

PATENT SPECIFICATION

(11) 1 475 177

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(21) Application No. 43373/74 (22) Filed 7 Oct. 1974

(31) Convention Application No. 405 736

(32) Filed 11 Oct. 1973

(31) Convention Application No. 492 941

(32) Filed 31 July 1974 in

(33) United States of America (US)

(44) Complete Specification published 1 June 1977

(51) INT CL² A61K 31/19 // C07D 241/32, 475/08

(52) Index at acceptance

A5B 248 24Y 384 38Y 420 421 426 42Y 431 43Y 451 45Y
480 482 483 48Y 491 49Y 500 50Y 510 511 513
51Y 542 543 54Y 552 55Y 565 566 56Y 576 57Y
586 58Y 595 596 597 59Y 605 606 60Y 640 641
647 64Y 650 65Y

C2C 1612 1620 214 215 220 226 22Y 247 250 252 25Y
29X 29Y 30Y 313 31Y 320 321 32Y 337 351 354
640 670 69Y 703 747 774 790 79Y LA NF

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(54) COMPOSITIONS CONTAINING INDANYLOXYALKANOIC ACID COMPOUNDS

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey 07065, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

Diuretics are valuable therapeutic agents as they are useful in the treatment of cardiovascular and renal diseases. Their use is indicated in the management of all types and grades of severity of congestive heart failure in which diuretic therapy improvement is required. Owing to the resulting loss of water and electrolyte, dramatic improvement is noted in peripheral and pulmonary oedema, dyspnea, orthopnea, cough, ascites and pleural effusion. For simplicity, the word diuretic is used herein in a common or generic sense, to apply to drugs that cause diuresis (increased urine excretion) and/or saluresis (increased electrolyte excretion).

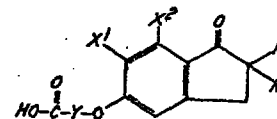
Diuretics also provide effective therapy in various forms of renal oedema; e.g., oedema associated with nephrosis and certain types of nephritis. Their administration results in prompt excretion of retained fluid and electrolytes, especially sodium chloride with consequent benefit to the patient. Diuretics are also especially useful in the treatment of hypertension and provide useful therapy in mild, moderate and severe forms of the disease.

Although diuretics are often life-saving because of the above beneficial therapeutic

effects, most of them have the disadvantage of causing the excretion of appreciable amounts of potassium ions. When an excessive loss of potassium ions occurs a severe muscular weakness and feeling of extreme physical exhaustion results. The patient eliminates the unwanted sodium ions due to the action of the diuretic drugs but the undesired elimination of the potassium ions produces an imbalance that should not be allowed to persist.

In addition to their other effects, these compounds are able to maintain the uric acid concentration in the body at pretreatment levels or to even effect a decrease in the uric acid concentration. Many of the currently available diuretics and saluretics have a tendency upon administration to induce hyperuricemia which may precipitate uric acid and/or sodium urate in the body, which may cause from mild to severe cases of gout.

The invention provides a composition comprising an indanyloxyalkanoic acid compound of the formula:—



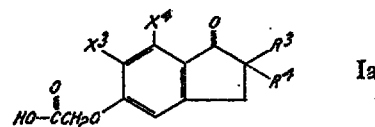
in which R is C₁₋₃, alkyl, cycloalkyl, aryl or substituted aryl, thienyl or substituted thienyl; R¹ is C₁₋₃, alkyl, C₃₋₅ alkenyl, C₃₋₅ alkynyl, phenyl-(C₁₋₃, alkyl), phenyl-(C₃₋₅, alkenyl), aryl, substituted aryl, thienyl or substituted thienyl; or R and R¹ are joined to form, together with the carbon atom to which they are attached, a cycloalkyl having from 3 to 7

nuclear atoms; X^1 is hydrogen, methyl or halogen and X^2 is methyl or halogen, or X^1 and X^2 are joined to form a hydrocarbylene chain containing 3 to 4 carbon atoms; and Y is an alkylene or haloalkylene radical containing a maximum of 4 carbon atoms; including the racemic form of the said compound and its enantiomers; together with a pyrazinoyl-guanidine compound, 6-phenyl-2,4,7-triaminopteridine or spironolactone, where the mole ratio of the indanyloxyalkanoic acid compound to the pyrazinoyl guanidine compound ranges from 0.2:1 to 4.0:1, the mole ratio of the indanyloxyalkanoic acid compound to 6-phenyl-2,4,7-triaminopteridine ranges from 1:7 to 1:3.5 and the mole ratio of the indanyloxyalkanoic acid compound to spironolactone ranges from 1:4.4 to 1:2.2. The indanyloxyalkanoic acid may form a salt with the pyrazine or pteridine compound, or a mixture with any of the three compounds. Use of compositions in accordance with the present invention can result in a reduction of the amount of potassium ions that are eliminated without a reduction in the amount of sodium ions that are eliminated, and can also reduce the risk of gout being induced.

