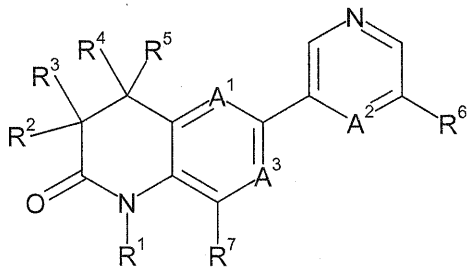
Administration of an orally active CYP11B2 inhibitor, LCI699, to patients with primary aldosteronism, lead to the conclusion that it effectively inhibits CYP11B2 in patients with primary aldosteronism resulting in significantly lower circulating aldosterone levels and that it corrected the hypokalemia 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.

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



(I)

wherein

R^1 is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^2 is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^3 is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^4 is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

or R^3 and R^4 together with the carbon atoms to which they are attached form a double bond;

R^5 is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^6 is H or R^8, wherein in case R^6 is H then at least one of A^1 and A^3 is N;

R^7 is H, halogen, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

or R^1 and R^7 together with the nitrogen and carbon atoms to which they are attached form a heterocycloalkyl substituted with one to three substitutents independently selected from H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^8 is $-O_m-(CR^9R^{10})_n-(CR^{11}R^{12})_p-(CR^{13}R^{14})_q-NR^{15}R^{16}$, $-N_mR^{17}-(CR^9R^{10})_n-(CR^{11}R^{12})_p-(CR^{13}R^{14})_q-NR^{15}R^{16}$ or $-S_m(O)_r-(CR^9R^{10})_n-(CR^{11}R^{12})_p-(CR^{13}R^{14})_q-NR^{15}R^{16}$;

R^9 is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^{10} is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^{11} is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

or R^{10} and R^{11} together with the carbon atoms to which they are attached form a double bond;

R^{12} is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

or R^{11} and R^{12} together with the carbon atom to which they are attached form a cycloalkyl or a heterocycloalkyl;

R^{13} is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^{14} is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

or R^{10} and R^{14} together form $-(CH_2)_t-$;

R^{15} is H, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, haloalkoxyalkyl or hydroxyalkyl;

R^{16} is H, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, phenylalkyl, substituted phenylalkyl, aryl, substituted aryl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl,

$-S(O)_2R^{18}$, $-S(O)R^{18}$, $-S(O)_2OR^{18}$, $-S(O)_2NR^{18}R^{19}$, $-C(O)R^{18}$, $-C(O)OR^{18}$ or $-C(O)NR^{18}R^{19}$, wherein substituted phenylalkyl, substituted aryl, substituted heterocycloalkyl and substituted heteroaryl are substituted with one to three substituents independently selected from alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, alkylcycloalkyl, halocycloalkyl, alkylcycloalkylalkyl, halocycloalkylalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxycarbonyl, halogen, hydroxy, oxo, cyano, triazolylalkyl, tetrazolylalkyl, amino, substituted amino, aminoalkyl, substituted aminoalkyl, aminocarbonyl, substituted aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl and cycloalkylcarbonylaminoalkyl, wherein substituted amino, substituted aminoalkyl and substituted aminocarbonyl are substituted on the nitrogen atom with one to two substituents independently selected from alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkylcycloalkylalkyl, hydroxyalkyl and alkoxyalkyl, wherein in case R^{15} is H or alkyl and R^{16} is H or alkyl, then the sum of n, p and q is at least 1;

or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a substituted heterocycloalkyl or a substituted heteroaryl, wherein substituted heterocycloalkyl and substituted heteroaryl are substituted with R^{23}, R^{24} and R^{25};

or R^{13} and R^{15} together with the nitrogen and carbon atoms to which they are attached form a substituted heterocycloalkyl, wherein substituted heterocycloalkyl is substituted with R^{23}, R^{24} and R^{25};

or R^{11} and R^{15} together with the nitrogen and carbon atoms to which they are attached form a substituted heterocycloalkyl, wherein substituted heterocycloalkyl is substituted with R^{23}, R^{24} and R^{25};

or R^{9} and R^{15} together with the nitrogen and carbon atoms to which they are attached form a substituted heterocycloalkyl, wherein substituted heterocycloalkyl is substituted with R^{23}, R^{24} and R^{25};

