A process to prepare a compound according to any one of claims 1 to 26 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III);



(II) (III) (I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, A^1, A^2, A^3, A^4, A^5 and n are as defined in claim 1 and wherein X is halogen or triflate.

28. A compound according to any one of claims 1 to 26 for use as therapeutically active substance.

29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 26 and a therapeutically inert carrier.

~~30. The use of a compound according to any one of claims 1 to 26 for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.~~

~~31~~30. A compound according to any one of claims 1 to 26 for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.

~~32~~31. The use of a compound according to any one of claims 1 to 26 for the preparation of a medicament for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.

~~33. A method for the treatment or prophylaxis chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom, which method comprises administering an effective amount of a compound according to any one of claims 1 to 26.~~

~~34~~32. A compound according to any one of claims 1 to 26, when manufactured according to a process of claim 27.