The preferred pyrazinoylguanidine compound is N-amidino-3,5-diamino-6-chloropyrazinecarboxamide (amiloride) which is described in the literature, and another advantage, in the case of the N-amidino-3,5-diamino-6-chloropyrazinecarboxamide salts of the (1-oxo-2,2-disubstituted-5-indanyloxy)-acetic acid diuretics, is their insolubility, which makes the salts' gastrointestinal absorption slower and more gradual, providing a chemical method of achieving the same effect as microencapsulation.

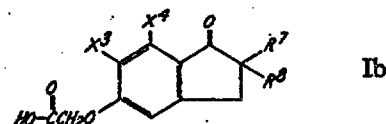
Among values of R are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, cyclopentyl, cyclohexyl, phenyl, substituted aryl in which the substituent is C_{1-3} alkyl, halogen, C_{2-3} alkoxy, hydroxy, amino or aminomethyl, and substituted thienyl in which the substituent is C_{1-3} alkyl or halogen; among possible values of R^1 are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, allyl, 1-, 2- or 3-butenyl, 1-, 2-, 3- or 4-pentenyl, propargyl, 1-, 2- or 3-butyryl, 1-, 2-, 3- or 4-pentynyl, benzyl, phenethyl, phenylpropyl, cinnamyl, phenyl, (C_{1-3} alkyl)aryl, haloaryl, (C_{1-3} alkyl)thienyl and halothienyl; among possible values of R and R^1 , when joined, together with carbon atom to which they are attached, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; among values of X^1 and X^2 are chlorine, bromine and fluorine; among values of X^1 and X^2 , when joined to form a bivalent hydrocarbon chain, are trimethylene, tetramethylene and 1,3-butadienylene; among values of Y are methylene, ethylidene, propylidene, isopropylidene, ethylene, trimethylene and fluoromethylene.

The preferred indanyloxyalkanoic acids have the following structural formula:



where R^3 is C_{1-3} alkyl, viz. methyl, ethyl, *n*-propyl or isopropyl, cyclopentyl or cyclohexyl and R^4 is C_{1-3} alkyl, viz. methyl, ethyl, *n*-propyl or isopropyl, phenyl (C_{1-3} alkyl)-phenyl, viz. tolyl, ethyl phenyl, *n*-propyl phenyl or isopropyl phenyl, halophenyl, methoxyphenyl, hydroxyphenyl, aminophenyl, aminomethylphenyl, thienyl, (C_{1-3} alkyl)-thienyl, viz. methylthienyl, ethylthienyl, *n*-propylthienyl, or isopropylthienyl, or halothienyl; or R^3 and R^4 are joined to form, together with the carbon atom to which they are attached, a cyclopentyl or cyclohexyl radical, and each of X^3 and X^4 , which are the same or different, is methyl or chlorine, including the racemic forms and enantiomers of such compounds.

The particularly preferred indanyloxyalkanoic acids have the formula:—



where R^1 is as methyl, ethyl, *n*-propyl, or isopropyl; R^2 is methyl, ethyl, *n*-propyl, isopropyl, phenyl, *p*-chlorophenyl or trienyl; and each of X^3 and X^4 , which are the same or different, is methyl or chlorine. Examples of compounds of Formula Ib are:

(1 - oxo - 2 - methyl - 2 - phenyl - 6,7-dichloro-5-indanyloxy) acetic acid;

levo - (1 - oxo - 2 - methyl - 2 - phenyl - 6,7-dichloro-5-indanyloxy)-acetic acid;

(1 - oxo - 2 - methyl - 2 - (*p* - chlorophenyl) - 6,7 - dichloro - 5 - indanyl - oxy) acetic acid;

(1 - oxo - 2 - methyl - 2 - (2 - thienyl) - 6,7-dichloro-5-indanyloxy)-acetic acid;

of which racemic and levo(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy) acetic acid are especially preferred.

The amiloride salt of a (1-oxo-2,2-disubstituted-5-indanyloxy) alkanolic acid is prepared by adding the (1-oxo-2,2-disubstituted-5-indanyloxy)alkanoic acid compound to a solution of amiloride in a suitable water-miscible organic solvent such as dimethylsulfoxide and then pouring the resulting solution into water from which the desired amiloride salt of the indanyloxyalkanoic acid separates and is collected by filtration.

