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Method to treat chronic heart failure and/or elevated cholesterol levels using
3,5-diiodothyropionic acid and method to prepare same

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(54) Title: METHOD TO TREAT CHRONIC HEART FAILURE AND/OR ELEVATED CHOLESTEROL LEVELS USING 3,5-DIIODOTHYROPROPIONIC ACID AND METHOD TO PREPARE SAME

(57) Abstract: Applicant's invention includes a method to treat a patient having congestive heart failure by administering a therapeutically effective amount of 3,5-diiodothyropropionic acid. Applicants' invention further includes a method to lower cholesterol blood levels of a patient by administering a therapeutically effective amount of 3,5-diiodothyropropionic acid. Applicants' invention further includes a synthetic method to prepare 3,5-diiodothyropropionic acid.

1 **METHOD TO TREAT CHRONIC HEART FAILURE AND/OR ELEVATED**
2 **CHOLESTEROL LEVELS USING 3,5-DIIODOTHYROPROPIONIC ACID**
3 **AND METHOD TO PREPARE SAME**

3 **Field Of The Invention**

4 The present invention relates to a treatment for patients having congestive heart
5 failure and/or elevated cholesterol blood levels by administering a therapeutically
6 effective amount of 3,5-Diiodothyropropionic acid. The present invention further relates
7 to a synthetic method to prepare 3,5-Diiodothyropropionic acid.

7 **Background Of The Invention**

8 Congestive heart failure continues to be a major health problem, affecting
9 about 4.6 million people in the United States, and its prevalence is predicted to
10 increase over the next several decades. The magnitude of heart failure as a clinical
11 problem has placed emphasis on the need to develop new treatment strategies.

11 One approach that has emerged is the use of thyroid hormone, which has
12 unique physiologic and biochemical actions that make it a novel and potentially useful
13 agent for treatment of heart failure. Thyroid hormone has been shown to act at the
14 transcriptional level on the content of myocardial calcium cycling proteins to
15 stimulate calcium uptake by sarcoplasmic reticulum. In addition, thyroid hormone
16 causes a reciprocal shift in cardiac myosin heavy chain (MHC) isoform expression,
17 increasing the expression of the high activity V₁ isoform and decreasing the low
18 activity V₃ form. These biochemical alterations may underlie the ability of thyroid
19 hormone to increase the rates of ventricular pressure development and relaxation.

20 Thyroid hormones include the L-forms of thyroxine (3,5,3',5'-L-thyronine;
21 hereinafter thyroxine or T₄) and triiodothyronine (3',3,5-L-triiodothyronine; hereinafter
22 triiodothyronine or T₃). 3',5',3-L-Triiodothyronine (hereinafter Reverse T₃ or r T₃), is
23 a normal metabolite of T₄. T₄ is synthesized in the thyroid gland and is the circulating
24 form of hormone found in plasma. Although small amounts of T₃ are synthesized by
25 the thyroid gland, the majority is formed from the metabolism of thyroxine in
26 peripheral tissues by the enzyme 5'-monodeiodinase. The molecular basis for the
27 actions of thyroid hormones is thought to be mediated through the binding of T₃ to
28 chromatin-bound nuclear receptors. There are two major subtypes of the thyroid
29 hormone receptor, TR α and TR β , which are the products of two different genes.

1 These genes are members of the *c-erbA* protooncogene family and are related to a
2 large number of steroid and peptide hormone receptors collectively known as the
3 steroid-thyroid hormone superfamily. The TR α and β subtypes are differentially
expressed in various tissues.

4 Thyroxine, synthesized by methods such as described in U.S. Pat. No.
5 2,803,654, is the principle thyroid hormone in current clinical use. This is largely
6 because of its long half-life of 6-7 days. Triiodothyronine, which is less strongly
7 bound to plasma proteins and has a more rapid onset of action, is available for
intravenous administration. However, T₃ has a relatively short half-life of two days or
8 less.

9 Numerous studies have been carried out to synthesize thyroid hormone
10 analogs that mimic the actions of the natural hormones. The objective of most of
11 these efforts has been to develop thyromimetics that lower plasma cholesterol without
adverse cardiac effects. A series of thyroxine analogs and methods of synthesis are
12 described in U.S. Pat. No. 3,109,023.

