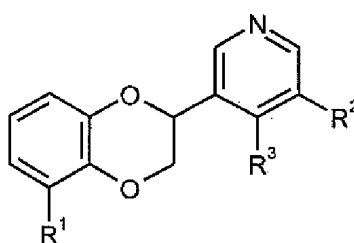


evidence that inhibitors of aldosterone synthesis will be useful for the treatment of diabetic kidney disease including diabetic nephropathy; non-diabetic kidney disease including glomerulosclerosis, glomerulonephritis, IGA nephropathy, nephritic syndrome and focal segmental glomerulosclerosis (FSGS); cardiovascular diseases including hypertension, pulmonary arterial hypertension, Conn's syndrome, systolic heart failure, diastolic heart failure, left ventricular dysfunction, left ventricular stiffness and fibrosis, left ventricular filing abnormalities, arterial stiffness, atherosclerosis and cardiovascular morbidity associated with primary or secondary hyperaldosteronism; adrenal hyperplasia and primary and secondary hyperaldosteronism.

BRIEF SUMMARY

The present disclosure provides novel compounds that inhibit aldosterone synthase and thus useful for treating a variety of diseases and disorders that can be alleviated by lowering levels of aldosterone including renal disease, diabetic nephropathy, cardiovascular diseases and fibrotic disorders. This disclosure also relates to pharmaceutical compositions comprising these compounds, methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

In one aspect, there is provided a compound of the formula I



I

wherein:

R¹ is selected from -C(O)NH₂, -C(O)NH(CH₃) and -CN;

R^2 is $-(X)-R^4$, wherein

$-(X)-$ is a bond, $-\text{CH}_2-$, or $-\text{O}-$; and

R^4 is selected from

$-\text{H}$;

$\text{C}_{1-3}\text{alkyl}$, optionally substituted with one to four groups selected from $-\text{F}$, $-\text{OH}$, and $-\text{SO}_2\text{C}_{1-3}\text{alkyl}$;

halogen;

$-\text{CN}$;

$-\text{SO}_2\text{C}_{1-3}\text{alkyl}$;

$-\text{C}(\text{O})\text{N}(\text{C}_{1-3}\text{alkyl})_2$, provided $-(X)-$ is not $-\text{O}-$;

$-\text{NHC}(\text{O})\text{R}^5$ or $-\text{N}(\text{CH}_3)\text{C}(\text{O})\text{R}^5$, provided that $-(X)-$ is $-\text{CH}_2-$ and wherein R^5 is selected from $\text{C}_{3-6}\text{cycloalkyl}$ and $\text{C}_{1-3}\text{alkyl}$ optionally substituted with one to three $-\text{F}$ groups ;

$-\text{NHSO}_2\text{C}_{1-3}\text{alkyl}$;

$-\text{CH}(\text{cyclopropyl})\text{NHSO}_2\text{C}_{1-3}\text{alkyl}$;

$-\text{OCH}_2\text{C}(\text{O})\text{N}(\text{C}_{1-3}\text{alkyl})_2$, provided that $-(X)-$ is $-\text{CH}_2-$;

$-\text{S}(=\text{O})(=\text{NH})\text{CH}_3$, provided that $-(X)-$ is $-\text{CH}_2-$;

heterocyclyl selected from tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, 1,1-dioxo[1,2]-thiazine, morpholinyl, oxazolidinyl, piperidinyl, azetidiny, wherein said heterocyclyl is optionally substituted with one to three groups selected from $-\text{C}(\text{O})\text{C}_{1-3}\text{alkyl}$, halogen, $-\text{OH}$, oxo and $\text{C}_{1-3}\text{alkyl}$;

$-\text{C}(\text{O})$ -heterocyclyl, provided that $-(X)-$ is $-\text{CH}_2-$, wherein said heterocyclyl is selected from morpholin-4-yl, pyrrolidin-1-yl and piperidin-1-yl, optionally substituted with one or two groups selected from $-\text{F}$ and $-\text{OH}$;

C₃₋₆cycloalkyl optionally substituted with –CN or –OH; and

phenyl, optionally substituted with –SO₂NH₂; and

R³ is H, or C₁₋₃alkyl optionally substituted with -OH; or

R₂ and R³ together form an annelated five-membered cycloalkyl ring optionally substituted with –OH;

or a salt or a stereoisomer thereof.

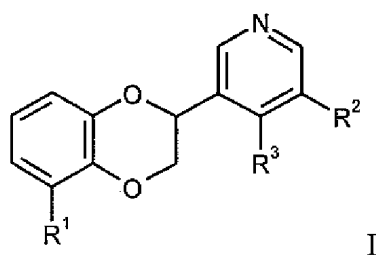
In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable excipient or carrier.

In another aspect, there is provided a compound as defined herein for use as a medicament.

In another aspect, there is provided use of a compound as defined herein in the manufacture of a medicament for the treatment of a disease or disorder that can be alleviated by inhibition of aldosterone synthase selected from diabetic nephropathy, glomerulosclerosis, glomerulonephritis, IGA nephropathy, nephritic syndrome focal segmental glomerulosclerosis (FSGS), hypertension, pulmonary arterial hypertension, Conn's syndrome, systolic heart failure, diastolic heart failure, left ventricular dysfunction, left ventricular stiffness and fibrosis, left ventricular filing abnormalities, arterial stiffness, atherosclerosis and cardiovascular morbidity associated with primary or secondary hyperaldosteronism, adrenal hyperplasia and primary and secondary hyperaldosteronism.

