COMONWELLTH PATENTS ACT

APPLICATION FOR A STANDARD PATENT

79094/81

To: SMITHKLINE CORPORATION, a corporation organized under the laws of the Commonwealth of Pennsylvania one of the United States of America of 1500 Spring Garden Street Philadelphia, Pennsylvania 19101, United States of America

hereby apply for the grant of a Standard Patent for an invention entitled:

2(3H)-INDOLONES, PROCESS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

which is described in the accompanying specification.

Dated this 20th day of December 1981.

To: THE COMMISSIONER OF PATENTS

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.
In support of the Application made for a patent for an invention entitled: 
2(3H)-INDOLONES, PROCESS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

1. (a) I am the applicant for the patent or the patent of addition
   or (b) I am authorized by
   SMITHKLINE CORPORATION
   the applicant for the patent or the patent of addition to make this declaration on behalf of the applicant.

2. (a) I am the actual inventor of the invention
     or (b) William Francis Huffman of 40 Crest Avenue, Malvern, Pennsylvania 19355, and James William Wilson of 15 Kinterra Road, Wayne, Pennsylvania 19087, both in the United States of America,

The said SMITHKLINE CORPORATION is the assignee of the said William Francis Huffman and James William Wilson

3. The basic application as defined by Section 141 of the Act was made in
   by
   in
   by
   in
   by

4. The basic application referred to in paragraph 3 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

Declared at Philadelphia, this 15th day of December, 1981

SMITHKLINE CORPORATION
William Howard Edgerton
Assistant Director, Corporate Patents

DAVIES & COLLISON, MELBOURNE and CANBERRA.
Claim

1. A compound of the structural formula:

![Structural Formula]

in which R is amino, lower (C₁-C₆) alkylamino, di-lower (C₁-C₆) alkylamino, di-N-allylamino or N-allyl-N-lower (C₁-C₆) alkylamino; R¹ is hydroxy or methoxy; and n is an integer from 1-3; or a pharmaceutically acceptable acid addition salt thereof.
Name of Applicant: SMITHKLINE CORPORATION

Address of Applicant: 1500 Spring Garden Street
                      PHILADELPHIA PENNSYLVANIA 19101
                      U.S.A.

Actual Inventor(s): WILLIAM FRANCIS HUFFMAN
                    JAMES WILLIAM WILSON

Address for Service: DAVIES & COLLISON, Patent Attorneys,
                    1 Little Collins Street, Melbourne, 3000.

Complete specification for the invention entitled:
2(3H)-INDOLONES, PROCESS FOR THEIR PREPARATION
AND COMPOSITIONS CONTAINING THEM

The following statement is a full description of the invention,
including the best method of performing it known to us

- 1 -
This invention concerns substituted 2(3H)-indolones, processes for their preparation and compositions containing them. The compounds of the invention have a beneficial effect on abnormal conditions of the cardiovascular system.


The compounds of this invention have structures which are characterized by a 2(3H)-indolone (oxindole) nucleus having an aminoalkyl substituent at the 4-position and an oxygen function at the 7-position. They are represented by the following structural formula:

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[Structural formula diagram]
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in which R is amino, lower alkylamino, dilower alkylamino; di-N-allylamino or N-allyl-N-lower alkylamino, R¹ is hydroxy or methoxy and n is an integer of from 1-3. Lower alkyl groups will have from 1-6 carbons.

It will be understood that the hydrogen at the 1- or N-position of the indolone nucleus may be tautomeric. The compounds of Formula I which are of particular interest are those in which R¹ is hydroxy. Of these compounds, those having notable biological activity also have n as 2 and R is dilower alkylamino, di-N-allylamino or N-allyl-N-lower alkylamino. A species of this invention is 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone together with its acid addition salts.

The invention also includes pharmaceutically acceptable acid addition salts of the free bases of Formula I. These can be prepared by methods well known to the art and be formed with both inorganic or organic acids, for example with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesaliclyc, methanesulfonic, ethane disulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids. The hydrohalic and especially methanesulfonic acid salts are preferred.
The compounds of the present invention can be prepared by removing the protecting group from a compound of formula

\[
\begin{align*}
&\text{NHR}^3 \\
&\text{(CH}_2^n\text{)} \\
&\text{OCH}_3
\end{align*}
\]

(where \(n\) is as hereinbefore defined and \(R^3\) is a protecting group, for example trifluoroacetyl) and subsequently converting the 4-position aminoalkyl group produced into a different group of formula \(-\text{(CH}_2^n\text{)}R^2\), and/or demethylating the methoxy group at the 7-position.

A preferred overall reaction sequence is shown in Scheme A below, the optional subsequent reactions being shown in Scheme B. In both Schemes, \(n\) is 1-3.

**Scheme A**

1. \(\text{NH}_2\text{ (CH}_2^n\text{)}\) \\
2. \(\text{NHCCOCF}^3\text{ (CH}_2^n\text{)}\) \\
3. \(\text{NHCCOCF}^3\text{ (CH}_2^n\text{)}\) \\
4. \(\text{NHCCOCF}^3\text{ (CH}_2^n\text{)}\) \\
5. \(\text{NHCOCH=NOH}\)
In this scheme n is 1-3.

Scheme B

In Scheme B, R² is lower alkylamino, dilower-alkylamino, N-allyl-N-lower alkylamino or di-N-allylamino.

Scheme A involves preparing an isatin (6) with an aminocalkyl at position 4 and hydroxy function at position 7, both protected from the reaction conditions of the
The 3-keto group of the isatin nucleus is then removed such as by reaction with ethanedithiol followed by removal of the 3,3-ethyleneedithio moiety (7) by hydrogenolysis. The resulting oxindole (8) is then further reacted to remove the N or O-protective groups after optional N-alkylation which can be carried out by standard chemical reactions.

The preparation of the compounds of Formula I in which \( R \) is hydroxy (i.e. Compounds 11 and 12 of Scheme B above) can be accomplished by reacting a suitable 0-methyl containing compound (i.e. Compounds 9 or 10 of Scheme B) with a dealkylating agent, for example hydrobromic acid, hydriodic acid, aluminum chloride, boron tribromide or boron trichloride. The reaction conditions may vary depending on the chemical characteristics of the dealkylating agent. Temperatures from ambient up to reflux temperatures are often used with acid agents such as hydrobromic acid or hydriodic acid which are of course used in a water medium.

The use of boron tribromide is particularly convenient in the cold in a halogenated organic solvent such as methylene dichloride. This procedure is preferred when the desired compound has an N-allyl group present in its structure, in order to minimize side reactions with the allyl group. If an N-protective group is present and must be removed, the acid reagents are preferred.

The compounds of this invention have a beneficial effect on abnormal cardiovascular conditions, especially on the kidney by means of increasing renal blood flow and decreasing renal vascular resistance. Bradycardia is also observed. This activity is demonstrated by monitoring mean arterial blood pressure (MAP), mean renal blood flow (RBF), renal vascular resistance (RVR) and heart rate (HR) by intravenous infusion in the normal anesthetized dog. A clinically effective compound, dopamine, is run in each test for comparison.
As examples of the activity of these compounds in the pharmacological test procedure described, the following results were obtained:

4-[(2-di-n-propylaminoethy1)-7-hydroxy-2(3H)-indolone hydrobromide (A);
4-[(2-di-n-propylaminoethy1)-7-methoxy-2(3H)-indolone hydrochloride (B);
4-[(2-aminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (C);
4-[(2-aminoethyl)-7-methoxy-2(3H)-indolone hydrochloride (D).

<table>
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<tr>
<th>Compound</th>
<th>Dose (base)</th>
<th>% Change</th>
<th>MAP</th>
<th>RBF</th>
<th>RVR</th>
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<td>Dopamine</td>
<td></td>
<td></td>
<td>MAP</td>
<td>RBF</td>
<td>RVR</td>
<td>HR</td>
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Administered in 10% dimethylsulfoxide in 0.9% saline.

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<tr>
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The invention therefore provides pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutical carrier.

The pharmaceutical compositions of this invention have pharmacodynamic activity in the cardiovascular system, i.e. renal vasodilatation, hypotensive activity and bradycardia, and they can be prepared in conventional dosage unit forms by incorporating a compound of Formula I, or a pharmaceutically acceptable acid addition salt or ester derivative thereof, with a nontoxic pharmaceutical carrier according to accepted procedures. The active ingredient will be present in a nontoxic amount sufficient to produce the desired pharmacodynamic activity in a subject, animal or human. Preferably the compositions will contain the active ingredient in an active but nontoxic amount selected from about 25 mg to about 500 mg preferably about 50-250 mg of active ingredient calculated as free base per dosage unit but this quantity depends on the potency of the compound compared with that of dopamine, which has the specific biological activity desired, the route of administration whether oral or parenteral, and the condition of the patient.

The pharmaceutical carrier employed can be solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid, and the like. Exemplary of liquid carriers are isotonic saline for parenteral use or syrup.
peanut, oil, olive oil, water and the like for soft gelatin capsules. Similarly the carrier or diluent can include a
time delay material well known to the art, for example
glyceryl monostearate or glyceryl distearate, alone or with
a wax. Such sustained release products as well as
derivatives which may be gradually metabolized to the active
carrier or diluent can include a parent can be employed to prolong the biological activity of
the compounds of this invention.

A wide variety of pharmaceutical forms can be
employed. Thus, if a solid carrier for oral administration
is used the compositions can be tableted, be placed in a
hard gelatin capsule in powder, be in regular or sustained
release pellet form, or be in the form of a troche or
lozenge. The amount of solid carrier can be varied widely
but preferably it will be from about 25 mg to about 1 g. If
a liquid carrier is used, the compositions wi' usualy be
in the form of a syrup, emulsion, soft gelatin capsule,
sterile injectable liquid, such as in an ampoule, or be an
aqueous or nonaqueous liquid suspension.
The pharmaceutical compositions can be made follow-
ing the conventional techniques of the pharmaceutical
chemist involving mixing, granulating and compressing, when
necessary, or variously mixing and dissolving the ingre-
dients as appropriate to give the desired end product.

An improvement in abnormal cardiovascular conditions
can be effected by inducing renal vasodilatation, antihyper-
tensive effects and bradycardia activity by administering
orally or parenterally to a subject in need of such activity
a compound of Formula I or a pharmaceutically acceptable
acid addition salt thereof, usually combined with a pharma-
25 ceutical carrier, in a nontoxic amount sufficient to produce
said activity as described above. The route of administra-
can be any route which effectively transports the
active compound to the cardiovascular system receptors which
are to be stimulated, for example orally or parenterally.
the oral route being preferred. The parenteral administra-
tion can be subcutaneous or intravenous. Advantageously,
equal oral doses within the ranges given above will be
administered several times, such as from one to five times a
day, with the daily dosage regimen in general being selected
from about 25 mg to about 1.0 g, preferably 75-500 mg, for
oral dosage units. When the method described above is
carried out, a dopaminergic activity is produced. For an
average size human for the preferred species (A) a preferred
oral dose to show antihypertensive activity would be
selected from the range of from about 100-250 mg of base for
each dosage unit adapted for oral administration to be
administered from 1-5 times daily.

The following Examples illustrate the preparation
of compounds of this invention. The temperatures are
Centigrade.

EXAMPLE 1

A solution of 50.0 g (0.331 mole) of p-methoxyphen-
ethylamine in 500 ml of dichloromethane was cooled to 0°C
under an argon atmosphere. A solution of 93.6 ml (0.664
mole) of trifluoroacetic anhydride in 60 ml of dichloro-
methane was added dropwise. The reaction mixture was
stirred at 0°C for 1/2 hour then at room temperature for
1-1/2 hours. The volatiles were removed and toluene was
added to the residue which was then evaporated. The residue
was crystallized from 800 ml of 1:1 ether-petroleum ether to
give 55.8 g (68.2%) of a first crop of (2-trifluoroacet-
amidoethyl)-4-methoxybenzene as white needles, m.p. 84.0°C.
Concentration of the mother liquors and recrystallization in
1:1 ether-petroleum ether afforded a second crop of off-
white solid, 16.6 g (20.2%), m.p. 82.5-84.0°C.

To a solution of 30 g (0.121 mole) of this amide in
254 ml of trifluoroacetic acid at 0°C under an argon
atmosphere was added dropwise with stirring a solution of
7.5 ml (0.12 mole) of conc. nitric acid in 56 ml of tri-
fluoroacetic acid. The reaction mixture was stirred at 0°
for 1/2 hour and at room temperature for 2 hours. The sol-
vents were evaporated. The residue was dissolved in ethyl
acetate which was extracted with 5% hydrochloric acid,
dilute sodium bicarbonate solution and brine, then dried
over anhydrous magnesium sulfate and activated charcoal.
After filtering, the solvents were removed to give 34.8 g
(98%) of crude (2-trifluoroacetamidoethyl)-3-nitro-4-methoxy-
benzene which was an amber-colored solid. This material was
recrystallized from 400 ml of 1:3 ethyl acetatehexane to
give 25.3 g (71.5%) of the product, m.p. 92.5-93.0°.
The mother liquors were concentrated and recrystallized to
give a second crop, 4.59 g (13%), m.p. 90-92°C.

A 50.0 g (0.17 mole) sample of this nitroanisole
was hydrogenated in 8-10 g batches using approximately 1.3 g
of 10% palladium-on-carbon and 250 ml of absolute ethanol
per batch. The hydrogenations were carried out at room tem-
perature and 50-55 p.s.i. hydrogen for 1/2 to 1 hr. The
crude amine was obtained after filtration of the hydrogrena-
tion mixtures and evaporation of solvents.

A mixture of 940 ml of distilled water and 11.5 ml
(0.207 mole) of conc. sulfuric acid under an argon atmo-
sphere was combined with the total crude amine from above
followed by 29.1 g (0.176 mole) of chloral hydrate, 87.5 g
(0.533 mole) of hydroxylamine sulfate, and 240 ml distilled
water. The mixture was heated rapidly to reflux and was
allowed to reflux for 4 minutes, then allowed to cool to
room temperature. The solid precipitate was separated and
washed with 1 liter of cold water and allowed to dry in the
air. This solid material was dissolved in hot ethyl acetate
and clarified with activated charcoal. Filtration and the
addition of hexane at reflux caused recrystallization which
gave 27.5 g (50%) of the oxime, m.p. 197-198°. A second
crop was obtained from the mother liquors, 9.9 g (13%), m.p.
192-195°.
A 50 ml portion of conc. sulfuric acid was heated with stirring under argon in an oil bath maintained at 80°. To this was added in one portion 5.0 g (0.015 mole) of the oxime. After all the solid had mixed into the sulfuric acid, the reaction was allowed to continue for 6 minutes, at which time the reaction mixture was poured onto 500 ml of ice. The aqueous solution was extracted with several 200 ml portions of ethyl acetate which were combined and washed with sodium bicarbonate solution, brine and then dried over anhydrous magnesium sulfate. The dried solution was filtered through 200 g of silica gel and evaporated to give 3.05 g (64%) of 4-trifluoroacetamidoethyl-7-methoxyisatin as a red solid, m.p. 234-237°. Recrystallization from ethyl acetate gave material with m.p. 236.5-238.5°.

A mixture of 23.9 g (0.076 mole) of the isatin, 28.0 ml (0.32 mole) of ethanedithiol and 700 ml anhydrous dichloromethane was stirred at room temperature under argon while 6.3 ml (0.051 mole) of freshly distilled boron trifluoride etherate was added. This reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.). The reaction mixture was stirred at room temperature overnight (16 hours). After this time an additional 1.0 ml (0.008 mole) of boron trifluoride etherate was added and stirring was continued until thin layer chromatographic analysis indicated that all of the starting material had reacted (about 7 hrs.).
A 20.0 g (0.051 mole) portion of this thioketal was reduced in two batches one of 15 g and the other of 5 g. In the 15 g run, approximately 120 g of Raney nickel and 750 ml of absolute ethanol were used. In the 5 g run the amounts were proportional - 40 g of Raney nickel and 250 ml of ethanol.

The thioketal was partially dissolved in approximately one-fifth of the total amount of ethanol and was stirred at room temperature under argon. To this was added the Raney nickel along with the remaining ethanol. The reaction mixture was stirred at room temperature until analysis indicated starting material had reacted (2 hrs.). Filtration, copious washing with ethanol, and evaporation gave a crude residue which was taken up in ethyl acetate and extracted with 3 N hydrochloric acid, water, bicarbonate solution, brine and then finally dried over anhydrous magnesium sulfate-active charcoal. Evaporation of the solvents gave a crude residue which was chromatographed on 500 g of silica gel (70-230 mesh). Elution with 10% ethyl acetate-methylene chloride removed most of the colored impurities and 20-50% ethyl acetate-methylene chloride removed the product. Evaporation of the solvents afforded 12.7 g (82%) of 4-(2-trifluoroacetamidoethyl)-7-methoxy-2(3H)-indolone, m.p. 175-178°. A more careful chromatography gave material with m.p. 178-179°.

A mixture of 8.0 g (0.026 mole) of the indolone, 59 ml of 6.0 N hydrochloric acid, and 117 ml of absolute ethanol was degassed, filled with argon, and stirred in an oil bath maintained at 90° for ca. 10 hours until analysis indicated no starting material remained. The solvents were removed and the orange solid residue was triturated with ethyl acetate to give 5.56 g (87%) of 4-(2-aminoethyl)-7-methoxy-2(3H)-indolone hydrochloride as a light-orange solid. This material was recrystallized from methanol-ethyl acetate to give an analytically pure sample of the product, m.p. 258-260.5°.
Example 1

Anal. Calcd. for $C_{11}H_{14}N_2O_2\cdot HCl \cdot 1/2 H_2O$:

C, 52.49; H, 6.41; N, 11.13. Found: C, 52.66; H, 6.44; N, 10.76.

Example 2

Sufficient quaternary ammonium polystyrene anion exchange resin ("Amberlite 400", made basic by ashing with 1 N sodium hydroxide solution and water) was added to a solution of 0.968 g (4.0 mmole) of the hydrochloride product of Example 1 to give a pH of 9.8. The resin was separated by filtration and then washed with water. The aqueous washes were evaporated to give the free base. This base along with 0.425 g of 10% palladium-on-carbon was suspended in 51 ml of glacial acetic acid containing 2.6 ml (0.035 mole) of propionaldehyde and hydrogenated at room temperature and 55 p.s.i. of hydrogen for one hour. The catalyst was separated and washed with acetic acid. Evaporation of the solvents gave a residue which was dissolved in methanol and treated at 0°C with a solution of methanolic hydrogen bromide. After several minutes the solvents were removed and the residue was chromatographed on 50 g of silica gel with elution with 4% methanol-chloroform to give 0.439 g of crude tertiary amine. This crude material was dissolved in chloroform to remove residual silica gel. After evaporating the chloroform, the resulting residue was recrystallized from methanol-ethyl acetate to afford 0.311 g (21%) of 4-(2-di-n-propylaminoethyl)-7-methoxy-2(3H)-indolone hydrobromide, m.p. 222-223°C.

Anal. Calc'd for $C_{17}H_{26}N_2O_2\cdot HBr$: C, 54.33; H, 7.38; N, 7.45. Found: C, 54.28; H, 7.12; 7.48.

In an identical reaction sequence the residue after hydrogenation was treated with ethereal hydrochloric acid. The crude hydrochloride salt (2.2 g) was chromatographed on 40 g silica gel and eluted with 10% methanol-chloroform. After the chloroform trituration, the resulting residue was recrystallized twice from methanol-ether to give 0.346 g (26%) of the hydrochloride salt, m.p. 231-234°C.
Anal. Calc'd for C_{17}H_{26}N_{2}O_{2} HCl: C, 62.47; H, 8.33; N, 8.57. Found: C, 62.51; H, 8.68; N, 8.62.

The hydrochloride salt (100 mg) is mixed with 200 mg of lactose and 2 mg of magnesium stearate, filled into a hard gelatin capsule and administered orally to a hypertensive patient from 2-5 times daily.

EXAMPLE 3

A 0.284 g (0.765 mmole) portion of 4-(2-di-n-propylaminoethyl)-7-methoxy-2(3H)-indolone hydrobromide was placed in a flask and approximately 5 ml of constant boiling hydrobromic acid was distilled (from stannous chloride) directly into the flask. The resulting mixture was stirred at reflux under an argon atmosphere for 3 hours. Evaporation of the solvents produced a solid residue which was recrystallized twice from methanol-ethyl acetate to provide 0.206 g of 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide. m.p. 252-254°.

Anal. Calc'd for C_{16}H_{24}N_{2}O_{2} HBr: C, 53.79; H, 7.05; N, 7.84. Found: C, 53.98; H, 7.00; N, 7.78.

This salt (75 mg) is mixed with 225 mg of lactose and 2 mg of magnesium stearate, then filled into a hard gelatin capsule. One capsule is administered orally to patients for treatment of high blood pressure from 1-5 times daily.

The hydrobromide salt (750 mg) is converted to the base as described in Example 2. The base (400 mg) is treated with an excess of methanesulfonic acid in isopropanol and isolated by evaporation and trituration with ether to give the methanesulfonic acid salt. The hydrochloride salt is similarly prepared.

EXAMPLE 4

A 10 ml portion of constant boiling hydrobromic acid (48%) was dissolved from stannous chloride directly into the reaction vessel. To this was added 0.533 g (1.76 mmole) of 4-(2-aminoethyl)-7-methoxy-2(3H)-indolone hydrobromide and the reaction mixture was stirred at reflux under
argon for 3 hours, then allowed to cool to room temperature. After being stored at 0°C overnight, the reaction mixture was filtered. The solid was washed with cold methanol to give 0.40 g (83%) of 4-(2-aminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide as a straw-brown solid. This material began to decompose with darkening at 250°C.

Anal. Calc’d for C_{10}H_{12}N_{10}O_{2} HBr: C, 43.98, H, 4.80; N, 10.26. Found: C, 43.88; H, 4.86; N, 10.46.

This compound (200 mg) is mixed with 150 mg of lactose and 2 mg of magnesium stearate, filled into a hard gelatin capsule and administered orally 3 times per day to a patient suffering from cardiovascular disorders caused by renal dysfunction.

**EXAMPLE 5**

Using 65 g of p-methoxybenzylamine for the starting material of Example 1 gives 4-aminoethyl-7-methoxy-2(3H)-indolone hydrochloride. This material (2 g) is converted to the base and alkylated using 1 mole equivalent of isovaleraldehyde as in Example 2 to give 4-isopentylaminomethyl-7-methoxy-2(3H)-indolone hydrobromide and 4-isopentylaminomethyl-7-hydroxy-2(3H)-indolone hydrobromide after demethylation using boron tribromide in methylene chloride at -20°C.

Using 50 g of p-methoxyphenylpropylamine for the starting material of Example 1 gives 4-(3-aminopropyl)-7-methoxy-2(3H)-indolone hydrochloride. This material (3 g) is converted to the base and alkylated using methyl formate-formaldehyde at reflux to give 4-(3-dimethylaminopropyl)-7-methoxy-2(3H)-indolone hydrochloride and, after treatment with boron tribromide in methylene chloride at -20°C, 4-(3-dimethyl-aminopropyl)-7-hydroxy-2(3H)-indolone hydrobromide.

**EXAMPLE 6**

Using the method of Example 2, but one mole of propionaldehyde in the reductive alkylation procedure, gives 4-n-propylaminoethyl-7-methoxy-2(3H)-indolone. Hydrolysis with an excess of 48% hydrobromic acid at reflux gives 4-n-propyl-aminoethyl-7-hydroxy-2(3H)-indolone hydrobromide.
4-Aminoethyl-7-methoxy-2(3H)-indolone (5 g) is reacted with two mole equivalents of allyl bromide and 4 mole equivalents of triethylamine in acetonitrile at mild heat for several hours. The mixture is then evaporated. The residue is suspended in water. The mixture is extracted with ethyl acetate. The extract is washed, dried and evaporated to give 4-di-N-allylaminoethyl-7-methoxy-2(3H)-indolone. Treatment of an aliquot of the base with methanesulfonic acid in ether-ethanol gives 4-di-N-allylaminoethyl-7-methoxy-2(3H)-indolone methanesulfonic acid salt.

Using this compound as the base in the boron tribromide demethylation procedure described above gives 4-di-N-allylaminoethyl-7-hydroxy-2(3H)-indolone hydrobromide.

Using 4-n-propylaminoethyl-7-methoxy-2(3H)-indolone (20 g) with one mole equivalent of allyl bromide and two equivalents of triethylamine gives 4-N-allyl-N-propylaminoethyl-7-methoxy-2(3H)-indolone base and the hydrochloride salt. The base is treated with boron tribromide to give 4-N-allyl-N-propylaminoethyl-7-hydroxy-2(3H)-indolone base and hydrobromide.
Claims

1. A compound of the structural formula:

\[
\begin{align*}
\text{R} & \quad (\text{CH}_2)^n \\
\text{H} & \quad \text{N}
\end{align*}
\]

in which \( R \) is amino, lower (C\(_1\)-C\(_6\)) alkylamino, di-lower (C\(_1\)-C\(_6\)) alkylamino, di-N-allylamino, or N-allyl-N-lower (C\(_1\)-C\(_6\)) alkylamino; \( R^1 \) is hydroxy or methoxy; and \( n \) is an integer from 1-3; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, in which \( R^1 \) is hydroxy.

3. A compound according to claim 1, in which \( R^1 \) is hydroxy and \( R \) is di-n-propylamino, di-N-allylamino or N-allyl-N-propylamino.

4. 4-(2-Di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone in the form of a pharmaceutically acceptable acid addition salt thereof.

5. 4-(2-Di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide.

6. 4-(2-Di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone as the base.

7. 4-(2-Di-n-propylaminoethyl)-7-methoxy-2(3H)-indolone or a pharmaceutically acceptable acid addition salt thereof.

8. 4-(2-Di-N-allylaminoethyl)-7-hydroxy-2(3H)-indolone or a pharmaceutically acceptable acid addition salt thereof.
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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the structural formula:

\[
\begin{align*}
\text{R} & \quad (\text{CH}_2)^n \\
\text{H} & \\
\text{O} & \\
\text{H} & \\
\text{R} & \\
\end{align*}
\]

in which R is amino, lower (C₁-C₆) alkylamino, di-lower (C₁-C₆) alkylamino, di-N-allylamino or N-allyl-N-lower (C₁-C₆) alkylamino; R² is hydroxy or methoxy; and n is an integer from 1-3; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, in which R¹ is hydroxy.

3. A compound according to claim 1, in which R¹ is hydroxy and R is di-n-propylamino, di-N-allylamino or N-allyl-N-propylamino.

4. 4-(2-Di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone in the form of a pharmaceutically acceptable acid addition salt thereof.

5. 4-(2-Di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide.

6. 4-(2-Di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone as the base.

7. 4-(2-Di-n-propylaminoethyl)-7-methoxy-2(3H)-indolone or a pharmaceutically acceptable acid addition salt thereof.

8. 4-(2-Di-N-allylaminoethyl)-7-hydroxy-2(3H)-indolone or a pharmaceutically acceptable acid addition salt thereof.
9. 4-(2-Aminoethyl)-7-hydroxy-2(3H)-indolone or a pharmaceutically acceptable acid addition salt thereof.

10. A process for preparing a compound according to any of the preceding claims which comprises removing the protecting group from a compound of formula

![Chemical structure]

(Where n is as defined in claim 1 and R³ is a protecting group) and if desired subsequently converting the 4-position aminoalkyl group produced into a different group of formula -(CH₂)ₙR², and/or demethylating the methoxy group at the 7-position.

11. A pharmaceutical composition comprising a compound according to any of claims 1 to 9 and a pharmaceutical carrier.

12. Compounds of the formula stated in Claim 1, methods for their manufacture and pharmaceutical compositions containing them, substantially as hereinbefore described with reference to the Examples.

13. The steps or features disclosed herein or any combination thereof.

DATED this 22nd day of February, 1982
SMITHKLINE CORPORATION
By its Patent Attorneys
DAVIES & COLLISON.