13 Thyroid hormone agonists that are highly selective for the thyroid hormone
14 receptor β subtype are described in U.S. Pat. No. 5,883,294. U.S. Pat. No. 5,284,971
15 describes a class of thyromimetics, which have the distinguishing characteristic of a
sulfonyl bridge in the diphenyl core.

16 A more recent development has been the use of thyroid hormones for the
17 treatment of cardiovascular compromise. A method for the treatment of patients with
18 sudden (acute) cardiovascular compromise by administration of thyroid hormone is
described in U.S. Pat. No. 5,158,978. The method teaches administration of T₄ and T₃
19 after cardiac arrest by injection into a vein, a central venous catheter, into the
pulmonary circulation or directly into the heart.

20 Short-term intravenous administration of T₃ to patients with advanced
21 congestive failure has been shown to improve cardiac output and decrease arterial
22 vascular resistance. Oral administration of L-thyroxine also has been shown to
23 improve cardiac performance and exercise capacity in patients with idiopathic dilated
cardiomyopathy when given for two weeks and 3 months. Although the number of
24 patients in these studies was small, the results were generally favorable and

1 established the basis for further investigation into the safety and potential benefits of
2 treatment of heart failure with thyroid hormone or thyroid hormone analogs.

3 Because of potential adverse effects of thyroid hormone, such as metabolic
4 stimulation and tachycardia, what is required are thyroid hormone analogs with fewer
5 undesirable side effects. Applicants have found that 3,5-Diiodothyropropionic acid
6 (DITPA) is a thyroid hormone analog that increases cardiac performance with
7 approximately half of the chronotropic effect and less metabolic stimulation than L-
8 thyroxine. Like thyroid hormone, DITPA binds to nuclear T₃ receptors of the c-erbA
9 proto-oncogene family. DITPA has been shown to improve left ventricular (LV)
10 performance in post-infarction experimental models of heart failure when
11 administered alone or in combination with an angiotensin I-converting enzyme
12 inhibitor.

13 In addition to its well-known chronotropic and inotropic actions on the heart,
14 thyroid hormone decreases arterial resistance, venous resistance and venous
15 compliance. The net effect of these changes is to increase cardiac output more than
16 arterial pressure, resulting in decreased calculated arterial vascular resistance. When
17 used in experimental models of heart failure DITPA acts similarly to thyroid
18 hormone, affecting both the heart and the peripheral circulation. Loss of the normal
19 increase in contractility with heart rate, referred to as the positive force-frequency
20 relationship, has been reported both in failing human myocardium and in animal
21 models of heart failure. DITPA administration prevents the flattened contraction-
22 frequency relationship in single myocytes from infarcted rabbit hearts. DITPA
23 improves myocyte function, enhances calcium transport in the sarcoplasmic reticulum
24 (SR) and prevents the down regulation of SR proteins associated with post-infarction
heart failure in rabbits. In normal primates, DITPA enhances the *in vivo* force-
frequency and relaxation-frequency relationships in a manner similar to thyroid
hormone. DITPA is able to bring about these hemodynamic changes without
increasing cardiac mass appreciably or adversely affecting ventricular dimensions. A
morphometric analysis indicates that in post-infarction rats treated with DITPA there
is an increase in capillary growth in the border zone around the infarct.

24

1 Summary of the Invention

2 Applicants have found that 3,5-Diiodothyropropionic acid (DITPA) is a
3 thyroid hormone analog that increases cardiac performance with approximately half
4 of the chronotropic effect and less metabolic stimulation than L-thyroxine. Like
5 thyroid hormone, DITPA binds to nuclear T₃ receptors of the c-erbA proto-oncogene
6 family. DITPA has been shown to improve left ventricular (LV) performance in post-
infarction experimental models of heart failure when administered alone or in
combination with an angiotensin I-converting enzyme inhibitor.

In addition to its well-known chronotropic and inotropic actions on the heart, thyroid hormone decreases arterial resistance, venous resistance and venous compliance. The net effect of these changes is to increase cardiac output more than arterial pressure, resulting in decreased calculated arterial vascular resistance.