DETAILED DESCRIPTION OF THE INVENTION

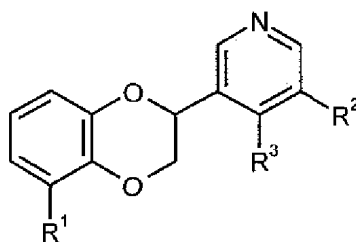
In an embodiment of the invention, there are provided compounds of the formula I



wherein:

What is claimed is:

1. A compound of the formula I



I

wherein:

R¹ is selected from -C(O)NH₂, -C(O)NH(CH₃) and -CN;

R² is -(X)-R⁴, wherein

-(X)- is a bond, -CH₂-, or -O-; and

R⁴ is selected from

-H;

C₁₋₃alkyl, optionally substituted with one to four groups selected from -F, -OH, and -SO₂C₁₋₃alkyl;

halogen;

-CN;

-SO₂C₁₋₃alkyl;

-C(O)N(C₁₋₃alkyl)₂, provided -(X)- is not -O-;

-NHC(O)R⁵ or -N(CH₃)C(O)R⁵, provided that -(X)- is -CH₂- and wherein R⁵ is selected from C₃₋₆cycloalkyl and C₁₋₃alkyl optionally substituted with one to three -F groups ;

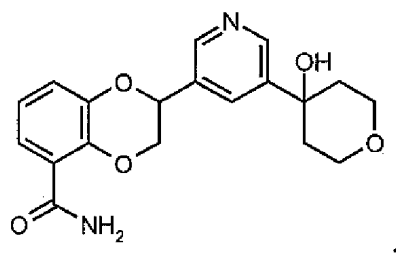
-NHSO₂C₁₋₃alkyl;

-CH(cyclopropyl)NHSO₂C₁₋₃alkyl;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

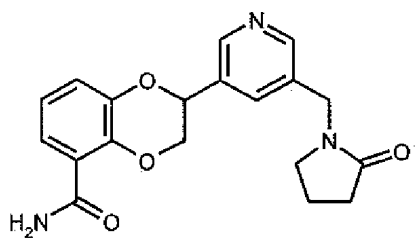
9. The compound according to claim 8 selected from the group consisting of compound numbers 1, 5, 12, 29, 37, 43, 56, 61, and 62 or a pharmaceutically acceptable salt or a stereoisomer thereof.

10. The compound according to claim 1, wherein the compound is



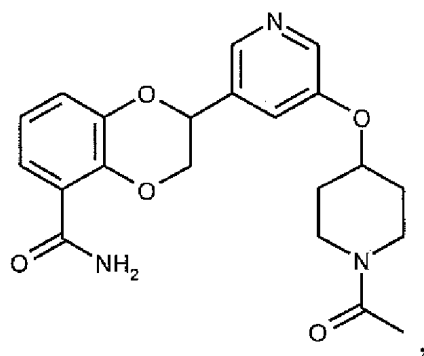
or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1, wherein the compound is



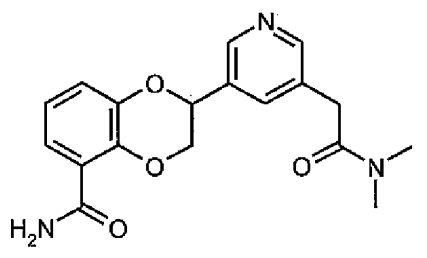
or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 1, wherein the compound is



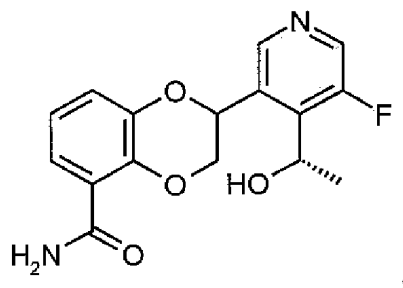
or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1, wherein the compound is



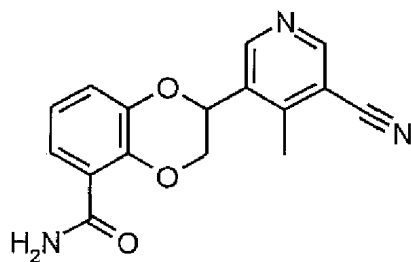
or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound according to any of claims 1 to 15 and a pharmaceutically acceptable excipient or carrier.

17. A compound according to any one of claims 1-15 for use as a medicament.

18. Use of a compound according to any of claims 1 to 15 in the manufacture of a medicament for the treatment of a disease or disorder that can be alleviated by inhibition of aldosterone synthase selected from diabetic nephropathy, glomerulosclerosis, glomerulonephritis, IGA nephropathy, nephritic syndrome focal segmental glomerulosclerosis (FSGS), hypertension, pulmonary arterial hypertension, Conn's syndrome, systolic heart failure, diastolic heart failure, left ventricular dysfunction, left ventricular stiffness and fibrosis, left ventricular filling abnormalities, arterial stiffness, atherosclerosis and cardiovascular morbidity associated with primary or secondary hyperaldosteronism, adrenal hyperplasia and primary and secondary hyperaldosteronism.

19. The use according to claim 18, wherein the disease or disorder is selected from diabetic nephropathy, glomerulosclerosis, glomerulonephritis, IGA nephropathy, nephritic syndrome and focal segmental glomerulosclerosis (FSGS).

20. The use according to claim 18 wherein the disease is diabetic nephropathy.