

There is ample preclinical evidence that MR-antagonists (spironolactone and eplerenone) improve blood pressure, cardiac and renal function in various pre-clinical models.

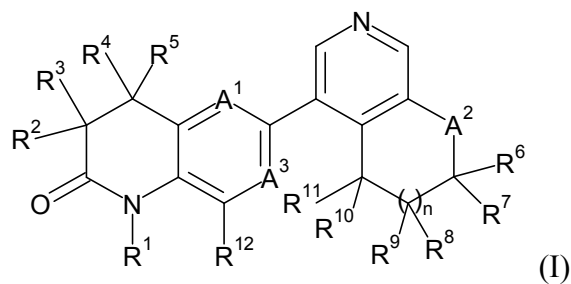
More recently preclinical studies highlight the important contribution of CYP11B2 to cardiovascular and renal morbidity and mortality. The CYP11B2 inhibitor FAD286 and the MR antagonist spironolactone were evaluated in a rat model of chronic kidney disease (high angiotensin II exposure; high salt and uni-nephrectomy). Angiotensin II and high salt treatment caused albuminuria, azotemia, renovascular hypertrophy, glomerular injury, 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 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 syndrome 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 syndrome.

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



wherein

R^1 is, C_1 - C_7 -alkyl;

10 R^2 is H;

R^3 is H;

R^4 is H;

R^5 is H;

R^6 is H, halogen or C_1 - C_7 -alkyl;

15 R^7 is H;

R^8 is H;

R^9 is H;

R^{10} is H;

R^{11} is H;

20 R^{12} is H or halogen;

A^1 is CR^{13} ;

A^2 is NR^{14} or $CR^{15}R^{16}$;

A^3 is CR^{17} ;

R^{13} is H or halogen;

5 R^{14} is $(CR^{20}R^{21})_q-(CR^{22}R^{23})_r-(CR^{24}R^{25})_p-NR^{26}R^{27}$, wherein the sum of q, r and p is at least 2;

R^{15} is $-(CR^{20}R^{21})_q-(CR^{22}R^{23})_r-(CR^{24}R^{25})_p-NR^{26}R^{27}$;

R^{16} is H;

10 or R^6 and R^{16} together with the carbon atoms to which they are attached form a double bond;

R^{17} is H;

R^{20} is H;

R^{21} is H;

R^{22} is H;

15 R^{23} is H;

R^{24} is H;

R^{25} is H;

R^{26} is H;

20 R^{27} is H, $-S(O)_2R^{31}$, $-C(O)R^{31}$ or $-C(O)OR^{31}$, wherein in case R^{26} is H and R^{27} is H, then the sum of q, r and p is at least 1;

R^{31} is C_1 - C_7 -alkyl, chloropyridinyl, hydroxyl- C_1 - C_7 -alkyl, C_3 - C_8 -cycloalkyl;

n is zero or 1;

p is zero or 1;

q is zero or 1;

r is zero or 1;

or pharmaceutically acceptable salts or esters.

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

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

10 In a fourth 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 syndrome.

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, ethoxy and
15 tert-butoxy.

The term “alkoxyalkoxy” denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by another alkoxy group. Examples of alkoxyalkoxy group include methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy. Particular alkoxyalkoxy groups
20 include methoxymethoxy and methoxyethoxy.

The term “alkoxyalkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxyalkoxy group. Examples of alkoxyalkoxyalkyl group include methoxymethoxymethyl, ethoxymethoxymethyl, methoxyethoxymethyl, ethoxyethoxymethyl, methoxypropoxymethyl,
25 ethoxypropoxymethyl, methoxymethoxyethyl, ethoxymethoxyethyl, methoxyethoxyethyl, ethoxyethoxyethyl, methoxypropoxyethyl and ethoxypropoxyethyl.

The term “alkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxy group. Exemplary alkoxyalkyl groups include methoxymethyl, ethoxymethyl, methoxyethyl, methoxypropyl and ethoxypropyl. Particular alkoxyalkyl group include methoxymethyl and methoxyethyl. More particular alkoxyalkyl group is methoxymethyl.

The term “alkoxycarbonyl” denotes a group of the formula $-C(O)-R'$, wherein R' is an alkoxy group. Examples of alkoxycarbonyl groups include groups of the formula $-C(O)-R'$, wherein R' is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. Particular alkoxycarbonyl group is a group of the formula $-C(O)-R'$, wherein R' is methoxy or tert-butoxy.