R^{17} is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^{18} is alkyl, cycloalkyl, haloalkyl, halocycloalkyl, hydroxyalkyl, halohydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, alkylcarbonyloxyalkyl, aryl, substituted aryl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl,

wherein substituted aryl, substituted heterocycloalkyl and substituted heteroaryl are substituted with one to three substituents independently selected from alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, alkylcycloalkyl, halocycloalkyl, alkylcycloalkylalkyl, halocycloalkylalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxycarbonyl, halogen, hydroxy, oxo, cyano, triazolylalkyl, tetrazolylalkyl, amino, substituted amino, aminoalkyl, substituted aminoalkyl, aminocarbonyl, substituted aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl and cycloalkylcarbonylaminoalkyl, wherein substituted amino, substituted aminoalkyl and substituted aminocarbonyl are substituted on the nitrogen atom with one to two substituents independently selected from alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkylcycloalkylalkyl, hydroxyalkyl and alkoxyalkyl;

R^{19} is H, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

A^1 is CR^{20} or N;

A^2 is CR^{21} or N;

A^3 is CR^{22} or N;

R^{20} is H, halogen, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^{21} is H, halogen, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^{22} is H, halogen, alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^{23}, R^{24} and R^{25} are each independently selected from H, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, alkylcycloalkyl, halocycloalkyl, alkylcycloalkylalkyl, halocycloalkylalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxycarbonyl, $-S(O)_2R^{18}$, $-C(O)R^{18}$, halogen, hydroxy, oxo, cyano, triazolylalkyl, tetrazolylalkyl, amino, substituted amino, aminoalkyl, substituted aminoalkyl, aminocarbonyl, substituted aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, alkylcarbonylaminoalkyl and cycloalkylcarbonylaminoalkyl, wherein substituted amino, substituted aminoalkyl and substituted aminocarbonyl are substituted on the nitrogen atom with one to two substituents independently

selected from alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkylcycloalkylalkyl, hydroxyalkyl and alkoxyalkyl;
wherein in case m is zero and R^9 and R^{15}, or R^{11} and R^{15} or R^{13} and R^{15} or R^{15} and R^{16} together with the nitrogen and carbon atoms to which they are attached form a substituted heterocycloalkyl or a substituted heteroaryl, then at least one of R^{23}, R^{24}, R^{25} and R^{16} is different from H, alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, hydroxy, cyano, amino, substituted amino, aminocarbonyl, substituted aminocarbonyl, wherein substituted amino and substituted aminocarbonyl are substituted on the nitrogen atom with one to two alkyl, and $-C(O)R^{18}$, $-S(O)_2R^{18}$, wherein R^{18} is alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, alkoxyalkyl or haloalkoxyalkyl;

m is zero or 1, wherein in case m is 1, then the sum of n and p is 2, 3 or 4;

n is zero, 1 or 2;

p is zero, 1 or 2;

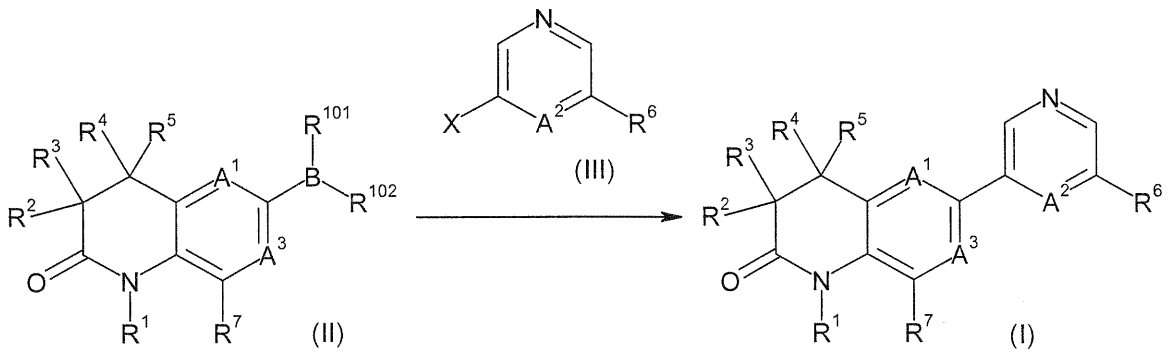
q is zero, 1 or 2;

r is zero, 1 or 2, wherein in case m is zero then r is zero;

t is zero, 1 or 2;

or pharmaceutically acceptable salts or esters.