When used in experimental models of heart failure DITPA acts similarly to thyroid hormone, affecting both the heart and the peripheral circulation. Loss of the normal increase in contractility with heart rate, referred to as the positive force-frequency relationship, has been reported both in failing human myocardium and in animal models of heart failure. DITPA administration prevents the flattened contraction-frequency relationship in single myocytes from infarcted rabbit hearts. In normal primates, DITPA enhances the *in vivo* force-frequency and relaxation-frequency relationships in a manner similar to thyroid hormone. DITPA is able to bring about these hemodynamic changes without increasing cardiac mass appreciably or adversely affecting ventricular dimensions. A morphometric analysis indicates that in post-infarction rats treated with DITPA there is an increase in capillary growth in the border zone around the infarct.

19 A dose-ranging study of DITPA was performed in seven normal volunteers.
20 After establishing that the drug was well tolerated, a double-blind comparison of the
21 effects of DITPA versus placebo was carried out in 19 patients with congestive
failure.

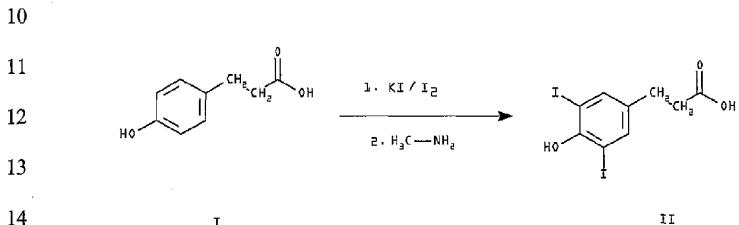
22 Detailed Description Of The Preferred Embodiments

23 In overview, DITPA was synthesized following good manufacturing
24 procedures by coupling dianisoleiodium trifluoroacetate with ethyl-3-(3',5'-diido-4'-
hydroxyphenyl)-propionate followed by removal of the methyl and ethyl protective

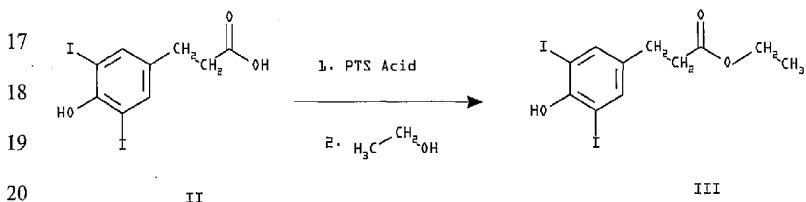
1 groups. This coupling strategy does not produce T₃ or T₄ as by products because the
2 compound giving rise to the outer ring does not contain iodine and the side chain of
3 the inner ring reactant lacks an amino group.

4 The structure of the DITPA prepared using this synthetic route was
5 authenticated by proton magnetic resonance and its purity was checked by reverse
6 phasic HPLC. The principle impurity was identified as the ethyl ester of DITPA.
Only batches of the final compound with greater than 95% purity were used in this
study.

7 Applicants' synthesis of DITPA uses 3-(4-hydroxyphenyl)-propionic acid,
8 compound I shown below, as a starting material. In a first synthetic step, compound I
9 is reacted with potassium iodide / iodine, and then with methylamine, to form 3-(3,5-
diiodo-4-hydroxyphenyl)propionic acid, compound II.

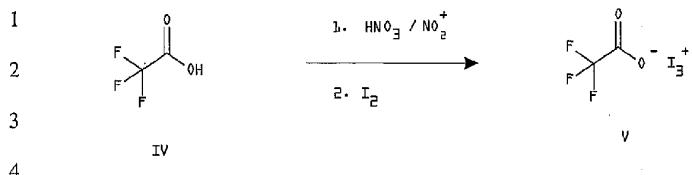


17 Compound II is next reacted with ethanol, using p-toluenesulfonic acid as a catalyst,
18 to form ethyl-3-(3,5-diiodo-4-hydroxyphenyl)propionate, compound III.

