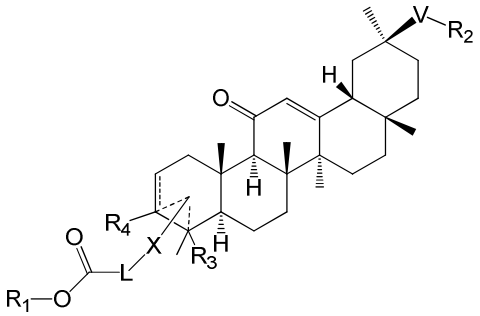
SUMMARY

In one aspect, the present disclosure refers to a compound of formula I or a salt thereof:



I

wherein,

X is a bond, -O-, -C(O)-, -N(R_x)-, -C(O)N(R_x)-, -N(R_x)-C(O)-, -S(O)$_n$-N(R_x)- or -N(R_x)-S(O)$_n$-;

V is -C(O)O-, -C(O)N(R_5)-, -C(O)N(R_5)O-, -NH-C(O)-N(R_5)- or NH-S(O)$_n$-;

L is a bond, alkylene wherein one or more non-adjacent methylene groups of said alkylene are replaced with -O-; divalent aryl or divalent heteroaryl; or L is alkylene-Y-alkylene wherein Y is O, NR_x, S, SO, SO_2 or a divalent heterocycle; wherein said alkylene groups are optionally substituted with OH, -C(O)O-R_1, alkyl or alkyl substituted with OH or -C(O)O-R_1; and wherein a carbon of said alkylene groups and R_x optionally together form a heterocycle; provided that when X is other than a bond, then L is other than a bond;

R_1 is alkyl optionally substituted with halogen, OH, amino, oxo, carboxy, acyloxy, alkoxycarbonyl, alkoxyacyloxy, alkoxycarbonyloxy, aminocarbonyl, a carbocycle optionally substituted with alkyl, haloalkyl, oxo, amino and halogen and a heterocycle optionally substituted with alkyl, oxo, amino and halogen; and a carbocycle or heterocycle optionally substituted with alkyl, haloalkyl, oxo, amino and halogen; wherein one or more non-adjacent methylene groups in any of the foregoing alkyl groups is replaced with O;

R_2 is H or R_1;

R_3 is absent, Me; provided that when -X-L-C(O)O-R_1 depends from the carbon to which R_3 depends then R_3 is absent; or R_3 is -Z-L-C(O)O-R_1 wherein Z is a bond, -O-, -N(R_x)-, -C(O)N(R_x)-, -N(R_x)-C(O)-, -S(O)$_n$-N(R_x)- or -N(R_x)-S(O)$_n$-; and

R_4 is absent, H or OH; provided that when -X-L-C(O)O-R_1 depends from the carbon to which R_4 depends then R_4 is H or absent;

R_5 is H or alkyl;

R_x is H, -C(O)O-R_1, or alkyl optionally substituted with -C(O)O-R_1; and

n is 1 or 2.

In one example, there are provided compositions comprising compounds of Formula I and a carrier, diluent or excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient.

In another example, there is provided a method of inhibiting conversion of cortisol to cortisone by HSD2 comprising contacting HSD2 with a compound of Formula I. In one aspect, the present disclosure refers to a method of inhibiting conversion of cortisol to cortisone by HSD2 comprising contacting HSD2 with a compound as disclosed herein or a pharmaceutically acceptable salt thereof. In another aspect, the present disclosure refers to use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease or condition mediated by the conversion of cortisol to cortisone by HSD2 in a mammal. In yet another aspect, the present disclosure refers to use of compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition, disease or disorder mediated by HSD2.

In another example, there is provided a method for promoting activation MR in a mammal, comprising administering to said mammal an effective amount of a compound of Formula I.

In another example, there is provided a method of reducing potassium levels in plasma of a mammal, comprising administering to said mammal an effective amount of a compound of Formula I.

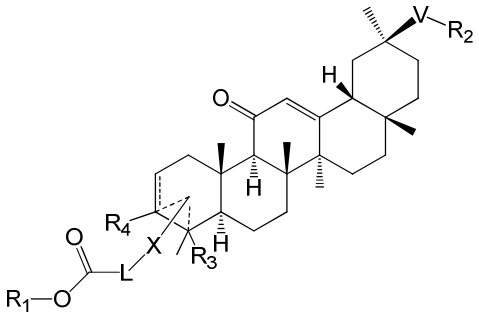
In another example, there is provided a method for promoting potassium ion secretion into the colonic lumen of a mammal, comprising administering to said mammal an effective amount of a compound of Formula I. In one aspect, the present disclosure refers to use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the promotion of potassium ion secretion into the colonic lumen of a mammal.

