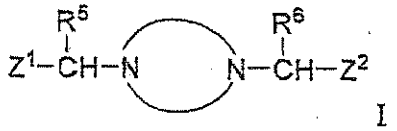
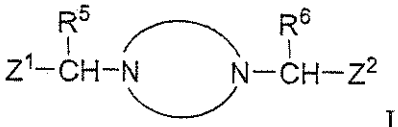
SUMMARY ~~OF THE INVENTION~~

~~One object of t~~The present disclosure relates to~~invention is to provide~~ compounds of Formula I



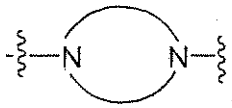
I

and the pharmaceutically acceptable salts thereof. In one aspect, there is provided a compound having structural Formula I:

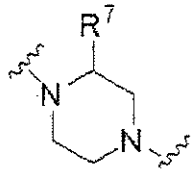


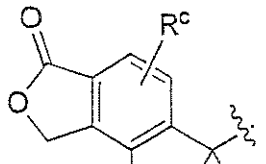
I

and the pharmaceutically acceptable salts thereof wherein:



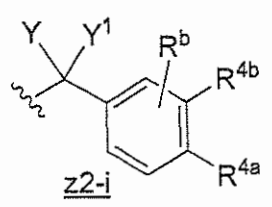
represents;

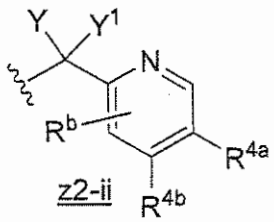


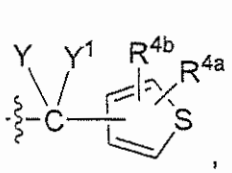
Z1 is 

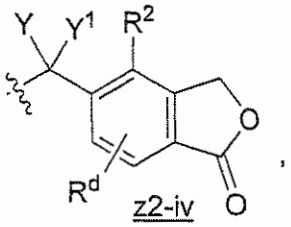
z1-iv ; R^1 X^1 X

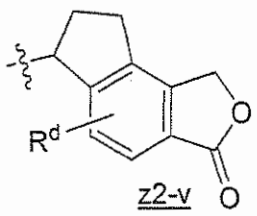
Z^2 is selected from the group consisting of:

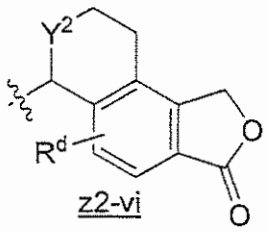

z2-i ,

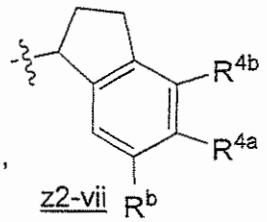

z2-ii ,

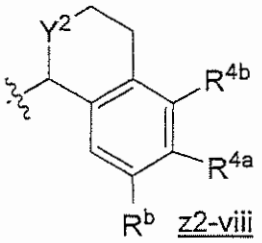

z2-iii ,

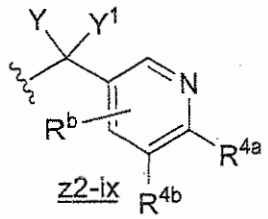

z2-iv ,

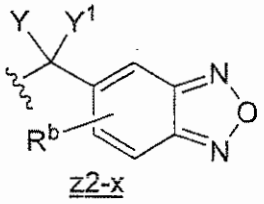

z2-v ,


z2-vi ,


z2-vii ,


z2-viii ,


z2-ix and


z2-x ;

X is selected from the group consisting of -H, -OH, -OC_{1-3}alkyl, -F, oxo, NH_2, and -CH_3;

Y is selected from the group consisting of -H, -OH, -OC_{1-3}alkyl, -F, oxo, NH_2, and -CH_3;

$\mathbf{X^1}$ and $\mathbf{Y^1}$ are each independently selected from the group consisting of -H and -CH_3;

$\mathbf{Y^2}$ is –O- ;

provided that when X is oxo then X^1 is absent and when Y is oxo then Y^1 is absent;

and further provided that when Z^2 is z2-i, z2-ii, z2-iii, z2-iv, z2-ix or z2-x, then at least one of X and Y is selected from the group consisting of -OH, -OC_{1-3}alkyl, -F and oxo, and when Z^2 is z2-v or z2-vii, then X is selected from the group consisting of -OH, -OC_{1-3}alkyl, -F and oxo, and when Z^2 is z2-v or z2-vii, then X is selected from the group consisting of -OH, -OC_{1-3}alkyl,-F and oxo;

$\mathbf{R^1}$ and $\mathbf{R^2}$ are each independently selected from the group consisting of -H, -halo, -C_3-C_6cycloalkyl, -OR^8, -SR^8, -SOR^8, -SO_2R^8, -$(CH_2)_nOR^8$ and C_1-C_6alkyl optionally substituted with 1-3 of -F;

one of $\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ is selected from the group consisting of -CN and -NO_2 and the other is R^f;