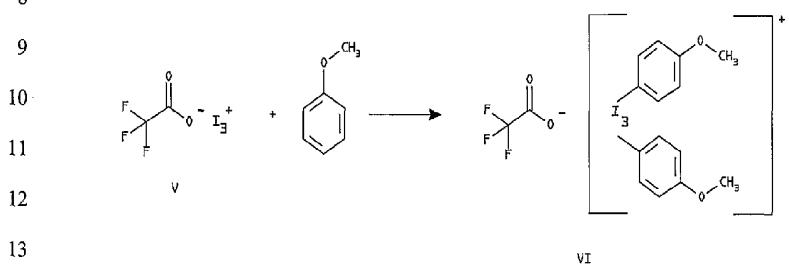


25 Compound III is subsequently reacted with coupling agent dianisoleiodonium
26 trifluoroacetate.

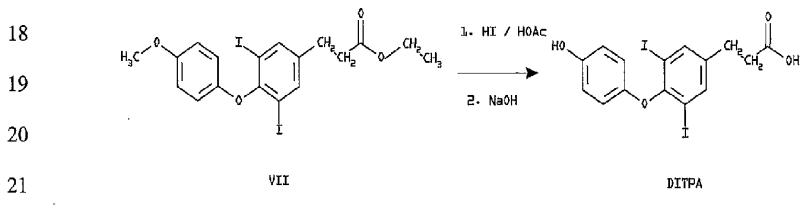
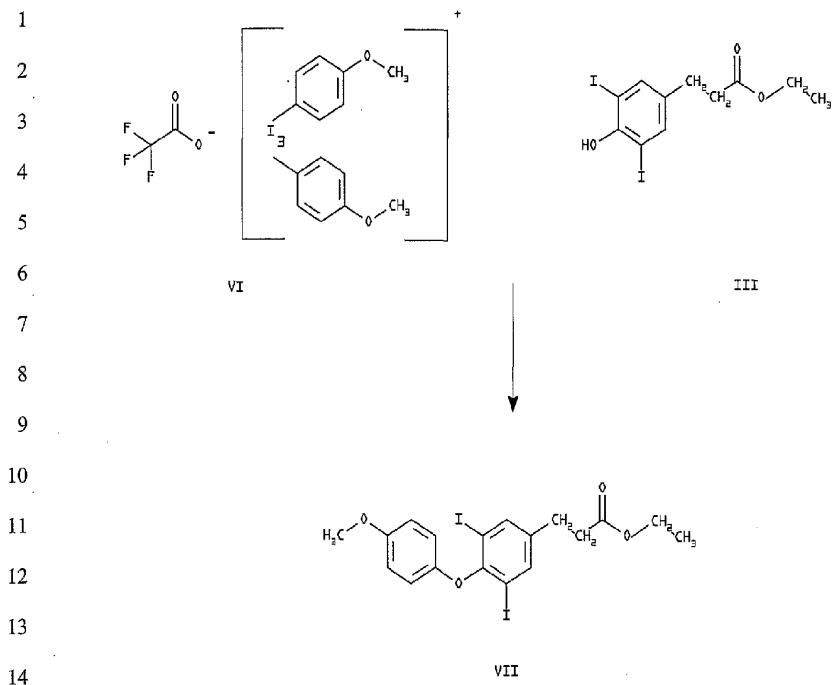
27 Coupling agent dianisoleiodonium trifluoroacetate is prepared by first reacting
28 trifluoroacetic acid, compound IV, with red fuming nitric acid and iodine to form
29 iodine(III)trifluoroacetate, compound V.



5 In a subsequent step, compound V is reacted with anisole, i.e. methoxybenzene, to
6 form dianisoleiodonium trifluoroacetate, compound VI. Applicants use
7 trifluoroacetate as the counterion in compound VI because use of other counterions
8 results in compounds that are more hygroscopic, and therefore, likely have limited
shelf lives.



15 Ethyl-3-(3,5-diiodo-4-hydroxyphenyl)propionate, compound III, is next
16 reacted with dianisoleiodonium trifluoroacetate, compound VI, to form ethyl-3-(4'-
methoxy-3,5-diiodothyro)propionate, compound VII.



1

EXAMPLE 1

2

Synthesis of 3-(3,5-diiodo-4-hydroxyphenyl)propionic acid

3

Step 1: Weigh out 50 g of KI. Transfer to the pressure equalizing dropping funnel with a closed stopcock and add 60 ml of H₂O and swirl until the salt is dissolved.

5

Weigh 52 g of I₂ and add to the dropping funnel, swirl until completely dissolved. Add 90 ml of H₂O (total of 150 ml) and stopper the dropping funnel. Place in a

7

secure location and go on to step 2.

8

Step 2: Weigh 16.2 g of 3-(4-hydroxyphenyl)-propionic acid and transfer into a 1.0 liter round bottom flask.

10

Add a magnetic stir bar, 100 ml of 40% aqueous methylamine and 100 ml of H₂O. Stopper the flask.

11

Clamp the flask above the magnetic stirrer and stir at a controlled rate until everything dissolves.

12

Step 3: Remove the stopper and replace it with the dropping funnel. Open the stopcock so that the iodine solution drips into the round bottom flask during a period of approximately 20 minutes. Allow the reaction to stir for 10 minutes after the addition is complete.

16

Step 4: Filter the reaction mixture, then pour into a 1 liter beaker and acidify with 2 N HCl (approximately 440 ml). Filter the resulting precipitate and rinse with cold H₂O. Cover the product with a piece of filter paper and dried overnight with suction.

20

Step 5: Recrystallize the product from ethanol. The ethanol has significant amounts of monoiiodinated compound. Determine the product weight and melting point.

23

24

1

EXAMPLE 2

2

Synthesis of Ethyl-3-(3,5-diido-4-hydroxyphenyl)propionate

3

4 Step 1: Weigh 100 g of 3-(3,5-diido-4-hydroxyphenyl)
5 propionic acid, transfer into a 500 ml round bottom
6 flask, and add a magnetic stir bar. Add 15 ml of
7 absolute ethanol and mix. Add 2.0 g of p-
8 toluenesulfonic acid and then 150 ml of chloroform.
9 Clamp the round bottom flask and place in the oil bath,
10 but do not turn on the heat. Set up an Allihn condenser
11 and a complete distillation assembly with a condenser to
12 be cooled with recirculating ice water.

13 Step 2: With the recirculating pump running and a
14 bucket of extra ice near by turn on the oil bath (setting
15 40 on the Variac). Adjust the Variac setting so that the
16 distillation proceeds slowly (the total time for this
17 esterification is 6-8 hours). After collecting 100 ml
18 (approximately 2 hours) add an additional 15 ml of
19 absolute ethanol and 100 ml of chloroform. When the
20 next 100 ml is collected add chloroform only and
21 continue to distill off the chloroform. When it is
22 believed that the amount of chloroform that remains is
23 not great turn off the Variac and allow the flask to cool.
24 Step 3: Add enough chloroform to bring the total
 volume to 100 ml. Transfer to a separatory funnel with
 the stopcock closed. Extract with an equal volume of a
 saturated sodium bicarbonate solution. Repeat the
 extraction with sodium bicarbonate and then extract
 with H₂O. Dry over calcium chloride powder.
 Reassemble the distillation assembly without the reflux

1 column. After adding dry ice to the trap, remove the
2 remaining chloroform under low pressure.

3 Step 4: Collect and weigh the product.

4 **EXAMPLE 3**

5 **Synthesis of Iodine(III)trifluoroacetate**

6 Step 1: In the hood, pour 14 ml of acetic anhydride into a
7 250 ml round bottom flask and cool to about -15°C (dry ice
8 and isopropyl alcohol). While stirring with a magnetic stir
9 bar, carefully add 5.4 ml of red fuming nitric acid (90%, sp.
10 gr. 1.51). Remove the round bottom flask from the dry
11 ice/isopropanol bath. Weigh out 5.0 g iodine and, with the
12 temperature below 20 °C, add the iodine to the round bottom
13 flask together with 9.4 ml of trifluoroacetic acid. Stir the
14 mixture for one-half hour. As the iodine dissolves, nitrous
15 oxide is generated and the temperature increases to 40-45 °C.
16 If the production of nitrous oxide continues, the iodine is still
17 reacting.

18 Step 2 If necessary, flush out the remaining nitrous oxide
19 with N₂ gas and then set up for low pressure distillation.
20 With the pot temperature below 40 °C, reduce the solution to
21 a dark viscous oil of iodine(III)trifluoroacetate.

22 **EXAMPLE 4**

23 **Synthesis of Dianisoleiodonium trifluoroacetate**

24 Step 1: Dissolve the iodine(III)trifluoroacetate in 30 ml of
25 acetic anhydride. Cool to -10 °C and hold the temperature
26 while adding a solution containing 17.4 ml anisole, 70 ml
27 acetic anhydride, and 10 ml trifluoroacetic acid over 20
28 minutes. Stopper the flask and store in the refrigerator

1 overnight and then allow 3 hours to come to room
2 temperature.
3 Step 2: Vacuum distill at the lowest temperature practical.
4 A thick dark oil will remain. Note: Caution must be used
5 when adding to the acid waste from the trap or the receiving
6 flask as the reactive anhydride will rapidly and vigorously
7 react with an aqueous solution. Add diethyl ether to the oil.
8 After approximately 400 ml a precipitate appears.
9 Step 3: Filter the precipitate and wash with ice cold dry
10 diethyl ether to give the crude dianisoleidonium
11 trifluoroacetate. Recrystallize from toluene to give white
 fcathery needles (mp 134-136 °C). Weigh the product. Save
 some of the product for NMR, if necessary, or a melting
 point determination.

12 **EXAMPLE 5**

13 **Synthesis of Ethyl-3-(4'-methoxy-3,5-**
14 **diiodothyro)propionate**

15 Step 1: Weigh out and combine in a 250 ml round bottom
16 flask 0.1 mole of the ethyl-3-(3,5-diido-4-hydroxyphenol)
17 propionate, 50 ml of methanol with 1.5 ml of triethylamine,
18 and 0.1 g of untarnished metallic copper powder. Add 5.9 g
19 of the dianesoleidonium trifluoroacetate to 70 ml of
20 methanol and then add this mixture to the round bottom
 flask. A stirring bar is added, the flask stoppered and stirred
 at room temperature for 24 hours.
21 Step 2: Filter to remove unreacted copper. Under reduced
22 pressure, remove the methanol to yield a syrup. Dissolve in
23 toluene. Add 1 N HCl and shake for 5 minutes. A large
24 amount of triethylamine will precipitate and must be
 removed by filtration. Wash the organic layer in the

1 separatory funnel with 10% NaOH and the with H₂O. The
2 organic phase is dried over sodium sulfate. Under low
3 pressure the toluene is remove to leave the product.
4 Step 3: Weigh the product and prepare a sample for NMR
5 and or HPLC analysis.

5 **EXAMPLE 6**
6 **Synthesis of DITPA**

7 Step 1: Weigh out 50 g of the coupled product and transfer
8 it to a round bottom flask. Add 100 ml of HI and 100 ml of
9 glacial acetic acid. Blanket with a very slow stream of CO₂.
10 Reflux for 5-6 hours and add 100 ml of HI, and reflux
11 overnight.

12 Step 2: Remove most of the acid with reduced pressure
13 distillation. Add 200 ml of H₂O and adjust the pH to 5 with
14 1 N NaOH. The precipitate is collected by filtration. The
15 filtrate is washed with ice cold H₂O and dried under a
16 blanket of CO₂.

17 Step 3: Recrystallize the product from ethanol. Prepare a
18 sample for NMR analysis and melting point determination.

19 Step 4 Store the final product in a desiccator below 0 °C in a
20 freezer that is locked and has limited access.

21 Prior to administration to either human patients, or to animals, DITPA may be
22 further compounded with one or more ingredients selected from the group consisting
23 of a carrier, a stabilizer, an excipient, a solubilizer, an antioxidant, a pain-alleviating
24 agent, an isotonic agent, and combinations thereof.

25 DITPA may be formulated in various ways such as liquid preparations, solid
26 preparations, capsule preparations, implant preparations and the like. DITPA may be
27 formulated for parenteral administration for injection with an appropriate
28 conventional carrier and for oral administration with an appropriate conventional
29 carrier. The formulation for parenteral administration for injection may be prepared

1 by conventional methods known to a person skilled in the art, such as a method
2 comprising the steps of; dissolving DITPA in an appropriate solvent such as sterilized
3 water, buffered solution, isotonic sodium chloride solution and the like; sterilizing by
4 filtration; and filling said solution to a sterilized bottle. An amount of DITPA in the
5 parenteral formulation is from about 0.0002 to about 0.2 (W/V %), and preferred
amount is from about 0.001 to about 0.1 (W/V %). The formulation may be prepared
by the conventional formulation technique.