In another example, there is provided a method for treating hyperkalemia in a mammal, comprising administering to said mammal an effective amount of a compound of Formula I. In one aspect, the present disclosure refers to use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hyperkalemia.

In another example, there is provided a method for treating or preventing hyperkalemia in a mammal comprising coadministering a compound of Formula I with an inhibitor of the renin-angiotensin-aldosterone system (RAAS).

WHAT IS CLAIMED IS:

1. A compound of formula I or a salt thereof:



I

wherein,

X is a bond, -O-, -C(O)-, -N(R_x)-, -C(O)N(R_x)-, -N(R_x)-C(O)-, -S(O)$_n$-N(R_x)- or -N(R_x)-S(O)$_n$-;

V is -C(O)O-, -C(O)N(R_5)-, -C(O)N(R_5)O-, -NH-C(O)-N(R_5)- or NH-S(O)$_n$-;

L is a bond, alkylene wherein one or more non-adjacent methylene groups of said alkylene are replaced with -O-; divalent aryl or divalent heteroaryl; or L is alkylene-Y-alkylene wherein Y is O, NR_x, S, SO, SO_2 or a divalent heterocycle; wherein said alkylene groups are optionally substituted with OH, -C(O)O-R_1, alkyl or alkyl substituted with OH or -C(O)O-R_1; and wherein a carbon of said alkylene groups and R_x optionally together form a heterocycle; provided that when X is other than a bond, then L is other than a bond;

R_1 is alkyl optionally substituted with halogen, OH, amino, oxo, carboxy, acyloxy, alkoxycarbonyl, alkoxyacyloxy, alkoxycarbonyloxy, aminocarbonyl, a carbocycle optionally substituted with alkyl, haloalkyl, oxo, amino and halogen and a heterocycle optionally substituted with alkyl, oxo, amino and halogen; and a carbocycle or heterocycle optionally substituted with alkyl, haloalkyl, oxo, amino and halogen; wherein one or more non-adjacent methylene groups in any of the foregoing alkyl groups is replaced with O;

R_2 is H or R_1;

R_3 is absent, Me; provided that when -X-L-C(O)O-R_1 depends from the carbon to which R_3 depends then R_3 is absent; or R_3 is -Z-L-C(O)O-R_1 wherein Z is a bond, -O-, -N(R_x)-, -C(O)N(R_x)-, -N(R_x)-C(O)-, -S(O)$_n$-N(R_x)- or -N(R_x)-S(O)$_n$-; and

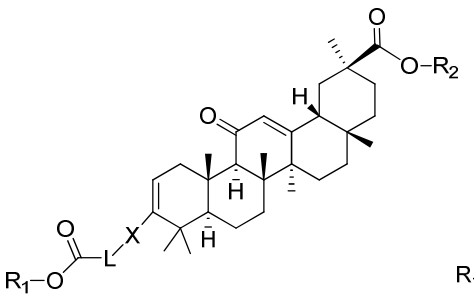
R_4 is absent, H or OH; provided that when -X-L-C(O)O-R_1 depends from the carbon to which R_4 depends then R_4 is H or absent;

R_5 is H or alkyl;

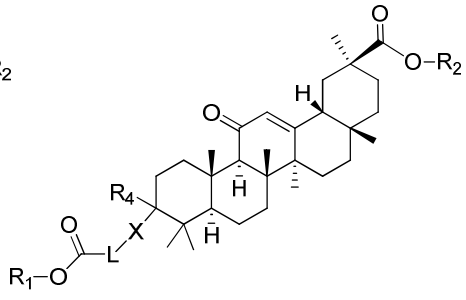
R_x is H, -C(O)O-R_1, or alkyl optionally substituted with -C(O)O-R_1; and

n is 1 or 2.

2. The compound or salt of claim 1, having the structure of any one of Formula Ia – Ir:



Ia



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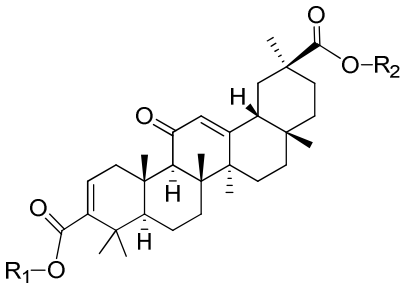

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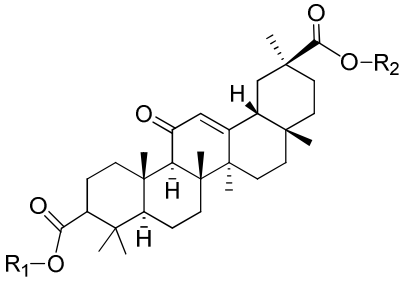

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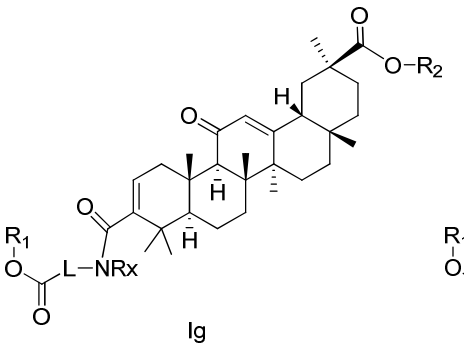

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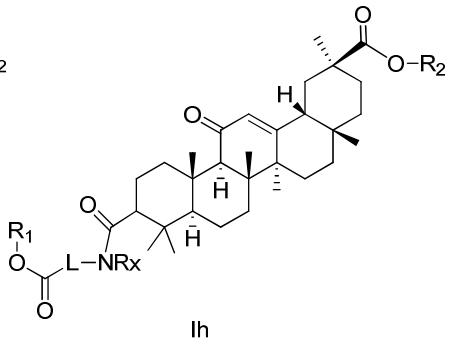

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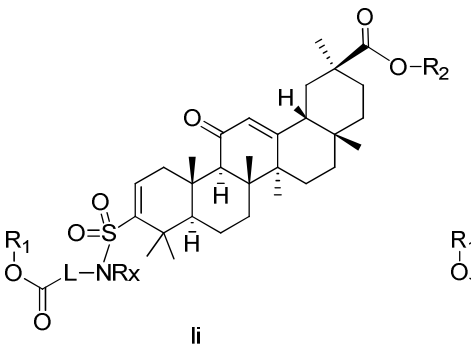

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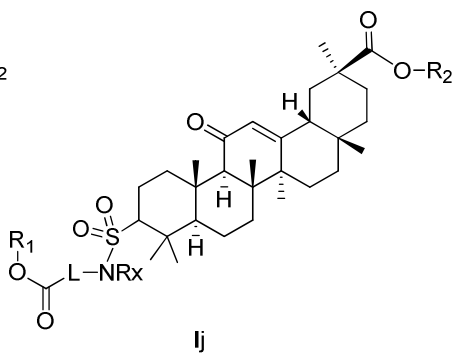

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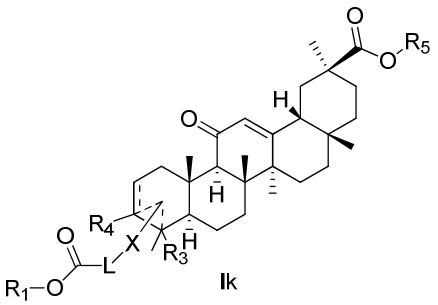

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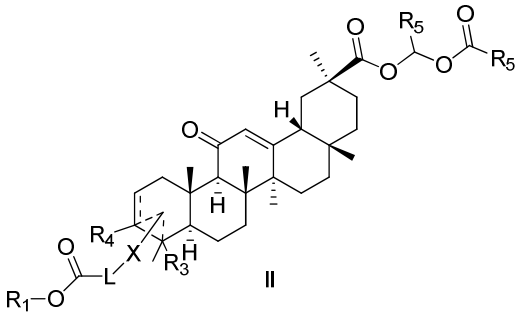

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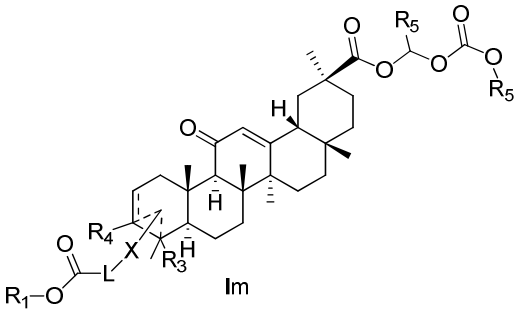

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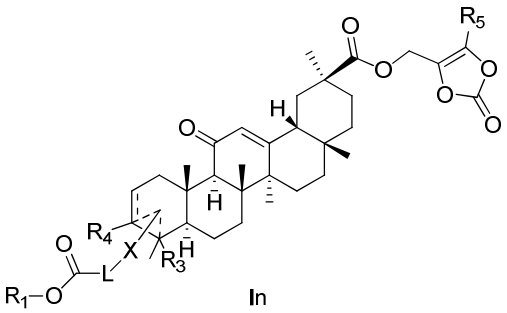

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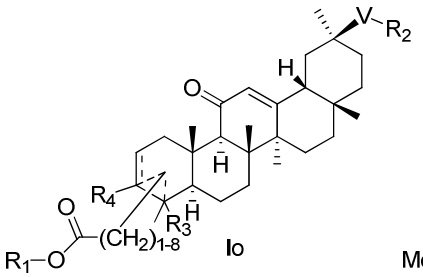

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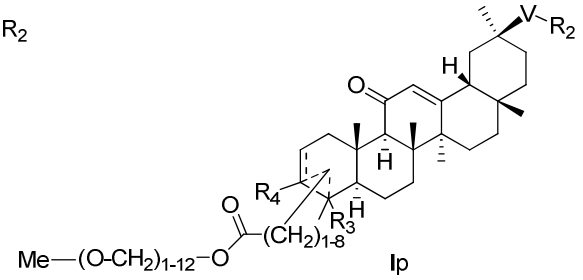

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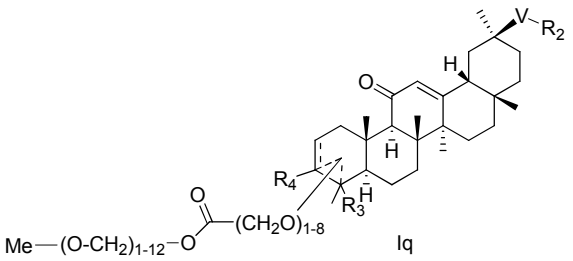

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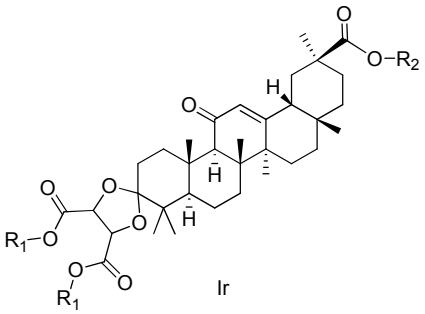

Ir

or a salt thereof.

3. The compound or salt of claim 1 or claim 2, wherein X is a bond.

4. The compound or salt of claim 1 or claim 2, wherein L is a bond.

5. The compound or salt of claim 1 or claim 2, wherein X and L are both bonds.

6. The compound or salt as claimed in any one of claims 1 to 5, wherein R_2 is H.

7. The compound or salt as claimed in any one of claims 1 to 6, wherein R_3 is H.

8. The compound or salt as claimed in any one of claims 1 to 7, wherein R_4 is H.

9. The compound salt as claimed in any one of claims 1 to 2 and 6 to 8, wherein X is absent and L is aryl or heteroaryl.

10. The compound or salt of claim 9, wherein L is phenyl, triazole or isoxazole.

11. The compound or salt of claim 10 wherein R_3 is hydrogen.

12. The compound or salt as claimed in claim 11 wherein R_2 and R_4 are each H.

13. The compound or salt as claimed in any one of claims 1 to 2 and 6 to 8, wherein X is O.

14. The compound or salt as claimed in any one of claims 1 to 2 and 6 to 8, wherein X is -C(O)-.

15. The compound or salt as claimed in any one of claims 1 to 14, wherein R_1 is alkyl optionally substituted with halogen, OH, amino, oxo, carboxy, acyloxy, alkoxycarbonyl, alkoxyacyloxy, alkoxycarbonyloxy, aminocarbonyl, a carbocycle optionally substituted with alkyl, haloalkyl, oxo, amino and halogen and a heterocycle optionally substituted with alkyl, oxo, amino and halogen; and heterocycle optionally substituted with alkyl, haloalkyl, oxo, amino and halogen; wherein one or more non-adjacent methylene groups in said alkyl is replaced with O.

16. The compound or salt of claim 15, wherein R_1 is methyl, propyl, hydroxyethyl, 2,2,2-trifluoroethyl, 1,1-trifluoromethylethyl, 2-morpholinoethyl, 2-(1H-imidazol-1-yl)ethyl, 2-(pyridin-2-yl)ethyl,-CH_2-C(O)OH, -CH_2-C(O)O-Me, -CH_2-C(O)NH_2, -CH_2-C(O)NMe_2, -CH_2-C(O)O-t-butyl, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, (pivaloyloxy)methyl, ((isopropoxycarbonyl)oxy)methyl, (S)-1-

((isopropoxycarbonyl)oxy)ethyl, (R)-1-((isopropoxycarbonyl)oxy)ethyl, 2-morpholino-2-oxoethyl, 2-(4-methylpiperazin-1-yl)-2-oxoethyl or (R)-quinuclidin-3-yl.

17. The compound or salt of claim 15, wherein R_1 is methyl.

18. A method of inhibiting conversion of cortisol to cortisone by HSD2 comprising contacting HSD2 with a compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof.

19. Use of a compound as claimed in any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease or condition mediated by the conversion of cortisol to cortisone by HSD2 in a mammal.

20. Use of a compound as claimed in any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the promotion of potassium ion secretion into the colonic lumen of a mammal.

21. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient.

22. Use of a compound of Claims 1 to 17 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition, disease or disorder mediated by HSD2.

23. Use of a compound of Claims 1 to 17 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hyperkalemia.