The compositions of the present invention are preferably orally administrable. The pre-

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The pre-

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ferred molar ratio of the indanyloxyalkanoic acid compound to the pyrazinoylguanidine compound, e.g. amiloride, ranges from 0.8:1 to 1.6:1. When indanyloxyalkanoic acid is racemic (1 - oxo - 2 - methyl - 2 - phenyl-6,7-dichloro-5-indanyloxy)acetic acid, the pre-
ferred absolute weights and weight ratios corresponding to the above recited molar ratios are set forth in Table 1-a. The corresponding data for the laevo isomer are recorded in Table 1-b.

TABLE 1-a

Absolute Weight of Components		Weight Ratio	Mole Ratio
(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	Amiloride	(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Amiloride	(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Amiloride
5	10	0.5:1	0.4:1
5	5	1:1	0.8:1
10	5	2:1	1.6:1
25	5	5:1	4:1

TABLE 1-b

Absolute Weight of Components		Weight Ratio	Mole Ratio
levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	Amiloride	levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Amiloride	levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Amiloride
2.5	10	0.25:1	0.2:1
2.5	5	0.5:1	0.4:1
15	5	1:1	0.8:1
12.5	5	2.5:1	2:1

15 The present invention also embraces compositions for oral administration in which the molar ratio of the (1-oxo-2,2-disubstituted-5-indanyloxy)alkanoic acid to 6-phenyl-2,4,7-triaminopteridine (triamterene) ranges from 1:7 to 1:3.5. When the indanyloxyalkanoic acid is racemic (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, the preferred absolute weights and weight ratios corresponding to the above recited molar ratios are set forth in Table 2-a. The corresponding data for the laevo isomer are recorded in Table 2-b.

TABLE 2-a

Absolute Weight of Components		Weight Ratio	Mole Ratio
(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	Triamterene	(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Triamterene	(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Triamterene
5	50	1:10	1:7
10	50	1:5	1:3.5
20	100	1:5	1:3.5

TABLE 2-b

Absolute Weight of Components		Weight Ratio	Mole Ratio
levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	Triamterene	levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Triamterene	levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Triamterene
2.5	50	1:20	1:14
5	50	1:10	1:7
10	100	1:10	1:7

5 The present invention also embraces compositions for oral administration in which the molar ratio of the (1-oxo-2,2-disubstituted-5-indanyloxy)alkanoic acid to spironolactone ranges from about 1:4.4 to 1:2.2. When the indanyloxyalkanoic acid is racemic (1-oxo-2-

methyl - 2 - phenyl - 6,7 - dichloro - 5-indanyloxy)acetic acid, the preferred absolute weights and weight ratios corresponding to the above recited molar ratios are set forth in Table 3-a. The corresponding data for the laevo isomer are recorded in Table 3-b.

TABLE 3-a

Absolute Weight of Components		Weight Ratio	Mole Ratio
(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	Spironolactone	(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Spironolactone	(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Spironolactone
5	25	1:5	1:4.4
10	25	1:2.5	1:2.2
20	50	1:2.5	1:2.2

TABLE 3-b

Absolute Weight of Components		Weight Ratio	Mole Ratio
levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid	Spironolactone	levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Spironolactone	levo-(1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid: Spironolactone
2.5	25	1:10	1:8.8
5	25	1:5	1:4.4
10	50	1:5	1:4.4

20 Representative examples to illustrate this invention follow. Examples 1 to 4 are concerned with salts that may be used in the compositions; Examples 5 to 12 with the compositions themselves. Screen and capsule sizes are U.S. standards.

EXAMPLE 1.

25 Preparation of N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide Salt of (1-Oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic Acid.
To a hot solution of N-amidino-3,5-diamino-6-chloropyrazinecarboxamide (1.15

g., 0.005 mole) in dimethylsulfoxide (25 ml.) is added (1-oxo-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid (1.85 g., 0.005 mole). The clear solution is poured into vigorously stirred water (200 ml.). The N-amidino-3,5-diamino-6-chloropyrazinecarboxamide salt of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, which separates, is filtered, rinsed with water and dried. m.p. 150° C.

Analysis Calc. for $C_{22}H_{22}Cl_3N_5O_3$;
Calculated: C, 48.46; H, 3.73; N, 16.48;
Found: C, 48.11; H, 3.42; N, 16.19.

EXAMPLE 2.

Preparation of 6 - Phenyl - 2,4,7 - triamino-
pteridine Salt of (1 - Oxo - 2 - methyl -
2 - phenyl - 6,7 - dichloro - 5 - in-
danyloxy)acetic Acid.