6 DITPA may be administered in the form of inhalation or insufflation. For
7 administration by inhalation or insufflation a DITPA solution is conveniently
8 delivered in the form of an aerosol spray presentation from pressurized packs or
9 nebulizer, with the use of suitable propellants such as carbon dioxide or other suitable
gasses. In addition, DITPA may be administered using conventional drug delivery
10 systems well known to a person skilled in the art. Examples of the preparations for
11 drug delivery system are microspheres (nanoparticle, microparticle, microcapsule,
bead, liposome, multiple emulsion, etc.) and the like.

12 A stabilizer may be added to the formulation, and the examples of a stabilizer
13 include albumin, globulin, gelatin, mannitol, glucose, dextran, ethylene glycol and the
14 like. The formulation of the present invention may include a necessary additive such
as an excipient, a solubilizer, an antioxidant agent, a pain-alleviating agent, an
15 isotonic agent and the like. The liquid formulation may be stored in frozen condition,
16 or after removal of water by a process such as freeze-drying. The freeze-dried
17 preparations are used by dissolving in pure water for injection and the like before use.

18 Effective dosages and schedules for administering DITPA may be determined
empirically, and such determinations are within the skill in the art. An administration
19 route of the preparation may vary depending on the form of preparation. For
example, the parenteral preparation may be administered intravenously,
intraarterially, subcutaneously or intramuscularly.

21 In addition, DITPA may also be formulated for transdermal or implant
22 administration. Such long acting implantation administrations include subcutaneous
23 or intramuscular implantation. Thus, for example, DITPA may be formulated with
24 suitable polymeric or hydrophobic materials (for example as an emulsion in an

1 acceptable oil) or ion exchange resins or as sparing soluble derivatives, for example as
2 a sparingly soluble salt.

3 Applicants' transdermal delivery system includes a carrier, such as a liquid, gel,
4 solid matrix, or pressure sensitive adhesive, into which DITPA is incorporated. In one
5 embodiment, Applicants' invention does not include a backing material. In an
6 alternative embodiment, Applicants' method includes use of a backing in combination
7 with a carrier. In this embodiment, the portions of the carrier that are not in physical
8 contact with the skin or mucosa are covered with a backing. The backing serves to
9 protect the carrier and the components contained in the carrier, including the DITPA
being delivered, from the environment. Backings suitable for use with Applicants'
method include metal foils, metalized plastic films, and single layered and multilayered
polymeric films.

10 In one embodiment, Applicants' method comprises transdermal delivery of
11 DITPA dissolved in a solvent system. The solvent system includes water, and optionally
12 one or more lower alcohols such as ethanol, isopropyl alcohol, propyl alcohol, and the
like. Preferably, such alcohols have carbon contents between 2 and about 6.

13 The solvent system may additionally include glycols such as ethylene glycol,
14 propylene glycol, glycerol, and the like. The solvent system may also include one or
15 more dialkylsulfoxides and/or dialkylsulfones. The solvent system may also include one
16 or more ketones, ethers, and esters. Examples include acetone, methylethylketone,
17 dimethylether, diethylether, dibutylether, and alkyl acetates, alkyl propionates, alkyl
butyrates, and the like.

18 Although solutions of DITPA are preferred, emulsions are also effective. Such
19 emulsions may be aqueous, wherein the aqueous phase is the major and continuous
20 phase, or non-aqueous, wherein a water-insoluble solvent system comprises the
continuous phase.

21 Applicants' method to treat chronic heart failure and/or lower LDL-cholesterol
22 levels using the transdermal delivery of DITPA is effective even without including a
23 substance capable of *in vivo* stimulation of adenosine 3', 5'-cyclic monophosphate, and
24 even without including a substance capable of *in vivo* stimulation of guanosine 3', 5'-
cyclic monophosphate. In a separate embodiment of Applicants' invention, substances
such as an extract of *Coleus Forskholii*, may optionally be included in Applicants'

1 transdermal delivery DITPA formulation at a level of between about 0.0001 weight
2 percent to about 1.0 weight percent.