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



wherein A^1, A^2, A^3, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above and wherein X is halogen or triflate, R^{101} and R^{102} are alkyl, cycloalkyl or together with the boron atom they are attached to form together a borolanyl.

According to a third aspect, there is provided a compound as defined above for use as therapeutically active substance.

According to a fourth aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a therapeutically inert carrier.

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

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

According to a seventh aspect, there is provided a compound as defined above, when manufactured as defined above.

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 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 include methoxymethoxy and methoxyethoxy.

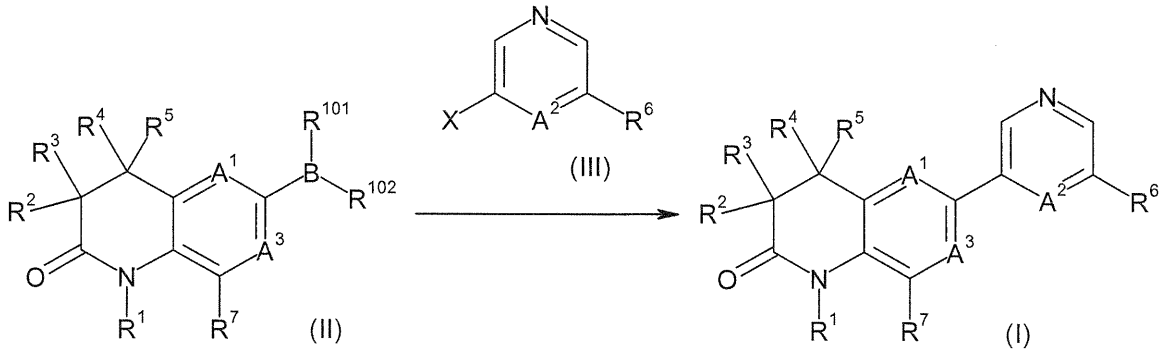
The term "alkoxyalkoxyalkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxyalkoxy group. Examples of alkoxyalkoxyalkyl group include methoxymethoxymethyl, ethoxymethoxymethyl, methoxyethoxymethyl, ethoxyethoxymethyl, methoxypropoxymethyl,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

3,5-Dimethyl-isoxazole-4-carboxylic acid {2-[5-(7-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-pyridin-3-yloxy]-ethyl}-amide;

1-Methyl-6-{5-[(S)-1-(1-methyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-pyridin-3-yl}-3,4-dihydro-1H-quinolin-2-one;

and pharmaceutically acceptable salts thereof.

99. A process to prepare a compound according to any one of claims 1 to 98 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III);



wherein A^1, A^2, A^3, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim1 and wherein X is halogen or triflate, R^{101} and R^{102} are alkyl, cycloalkyl or together with the boron atom they are attached to form together a borolanyl.

100. A compound according to any one of claims 1 to 98 for use as therapeutically active substance.

101. A pharmaceutical composition comprising a compound according to any one of claims 1 to 98 and a therapeutically inert carrier.

~~102. The use of a compound according to any one of claims 1 to 98 for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.~~

~~103~~102. A compound according to any one of claims 1 to 98 for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.

~~104~~103.The use of a compound according to any one of claims 1 to 98 for the preparation of a medicament for the treatment or prophylaxis of chronic kidney disease, congestive heart failure, hypertension, primary aldosteronism and Cushing syndrom.

~~105. 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 98.~~

~~106~~104. A compound according to any one of claims 1 to 98, when manufactured according to a process of claim 99.