- 5 To a hot solution of 6-phenyl-2,4,7-tri-
aminopteridine (1.27 g., 0.005 mole) in di-
methylsulfoxide (25 ml.) is added (1-oxo-2-
methyl - 2 - phenyl - 6,7 - dichloro - 5 -
10 indanyloxy)acetic acid (1.85 g., 0.005 mole).
The clear solution is poured into 200 ml. of
vigorously stirred water. The 6-phenyl-2,4,7-
triaminopteridine salt of (1-oxo-2-methyl-2-
phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic
15 acid, which separates, is filtered, rinsed with
water and dried.

EXAMPLE 3.

Preparation of N - Amidino - 3,5 - diamino-
6 - chloropyrazine - carboxamide Salt
of Laevo(1 - Oxo - 2 - methyl - 2 -
phenyl - 6,7 - dichloro - 5 - indanyloxy)-
acetic Acid.

- 20 To a hot solution of N-amidino-3,5-di-
amino-6-chloropyrazinecarboxamide (1.15 g.,
0.005 mole) in dimethylsulfoxide (25 ml.) is
added laevo(1 - oxo - 2 - methyl - 2 - phenyl -
25 6,7 - dichloro - 5 - indanyloxy)acetic acid
(1.85 g., 0.005 mole). The clear solution is
poured into vigorously stirred water (200 ml.).
30 The N - amidino - 3,5 - diamino - 6 - chloro-
pyrazinecarboxamide salt of laevo(1 - oxo -
2 - methyl - 2 - phenyl - 6,7 - dichloro - 5 -
indanyloxy)acetic acid, which separates, is
filtered, rinsed with water and dried.

EXAMPLE 4.

Preparation of 6 - Phenyl - 2,4,7 - triamino-
pteridine Salt of laevo(1 - Oxo - 2 -
methyl - 2 - phenyl - 6,7 - dichloro - 5 -
indanyloxy)acetic acid.

- 40 To a hot solution of 6-phenyl-2,4,7-tri-
aminopteridine (1.27 g., 0.005 mole) in di-
methylsulfoxide (25 ml.) is added laevo(1-
oxo - 2 - methyl - 2 - phenyl - 6,7 - dichloro -
5-indanyloxy)acetic acid (1.85 g., 0.005 mole).
45 The clear solution is poured into 200 ml. of
vigorously stirred water. The 6-phenyl-2,4,7-
triaminopteridine salt of laevo(1-oxo-2-
methyl - 2 - phenyl - 6,7 - dichloro - 5 -
indanyloxy)acetic acid, which separates, is
50 filtered, rinsed with water and dried.

The compositions of this invention, whether
in the form of mixtures or of salts, can be ad-
ministered in a wide variety of therapeutic
dosages in conventional vehicles, for example,
55 by oral administration in the form of a tablet.
Also, the daily dosage of the products may be
varied over a wide range, for example, in the
form of scored tablets containing 2.5, 5, 10,
15, 25, 50 and 100 milligrams of the active

60 ingredients for the symptomatic adjustment of
the dosage to the patient to be treated. The
daily dosage is preferably administered in sub-
divided doses spread out over a 24 hour
period. These dosages are well below the toxic
or lethal dose of the products.

65 A suitable combined dosage form of the
composition of this invention can be admin-
istered by mixing 5 mg. of a racemic (1-oxo-
2,2-disubstituted-5-indanyloxy)-alkanoic acid
or its pure enantiomer with 5 mg. of amiloride,
70 50 mg. of triamterene or 25 mg. of spirono-
lactone with 189 mg., 144 mg. or 169 mg. re-
spectively of lactose and 1 mg. of magnesium
stearate and placing the mixture into a No. 1
gelatin capsule. Similarly, by using more of
75 the active ingredient and less lactose, other
dosage forms can be put up in No. 1 gelatin
capsules. Should it be necessary, compressed
tablets, pills, or other desired combined dos-
80 ages can be prepared to incorporate the com-
positions of this invention by conventional
methods. An effective amount of the active in-
gredients of the mixture is ordinarily supplied
at a dosage level of from 0.01 mg. to 5.0
mg./kg. of body weight. Preferably the range
85 is from 0.05 mg. to 2 mg./kg. of body weight.

It is also within the scope of this invention
to combine the amiloride or triamterene salt
of a (1-oxo-2,2-disubstituted-5-indanyloxy)-
alkanoic acid of structure (I) with lactose and
90 magnesium stearate in unit dosage form. An
effective amount of the salt is ordinarily
supplied at a dosage level of from 0.01 mg.
to 5 mg./kg. of body weight. Preferably the
range is from 0.05 mg. to 2 mg./kg. of body
95 weight.

A suitable unit dosage form of the amiloride
salt of a (1 - oxo - 2,2 - disubstituted - 5 -
indanyloxy)-alkanoic acid of structure (I) is
composed of 10 mg. to 30 mg. of the salt
100 mixed with 189 mg. or 169 mg. respectively
of lactose and 1 mg. magnesium stearate.

The following examples are included to
illustrate the preparation of representative
combined dosage forms containing a mixture
105 of a (1-oxo-2,2-disubstituted-5-indanyloxy)-
alkanoic acid and amiloride, triamterene or
spironolactone.

EXAMPLE 5.

Combined Dosage Form in Dry-filled Capsule.		110
Per capsule		
(1 - Oxo - 2 - methyl - 2 - phenyl - 6,7 - dichloro - 5 - indanyloxy)- acetic acid	10 mg.	115
N - Amidino - 3,5 - diamino - 6 - chloro-pyrazinecarboxamide	5 mg.	
Lactose	184 mg.	
Magnesium stearate	1 mg.	
Capsule (size No. 1)	200 mg.	

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water and

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9.

EXAMPLE 6.

Combined Dosage Form in Dry-filled Capsule.		Per capsule
5	levo(1 - Oxo - 2 - methyl - 2-phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic acid	5 mg.
	N - Amidino - 3,5 - diamino - 6-chloro-pyrazinecarboxamide	5 mg.
	Lactose	189 mg.
10	Magnesium stearate	1 mg.
Capsule (size No. 1)		200 mg.

EXAMPLE 7.

Combined Dosage Form in Dry-filled Capsule.		Per capsule
15	(1 - Oxo - 2 - methyl - 2 - phenyl-6,7 - dichloro - 5 - indanyloxy)-acetic acid	10 mg.
	6-Phenyl-2,4,7-triaminopteridine	50 mg.
	Lactose	139 mg.
20	Magnesium stearate	1 mg.
Capsule (size No. 1)		200 mg.

EXAMPLE 8.

Combined Dosage Form in Dry-filled Capsule.		Per capsule
25	(1 - Oxo - 2 - methyl - 2 - phenyl-6,7 - dichloro - 5 - indanyloxy)-acetic acid	10 mg.
	Spirolactone	25 mg.
	Lactose	164 mg.
30	Magnesium stearate	1 mg.
Capsule (size No. 1)		200 mg.

The (1 - oxo - 2 - methyl - 2 - phenyl-6,7 - dichloro - 5 - indanyloxy)acetic acid and N - amidino - 6 - chloropyrazinecarboxamide, 6-phenyl-2,4,7-triaminopteridine or spirolactone are mixed and reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for ten minutes and then filled into a No. 1 dry gelatin capsule.

Similar combined dosage form dry-filled capsules are prepared by replacing the indanyloxy acetic acid ingredient of Examples 4, 5, 7 and 8 by any of the other indanyloxy-alkanoic acid compounds recited in this invention. If, in Examples 5, 7 and 8, one of the other mentioned indanyloxyalkanoic acid diuretics is substituted for (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid, it would be used in a greater or lesser amount depending upon its known relative diuretic activity with respect to (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid.

EXAMPLE 9.

Combined Dosage Form in Dry-filled Capsule.		Per capsule
	laevo - (1 - Oxo - 2 - methyl - 2-phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic acid	5 mg.
	6-Phenyl-2,4,7-triaminopteridine	50 mg.
	Lactose	144 mg.
	Magnesium stearate	1 mg.
Capsule (size No. 1)		200 mg.

EXAMPLE 10.

Combined Dosage Form in Dry-filled Capsule.		Per capsule
	laevo - (1 - Oxo - 2 - methyl - 2-phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic acid	5 mg.
	Spirolactone	25 mg.
	Lactose	169 mg.
	Magnesium stearate	1 mg.
Capsule (size No. 1)		200 mg.

The laevo - (1 - oxo - 2 - methyl - 2-phenyl - 6,7 - dichloro - 5 - indanyloxy)-acetic acid and N-amidino-3,5-diamino-6-chloropyrazinecarboxamide, 6-phenyl-2,4,7-triaminopteridine or spirolactone are mixed and reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for ten minutes and then filled into a No. 1 dry gelatin capsule.

The following examples are included to illustrate the preparation of representative dosage forms containing an amiloride salt of a (1 - oxo - 2,2 - disubstituted - 6,7 - dichloro - 5 - indanyloxy)alkanoic acid.

EXAMPLE 11.

Dry-filled Capsule.

		Per capsule
	N - amidino - 3,5 - diamino - 6-chloropyrazinecarboxamide salt of (1 - oxo - 2 - methyl - 2-phenyl - 6,7 - dichloro - 5-indanyloxy)acetic acid	20 mg.
	Lactose	179 mg.
	Magnesium stearate	1 mg.
Capsule (size No. 1)		200 mg.

The amiloride salt of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid is reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for 10 minutes and then filled into a No. 1 dry gelatin capsule.

6	55
7	60
8	65
9	70
10	75
11	80
12	85
13	90
14	95
15	100
16	105

5 mg.
25 mg.
169 mg.
1 mg.
200 mg.

5 mg.
25 mg.
169 mg.
1 mg.
200 mg.

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1 mg.
200 mg.

5 mg.
25 mg.
169 mg.
1 mg.
200 mg.

5 mg.
25 mg.
169 mg.
1 mg.
200 mg.

7

Similar dry-filled capsules can be prepared by replacing the indanyloxyacetic acid ingredient of the above example by a molar equivalent amount of other indanyloxyalkanoic acid compounds recited in this invention.

EXAMPLE 12. Dry-filled Capsule.

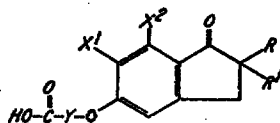
	Per capsule
10 N - amidino - 3,5 - diamino - 6-chloropyrazinecarboxamide salt of laevo - (1 - oxo - 2 - methyl - 2 - phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic acid	10 mg.
Lactose	189 mg.
15 Magnesium stearate	1 mg.

Capsule (size No. 1) 200 mg.

The amiloride salt of laevo-(1-oxo-2-methyl - 2 - phenyl - 6,7 - dichloro - 5-indanyloxy)acetic acid is reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for 10 minutes and then filled into a No. 1 dry gelatin capsule.

WHAT WE CLAIM IS:—

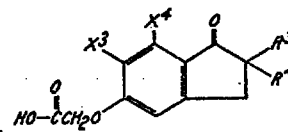
1. A composition comprising an indanyloxyalkanoic acid compound of the formula:



- in which R is C₁₋₅ alkyl, cycloalkyl, aryl or substituted aryl, thienyl or substituted thienyl; R¹ is C₁₋₅ alkyl, C₃₋₅ alkenyl, C₃₋₅ alkynyl, phenyl-(C₁₋₃ alkyl), phenyl-(C₃₋₅ alkenyl), aryl, substituted aryl, thienyl or substituted thienyl; or R and R¹ are joined to form, together with the carbon atom to which they are attached, a cycloalkyl having from 3 to 7 nuclear atoms; X¹ is hydrogen, methyl or halogen and X² is methyl or halogen, or X¹ and X² are joined to form a hydrocarbylene chain containing 3 or 4 carbon atoms, and Y is an alkylene or haloalkylene radical containing a maximum of 4 carbon atoms; including the racemic form of the said compound and its enantiomers; together with a pyrazinoylguanidine compound, 6-phenyl-2,4,7-triaminopteridine or spironolactone, where the mole ratio of the indanyloxyalkanoic acid compound to the pyrazinoylguanidine compound ranges from 0.2:1 to 4.0:1, the mole ratio of the indanyloxyalkanoic acid compound to 6-phenyl-2,4,7-triaminopteridine ranges from 1:7 to 1:3.5 and the mole ratio of the indanyloxyalkanoic acid compound to spironolactone ranges from 1:4.4 to 1:2.2.

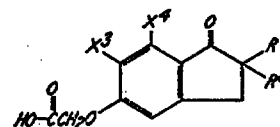
2. A composition as claimed in Claim 1 in

which the indanyloxyalkanoic acid compound has the formula:



where R³ is C₁₋₃ alkyl, cyclopentyl or cyclohexyl; R⁴ is C₁₋₃ alkyl having from 1 to 3 carbon atoms, phenyl, (C₁₋₃ alkyl)phenyl, halophenyl, methoxyphenyl, hydroxyphenyl, aminophenyl, aminomethylphenyl, thienyl, (C₁₋₃ alkyl)-thienyl or halothienyl, or R³ and R⁴ are joined to form, together with the carbon atom to which they are attached, cyclopentyl or cyclohexyl radical; and each of X³ and X⁴, which are the same or different, is methyl or chlorine.

3. A composition as claimed in Claim 1 in which the indanyloxyalkanoic acid compound has the formula:



where R⁷ is C₁₋₃ alkyl, R⁸ is C₁₋₃ alkyl, phenyl, p-chlorophenyl or thienyl; and each of X³ and X⁴, which are the same or different, is methyl or chlorine.

4. A composition according to Claim 3 in which the indanyloxyalkanoic acid is (1-oxo-2 - methyl - 2 - phenyl - 6,7 - dichloro - 5-indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N-amidino-3,5-diamino-6-chloropyrazinecarboxamide.

5. A composition according to claim 3 in which the indanyloxyalkanoic acid is (1-oxo-2 - methyl - 2 - (p - chlorophenyl) - 6,7-dichloro - 5 - indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N - amidino - 3,5 - diamino - 6 - chloropyrazinecarboxamide.

6. A composition according to claim 3 in which the indanyloxyalkanoic acid is (1-oxo-2 - methyl - 2 - (2 - thienyl) - 6,7 - dichloro-5-indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N-amidino-3,5-diamino-6-chloropyrazinecarboxamide.

7. A composition according to claim 3 in which the indanyloxyalkanoic acid is levo-(1 - oxo - 2 - methyl - 2 - phenyl - 6,7-dichloro-5-indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N-amidino - 3,5 - diamino - 6 - chloropyrazinecarboxamide.

8. A composition according to claim 4 in which the mole ratio of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid to N - amidino - 3,5 - diamino - 6 - chloro-

Similar dry-filled capsules can be prepared by replacing the indanyloxyacetic acid ingredient of the above example by a molar equivalent amount of other indanyloxyalkanoic acid compounds recited in this invention.

EXAMPLE 12. Dry-filled Capsule.

	Per capsule
10 N - amidino - 3,5 - diamino - 6-chloropyrazinecarboxamide salt of laevo - (1 - oxo - 2 - methyl - 2 - phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic acid	10 mg.
15 Lactose	189 mg.
Magnesium stearate	1 mg.

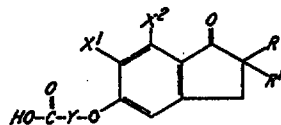
Capsule (size No. 1)

200 mg.

- The amiloride salt of laevo-(1-oxo-2-methyl - 2 - phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic acid is reduced to a No. 60 powder and then lactose and magnesium stearate are passed through a No. 60 bolting cloth onto the powder and the combined ingredients admixed for 10 minutes and then filled into a No. 1 dry gelatin capsule.

25 WHAT WE CLAIM IS:—

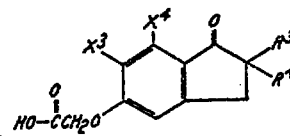
1. A composition comprising an indanyloxyalkanoic acid compound of the formula:



- in which R is C₁₋₃ alkyl, cycloalkyl, aryl or substituted aryl, thienyl or substituted thienyl; R¹ is C₁₋₃ alkyl, C₃₋₅ alkenyl, C₃₋₅ alkynyl, phenyl-(C₁₋₃ alkyl), phenyl-(C₃₋₅ alkenyl), aryl, substituted aryl, thienyl or substituted thienyl; or R and R¹ are joined to form, together with the carbon atom to which they are attached, a cycloalkyl having from 3 to 7 nuclear atoms; X¹ is hydrogen, methyl or halogen and X² is methyl or halogen, or X¹ and X² are joined to form a hydrocarbylene chain containing 3 or 4 carbon atoms, and Y is an alkylene or haloalkylene radical containing a maximum of 4 carbon atoms; including the racemic form of the said compound and its enantiomers; together with a pyrazinoylguanidine compound, 6-phenyl-2,4,7-triaminopteridine or spironolactone, where the mole ratio of the indanyloxyalkanoic acid compound to the pyrazinoylguanidine compound ranges from 0.2:1 to 4.0:1, the mole ratio of the indanyloxyalkanoic acid compound to 6-phenyl-2,4,7-triaminopteridine ranges from 1:7 to 1:3.5 and the mole ratio of the indanyloxyalkanoic acid compound to spironolactone ranges from 1:4.4 to 1:2.2.

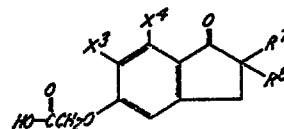
2. A composition as claimed in Claim 1 in

which the indanyloxyalkanoic acid compound has the formula:



where R³ is C₁₋₃ alkyl, cyclopentyl or cyclohexyl; R⁴ is C₁₋₃ alkyl having from 1 to 3 carbon atoms, phenyl, (C₁₋₃ alkyl)phenyl, halophenyl, methoxyphenyl, hydroxyphenyl, aminophenyl, aminomethylphenyl, thienyl, (C₁₋₃ alkyl)-thienyl or halothienyl, or R³ and R⁴ are joined to form, together with the carbon atom to which they are attached, cyclopentyl or cyclohexyl radical; and each of X³ and X⁴, which are the same or different, is methyl or chlorine.

3. A composition as claimed in Claim 1 in which the indanyloxyalkanoic acid compound has the formula:



where R⁷ is C₁₋₃ alkyl, R⁸ is C₁₋₃ alkyl, phenyl, p-chlorophenyl or thienyl; and each of X³ and X⁴, which are the same or different, is methyl or chlorine.

4. A composition according to Claim 3 in which the indanyloxyalkanoic acid is (1-oxo-2 - methyl - 2 - phenyl - 6,7 - dichloro - 5 - indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N-amidino-3,5-diamino-6-chloropyrazinecarboxamide.

5. A composition according to claim 3 in which the indanyloxyalkanoic acid is (1-oxo-2 - methyl - 2 - (p - chlorophenyl) - 6,7 - dichloro - 5 - indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N - amidino - 3,5 - diamino - 6 - chloropyrazinecarboxamide.

6. A composition according to claim 3 in which the indanyloxyalkanoic acid is (1-oxo-2 - methyl - 2 - (2 - thienyl) - 6,7 - dichloro-5-indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N-amidino-3,5-diamino-6-chloropyrazinecarboxamide.

7. A composition according to claim 3 in which the indanyloxyalkanoic acid is levo-(1 - oxo - 2 - methyl - 2 - phenyl - 6,7 - dichloro-5-indanyloxy)acetic acid and the pyrazinoylguanidine compound, if used, is N-amidino - 3,5 - diamino - 6 - chloropyrazinecarboxamide.

8. A composition according to claim 4 in which the mole ratio of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid to N - amidino - 3,5 - diamino - 6 - chloro-



- pyrazinecarboxamide ranges from 0.8:1 to 1.6:1, the mole ratio of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid to 6-phenyl-2,4,7-triaminopteridine is about 1:3.5 and the mole ratio of (1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid to spironolactone is about 1:2.2.
9. A composition according to claim 5 in which the mole ratio of (1-oxo-2-methyl-2-(p-chlorophenyl)-6,7-dichloro-5-indanyloxy)acetic acid to N-amidino-3,5-diamino-6-chloropyrazinecarboxamide ranges from 0.8:1 to 1.6:1, the mole ratio of (1-oxo-2-methyl-2-(p-chlorophenyl)-6,7-dichloroindanyloxy)acetic acid to 6-phenyl-2,4,7-triaminopteridine is about 1:3.5 and the mole ratio of (1-oxo-2-methyl-2-(p-chlorophenyl)-6,7-dichloro-5-indanyloxy)acetic acid to spironolactone is about 1:2.2.
10. A composition according to claim 6 in which the mole ratio of (1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid to N-amidino-3,5-diamino-6-chloropyrazinecarboxamide ranges from 0.8:1 to 1.6:1, the mole ratio of (1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloroindanyloxy)acetic acid to 6-phenyl-2,4,7-triaminopteridine is about 1:3.5 and the mole ratio of (1-oxo-2-methyl-2-(2-thienyl)-6,7-dichloro-5-indanyloxy)acetic acid to spironolactone is about 1:2.2.
11. A composition according to claim 7 in which the mole ratio of levo-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-indanyloxy)acetic acid to N-amidino-3,5-diamino-6-chloropyrazinecarboxamide ranges from 0.4:1 to 0.8:1, the mole ratio of levo-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid to 6-phenyl-2,4,7-triaminopteridine is about 1:7.0 and the mole ratio of levo-(1-oxo-2-methyl-2-phenyl-6,7-dichloro-5-indanyloxy)acetic acid to spironolactone is about 1:4.4.
12. A composition as claimed in any one of claims 1—11, in orally administrable form.
13. A composition as claimed in claim 12, in the form of a tablet, pill or capsule.
14. A composition as claimed in any one of claims 1—3, in which the indanyloxyalkanoic acid and the N-amidino-3,5-diamino-6-chloropyrazinecarboxamide are used in the form of a salt.
15. A composition as claimed in any one of claims 1—3, in which the indanyloxyalkanoic acid and the 6-phenyl-2,4,7-triaminopteridine are used in the form of a salt.
16. A composition as claimed in claim 1 substantially as hereinbefore described in any one of Examples 5 to 12.
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