$\mathbf{R^5}$ and $\mathbf{R^6}$ are each independently selected from the group consisting of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -CF_3, -CHF_2, -CH_2F and -CH_2OH;

$\mathbf{R^7}$ is selected from the group consisting of –H, -CH_3, -CF_3, -CHF_2, -CH_2F and -CH_2OH;

$\mathbf{R^b}$ is selected from the group consisting of (a) -H, (b) halo, (c) -C_{1-6} alkyl optionally substituted with 1-3 of -F, (d) -C_{3-6} cycloalkyl, (e) -OC_{1-3}alkyl optionally substituted with 1-3 of -F, (f) –OR^8, (g) -CO_2C_{1-6}alkyl optionally substituted with 1-3 of -F, (h) -$(CH_2)_nOR^8$, (i) -SR^8, (j) -SOR^8, (k) -SO_2R^8, (l) –$NHCOR^8$ and (m) -$NHSO_2R^8$;

R^c and R^d are each independently selected from the group consisting of (a) -H, (b) halo, (c) -C_{1-6} alkyl optionally substituted with 1-3 of -F, (d) -C_{3-6} cycloalkyl, (e) -OC_{1-3}alkyl optionally substituted with 1-3 of -F, (f) $-OR^8$, (g) -CO_2C_{1-6}alkyl optionally substituted with 1-3 of -F, (h) -$(CH_2)_nOR^8$, (i) $-SR^8$, (j) -SOR^8, (k) -SO_2R^8, (l) $-NHCOR^8$ and (m) -$NHSO_2R^8$;

R^f is selected from the group consisting of (a) -H, (b) halo, (c) -C_{1-6} alkyl optionally substituted with 1-3 of -F, (d) -C_{3-6} cycloalkyl, (e) -OC_{1-3}alkyl optionally substituted with 1-3 of -F, (f) $-OR^8$, (g) -CO_2C_{1-6}alkyl optionally substituted with 1-3 of -F, (h) -$(CH_2)_nOR^8$, (i) $-SR^8$, (j) -SOR^8, (k) -SO_2R^8, (l) $-NHCOR^8$ and (m) -$NHSO_2R^8$;

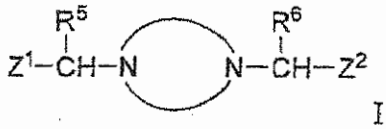
n is an integer selected from 1, 2 and 3; and

R^8 is independently selected at each occurrence from the group consisting of -H, -C_{3-6}cycloalkyl and -C_{1-6}alkyl optionally substituted with 1-3 of -F.

The compounds of Formula I are inhibitors of the ROMK (Kir1.1) channel and can act as diuretics and natriuretics and are valuable pharmaceutically active compounds for the therapy and prophylaxis of diseases, including, but not limited to, cardiovascular diseases such as hypertension and conditions resulting from excessive salt and water retention. The present disclosure may relate to~~Therefore, an object of the invention is to provide~~ methods of treatment comprising administering a therapeutically or prophylactically effective amount of a compound of Formula I to a patient in need of a diuretic and/or natriuretic agent. The present disclosure may also relate to~~A further object is to provide~~ the use of compounds of Formula I in combination with other therapeutically effective agents, including other drugs useful for the treatment of hypertension and conditions resulting from excessive salt and water retention. In another aspect, there is provided the use of a therapeutically effective amount of a compound as defined above or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for causing diuresis, natriuresis or both, in a patient. In another aspect, there is provided the use of a compound as defined above or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hypertension. In another aspect, there is provided the use of a compound as defined above or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of heart failure. In another aspect, there is provided the use of a compound as defined above or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of one or more disorders selected from the group consisting of hepatic cirrhosis, acute and chronic kidney insufficiency and nephrotic syndrome. The disclosure~~invention~~ furthermore relates to processes for preparing compounds of Formula I, and pharmaceutical compositions which comprise compounds of Formula I. In another aspect, there is provided a pharmaceutical composition comprised of a compound as defined above or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. These and other objects of the embodiments disclosed herein will be evident from the description contained herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds having structural Formula I:

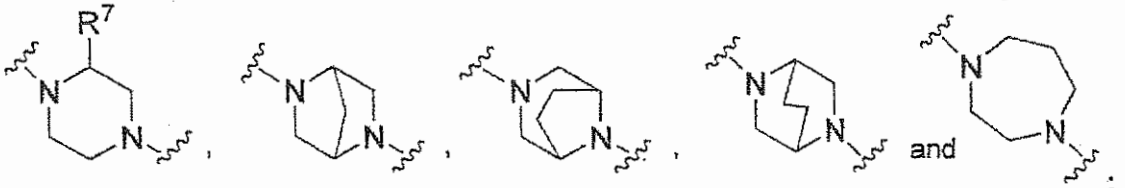


I

and the pharmaceutically acceptable salts thereof wherein:



represents a heterocyclic ring selected from the group consisting of:



and

;

Z^1 is selected from the group consisting of: