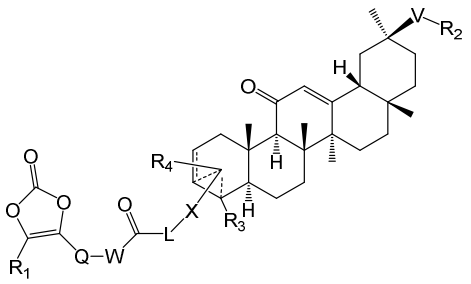
The mineralocorticoid receptor (or MR, MLR, MCR), also known as the aldosterone receptor or nuclear receptor subfamily 3, group C, member 2, (NR3C2) is a protein that in humans is encoded by the *NR3C2* gene that is located on chromosome 4q31.1-31.2. MR is a receptor with equal affinity for mineralocorticoids and glucocorticoids including cortisol. It belongs to the nuclear receptor family where the ligand diffuses into cells, interacts with the receptor and results in a signal transduction affecting specific gene expression in the nucleus. MR is expressed in many tissues, such as the kidney, colon, heart, central nervous system (hippocampus), brown adipose tissue and sweat glands. Activation of the mineralocorticoid receptor by ligands aldosterone and cortisol in epithelial tissues promotes excretion of potassium. In intact animals, the MR is "protected" from the greater concentration of cortisol (100-1000 fold) by co-localization of an enzyme, 11β-hydroxysteroid dehydrogenase 2; (also referred to herein as 11β-HSD2 and HSD2 herein), that oxidizes cortisol to the inactive metabolite cortisone. HSD2, thus prevents MR activation and therefore inhibits excretion of potassium.

Accordingly, inhibition of HSD2 to prevent inactivation of cortisol activation of the MR is a promising mechanism for promoting potassium excretion, for example, in the treatment of hyperkalemia.

SUMMARY

In one example of the present disclosure there is provided 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)$_n$-;

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;

W is O or S;

Q is a bond or alkylene;

R_1 is H, alkyl, a carbocycle or a heterocycle wherein said alkyl, carbocycle and heterocycle are each 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;

V is -C(O)O-, -C(O)O-(CHR_5)-O-C(O)-, -C(O)O-(CHR_5)-O-C(O)-O-, -C(O)N(R_5)-, -C(O)N(R_5)O-, -NH-C(O)-N(R_5)- or NH-S(O)$_n$-;

R_2 is H or R_5;

R_3 is absent or alkyl;

R_4 is absent, H, OH, =O, -R_6, -O-R_6, -C(O)O-R_6, -O-C(O)-R_6, -O-C(O)-O-R_6, -O-C(O)-NR_5R_6, -NR_5R_6, -NR_5-C(O)-R_6, -NR_5-C(O)-O-R_6, -NR_5-SO_2-R_6, =N-O-R_5;

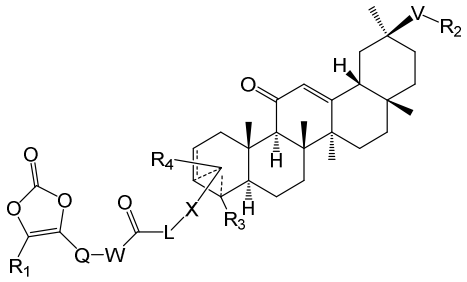
R_5 is H or alkyl optionally substituted with a carbocycle or heterocycle wherein said carbocycle and heterocycle are optionally substituted with halogen, OH, oxo and alkyl;

R_6 is H, alkyl, a carbocycle, a heterocycle wherein said alkyl, carbocycle and heterocycle are optionally substituted with halogen, OH, SH, alkylthio, -S(O)-alkyl, -SO_2-alkyl, amino, -NHC(O)-alkyl, oxo, alkyl, carboxyl, acyl, acyloxy, alkoxy, alkoxycarbonyl, a carbocycle optionally substituted with halogen, OH, amino or alkyl, or a heterocycle optionally substituted with halogen, OH, amino or alkyl; and wherein one or more non-adjacent methylene groups in each of said alkyl groups of R_6 are optionally replaced with -O- or -S-;

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 aspect, the present disclosure provides 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)$_n$-;

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;

W is O or S;

Q is a bond or alkylene;

R_1 is H, alkyl, a carbocycle or a heterocycle wherein said alkyl, carbocycle and heterocycle are each 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;

V is -C(O)O-, -C(O)O-(CHR_5)-O-C(O)-, -C(O)O-(CHR_5)-O-C(O)-O-, -C(O)O-(CH_2)$_n$-Y-, -C(O)N(R_5)-, -C(O)N(R_5)-O-, -NH-C(O)-N(R_5)- or NH-S(O)$_n$-; wherein Y is a divalent heterocycle optionally substituted with alkyl, halogen, OH, amino, carboxyl and oxo;

R_2 is H or R_5;

R_3 is absent or alkyl;

R_4 is absent, H, OH, =O, -R_6, -O-R_6, -C(O)O-R_6, -O-C(O)-R_6, -O-C(O)-O-R_6, -O-C(O)-NR_5R_6, -NR_5R_6, -NR_5-C(O)-R_6, -NR_5-C(O)-O-R_6, -NR_5-SO_2-R_6, =N-O-R_5;

R_5 is H or alkyl optionally substituted with a carbocycle or heterocycle wherein said carbocycle and heterocycle are optionally substituted with halogen, OH, oxo and alkyl;

R_6 is H, alkyl, a carbocycle, a heterocycle wherein said alkyl, carbocycle and heterocycle are optionally substituted with halogen, OH, SH, alkylthio, -S(O)-alkyl, -SO_2-alkyl, amino, -

NHC(O)-alkyl, oxo, alkyl, carboxyl, acyl, acyloxy, alkoxy, alkoxycarbonyl, a carbocycle optionally substituted with halogen, OH, amino or alkyl, or a heterocycle optionally substituted with halogen, OH, amino or alkyl; and wherein one or more non-adjacent methylene groups in each of said alkyl groups of R_6 are optionally replaced with -O- or -S-;

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 aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aS,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,9,12a-Heptamethyl-10-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-10-(4,4-difluoropiperidin-1-yl)-9-((((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-9-((((5-ethyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-10-(propionyloxy)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,12a-hexamethyl-9-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-10-(methylsulfonamido)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-10-((2,5,8,11-Tetraoxadodecanoyl)oxy)-2,4a,6a,6b,9,12a-hexamethyl-9-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,9,12a-heptamethyl-10-(2-((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)-2-oxoethoxy)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-9-(((5-ethyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-10-((S)-2-(methoxycarbonyl)pyrrolidin-1-yl)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,12a-hexamethyl-9-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-10-(1-methylcyclopropane-1-carboxamido)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-10-acetoxy-9-(((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,12a-hexamethyl-10-((((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)oxy)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a, 12b,13,14b-icosahydropicene-2,9-dicarboxylic acid or a pharmaceutically acceptable salt thereof.

In another example of the disclosure, 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 any one of the compounds as described herein and a pharmaceutically acceptable carrier, diluent or excipient.

In another example of the disclosure, there is provided a method of inhibiting conversion of cortisol to cortisone by HSD2 comprising contacting HSD2 with a compound of Formula I.

In another example of the disclosure, 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 of the disclosure, 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 of the disclosure, 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 another example of the disclosure, 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 any one of the compounds as described herein in the manufacture of a medicament for the treatment of hyperkalemia.

In another example of the disclosure, 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).

BRIEF DESCRIPTION OF THE FIGURES

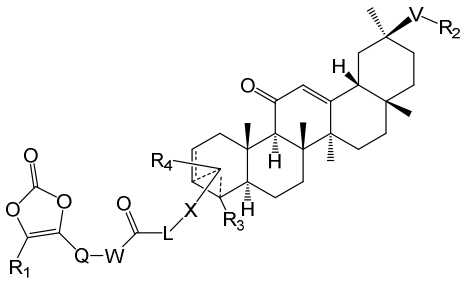
Figure 1 illustrates the synergistic effect on potassium excretion in feces upon administration of an HSD2 inhibitor in combination with an NHE3 inhibitor.

Figure 2 is an illustration of HSD2 inhibition in an epithelial cell allowing cortisol to activate the mineralocorticoid receptor (MR) which facilitates excretion of potassium into the lumen.

Figure 3 depicts the structure of glycyrrhetinic acid with the numbering of the carbon atoms.

CLAIMS

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)$_n$-;

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;

W is O or S;

Q is a bond or alkylene;

R_1 is H, alkyl, a carbocycle or a heterocycle wherein said alkyl, carbocycle and heterocycle are each 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;

V is -C(O)O-, -C(O)O-(CHR_5)-O-C(O)-, -C(O)O-(CHR_5)-O-C(O)-O-, -C(O)O-(CH_2)$_n$-Y-, -C(O)N(R_5)-, -C(O)N(R_5)-O-, -NH-C(O)-N(R_5)- or NH-S(O)$_n$-; wherein Y is a divalent heterocycle optionally substituted with alkyl, halogen, OH, amino, carboxyl and oxo;

R_2 is H or R_5;

R_3 is absent or alkyl;

R_4 is absent, H, OH, =O, -R_6, -O-R_6, -C(O)O-R_6, -O-C(O)-R_6, -O-C(O)-O-R_6, -O-C(O)-NR_5R_6, -NR_5R_6, -NR_5-C(O)-R_6, -NR_5-C(O)-O-R_6, -NR_5-SO_2-R_6, =N-O-R_5;

R_5 is H or alkyl optionally substituted with a carbocycle or heterocycle wherein said

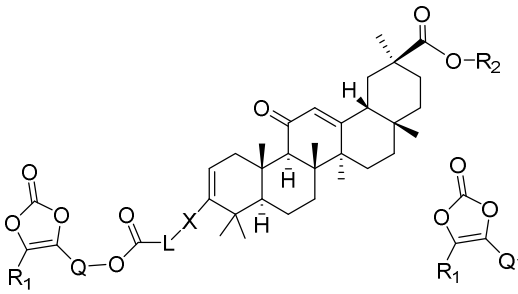
carbocycle and heterocycle are optionally substituted with halogen, OH, oxo and alkyl;

R_6 is H, alkyl, a carbocycle, a heterocycle wherein said alkyl, carbocycle and heterocycle are optionally substituted with halogen, OH, SH, alkylthio, -S(O)-alkyl, -SO_2-alkyl, amino, -NHC(O)-alkyl, oxo, alkyl, carboxyl, acyl, acyloxy, alkoxy, alkoxycarbonyl, a carbocycle optionally substituted with halogen, OH, amino or alkyl, or a heterocycle optionally substituted with halogen, OH, amino or alkyl; and wherein one or more non-adjacent methylene groups in each of said alkyl groups of R_6 are optionally replaced with -O- or -S-;

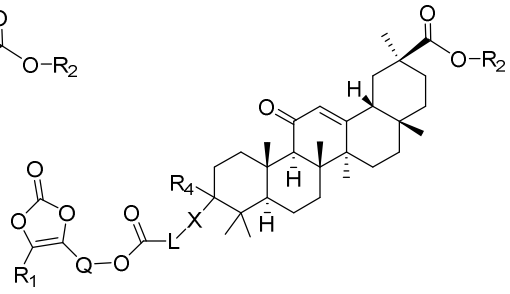
R_x is H, -C(O)O-R_1, or alkyl optionally substituted with -C(O)O-R_1; and

n is 1 or 2.

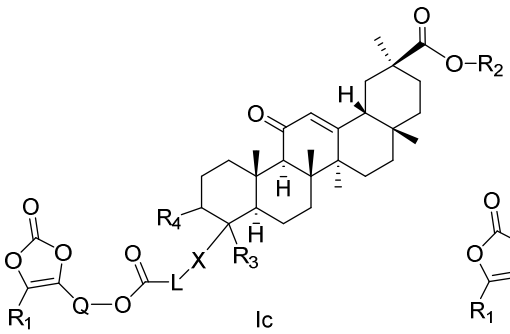
2. The compound of claim 1, having the structure of any one of Ia – Io:



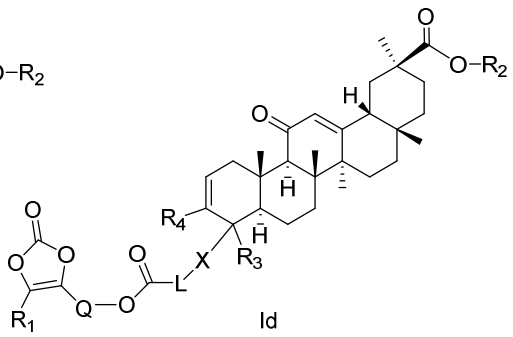
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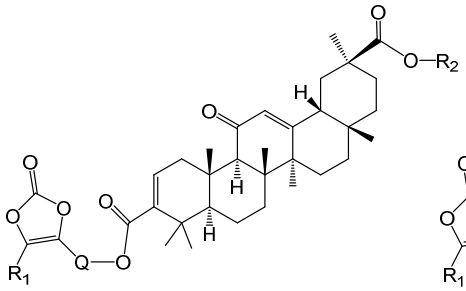
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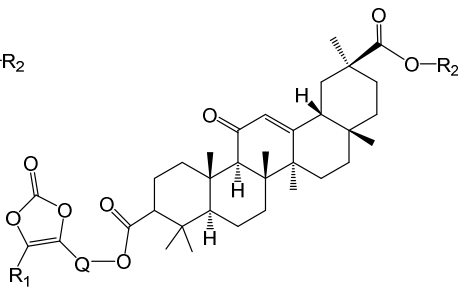
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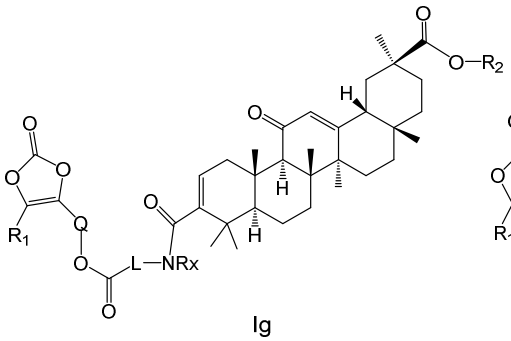
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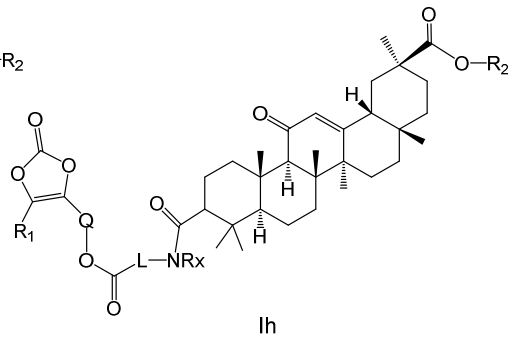
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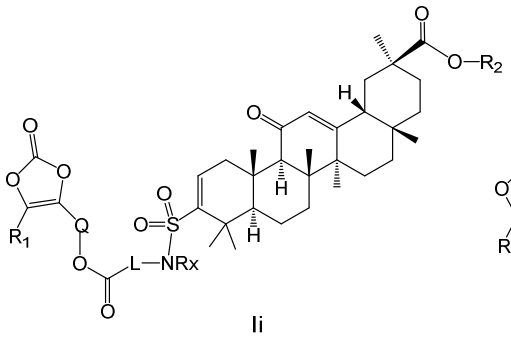
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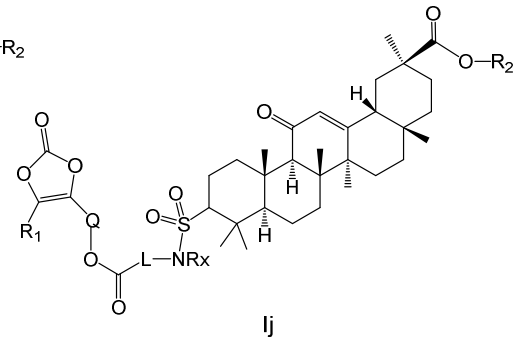
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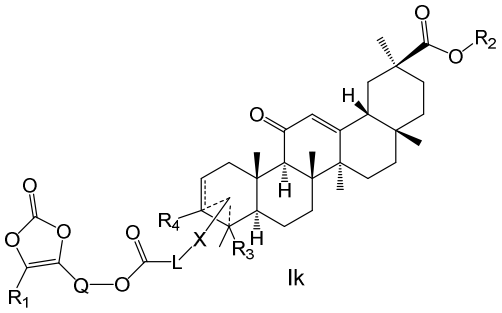
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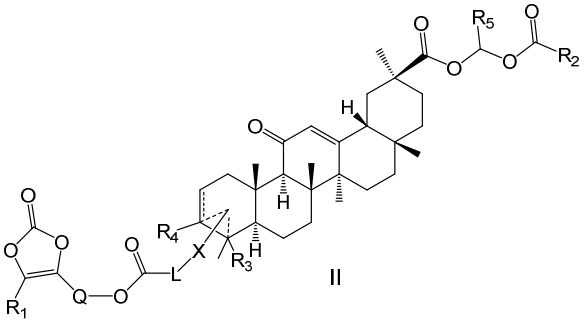
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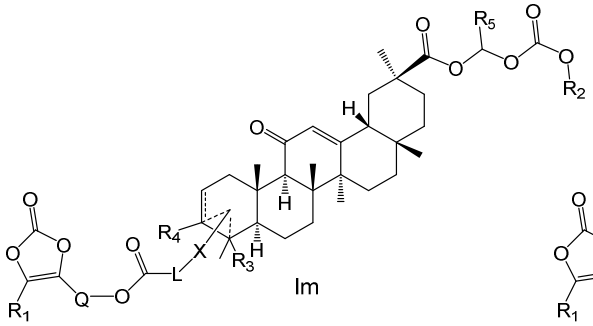
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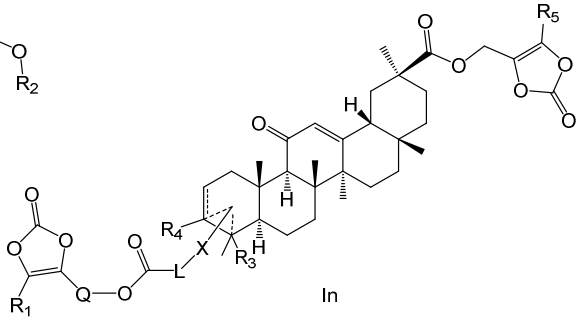
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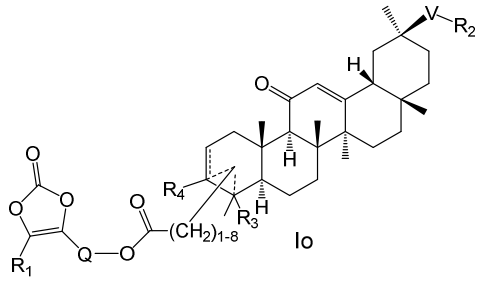
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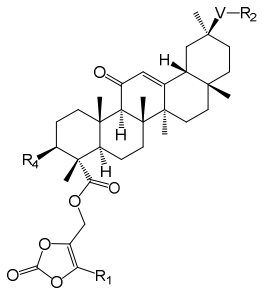


In

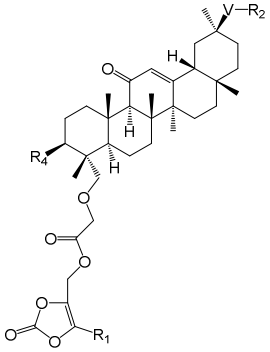


Io

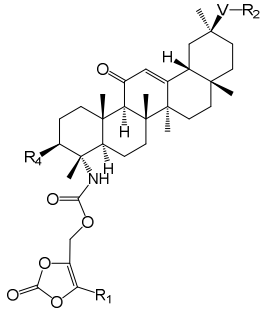
or Formula Ia'- If':



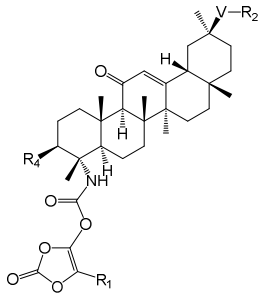
Ia'



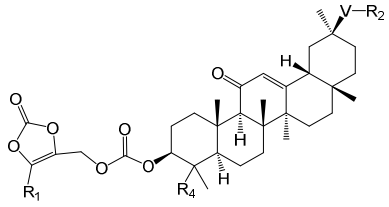
Ib'



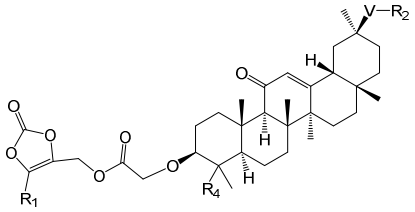
Ic'



Id'



Ie'



If'

.

3. The compound of claim 1 or claim 2, wherein V is -C(O)-O- and R_2 is H.

4. The compound of claim 1 or claim 2, wherein R_1 is methyl, ethyl or isopropyl.

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

6. The compound as claimed in any one of claims 1 to 5, wherein Q is O.

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

8. The compound as claimed in any one of claims 1 to 7, wherein R_4 is -O-C(O)-R_6 and R_6 is alkyl, carbocycle or heterocycle; wherein said alkyl is optionally substituted with

hydroxyl, halogen carboxy, alkoxy, alkylthio, amino, NHC(O)-alkyl, a heterocycle optionally substituted with alkyl; and said carbocycle and heterocycle are optionally substituted with halogen, hydroxyl and alkyl, wherein said alkyl is optionally substituted with hydroxyl, halogen carboxy; and wherein one or more non-adjacent methylene groups is replaced with -O-.

9. The compound as claimed in any one of claims 1 to 7, wherein R_4 is NH_2, alkoxy, OH, =N-O-alkyl, =N-OH.

10. The compound as claimed in any one of claims 1 to 7, wherein R_4 is R_6 and R_6 is phenyl optionally substituted with alkoxy.

11. The compound as claimed in any one of claims 1 to 7, wherein R_4 is R_6 and R_6 is a heterocycle optionally substituted with halogen, alkyl, oxo and alkoxycarbonyl.

12. The compound as claimed in any one of claims 1 to 7, wherein R_4 is -NHC(O)-R_6.

13. The compound as claimed in any one of claims 1 to 7, wherein R_4 is -NHC(O)-O-R_6.

14. The compound as claimed in any one of claims 1 to 7, wherein R_4 is -O-C(O)-O-R_6.

15. The compound as claimed in any one of claims 1 to 7, wherein R_4 is O-R_6.

16. The compound as claimed in any one of claims 1 to 7, wherein R_4 is -NR_5R_6.

17. The compound as claimed in any one of claims 1 to 7, wherein R_4 is -O-C(O)-R_6 and R_6 is methyl, ethyl or cyclopropyl.

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

19. Use of a compound of Claims 1 to 17 in the manufacture of a medicament for the treatment of hyperkalemia.

20. (2S,4aS,6aS,6bR,8aS,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,9,12a-Heptamethyl-10-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

21. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-10-(4,4-difluoropiperidin-1-yl)-9-((((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

22. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-9-((((5-ethyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-10-(propionyloxy)-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

23. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,12a-hexamethyl-9-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-10-(methylsulfonamido)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

24. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-10-((2,5,8,11-Tetraoxadodecanoyl)oxy)-2,4a,6a,6b,9,12a-hexamethyl-9-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

25. (2S,4aS,6aS,6bR,8aR,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,9,12a-heptamethyl-10-(2-((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)-2-oxoethoxy)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

26. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-9-(((5-ethyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-10-((S)-2-(methoxycarbonyl)pyrrolidin-1-yl)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

27. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,12a-hexamethyl-9-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-10-(1-methylcyclopropane-1-carboxamido)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

28. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-10-acetoxy-9-(((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-2,4a,6a,6b,9,12a-hexamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.

29. (2S,4aS,6aS,6bR,8aR,9S,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,12a-hexamethyl-10-((((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)oxy)-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a, 12b,13,14b-icosahydropicene-2,9-dicarboxylic acid or a pharmaceutically acceptable salt thereof.