3 Applicants' transdermal formulation may also contain agents known to
4 accelerate the delivery of medicaments through the skin or mucosa of animals,
5 including humans. These agents are sometimes known as penetration enhancers,
6 accelerants, adjuvants, and sorption promoters, and are collectively referred to herein
7 as "enhancers." Some examples of enhancers include polyhydric alcohols such as
8 dipropylene glycol; oils such as olive oil, squalene, and lanolin; polyethylene glycol
9 ethers and fatty ethers such as cetyl ether and oleyl ether; fatty acid esters such as
10 isopropyl myristate; fatty acid alcohols such as oleyl alcohol; urea and urea
11 derivatives such as allantoin; polar solvents such as dimethyldecylphosphoxide,
12 methyloctylsulfoxide, dimethylacetone, dimethyllaurylamine, dodecylpyrrolidone,
13 isosorbitol, decylmethylsulfoxide, and dimethylformamide; salicylic acid; benzyl
14 nicotinate; bile salts; higher molecular weight aliphatic surfactants such as lauryl
15 sulfate salts. Other agents include oleic acid and linoleic acids, ascorbic acid,
16 panthenol, butylated hydroxytoluene, tocopherol, tocopherol acetate, tocopherol
17 linoleate, propylene, isopropyl palmitate, oleamide, polyoxyethylene lauryl ether,
18 polyoxyethylene oleyl ether and polyoxyethylene oleyl ether. In this embodiment,
19 these skin penetration enhancers are present from about 0.01 weight percent to about
20 5 weight percent.

21 Applicants' transdermal delivery system of this embodiment can be prepared
22 using conventional methods to apply an appropriate carrier to an appropriate backing.
23 For example, a DITPA-in-adhesive device can be prepared by using the following
24 method; preparing a coating formulation by mixing a solution of the adhesive in a
solvent system containing DITPA, and any other desired components, to form a
homogeneous solution or suspension; applying the formulation to a substrate such as a
backing or a release liner; using well known knife or bar or extrusion die coating
methods; drying the coated substrate to remove the solvent; and laminating the exposed
surface to a release liner or backing.

25 The following clinical studies are presented to further illustrate to persons
26 skilled in the art how to make and use Applicants' invention and to identify presently
27 preferred embodiments thereof. These clinical studies are not intended as limitations,

1 however, upon the scope of Applicants' invention, which is defined only by the
2 appended claims.

CLINICAL STUDIES

3 In clinical trials discussed below wherein DITPA was orally administered to
4 volunteers and patients, the DITPA was mixed under the supervision of a registered
5 pharmacist with lactose and packed into gelatin capsules containing 50 mg of the
6 active ingredient. Identical capsules were packed with lactose to serve as placebo
medication.

7 A dose-ranging study was performed with seven (7) normal volunteers. Study
8 participants comprised men between the ages of 18 and 65 years of age. Before
9 participating in the study, a complete physical examination, electrocardiogram, and
10 echocardiogram were obtained. A complete blood count (CBC), blood chemistries
11 (including liver enzymes and lipids profile), and thyroid function studies (total T₃,
total T₄, free T₄, rT₃, and thyrotropin) were measured.

12 On day 1, these normal volunteers were started on 1.875 mg/kg in two divided
13 doses per day. This treatment regimen was continued for two weeks. At the end of
14 the second week, the initial laboratory studies were repeated. The dose was then
15 doubled to 3.75 mg/kg and the volunteers were treated for two additional weeks. At
the end of this time physical examination and all laboratory variables again were
measured.

16 Volunteer data were analyzed using Student's paired t-test. Baseline data in
17 DITPA and placebo groups were compared by Student's unpaired t-test. Comparison
18 of placebo and drug treated groups was made by repeated measures ANOVA (SPSS
Version 9.5, SPSS Chicago, 11). If P values for drug-time interactions were
19 significant *a priori* contrasts were performed of the drug-time interaction for two
20 weeks versus baseline. When data were available only at baseline and four week,
21 comparisons were made by difference scores. Baseline values for each participant
22 were subtracted from values after four weeks of treatment and the differences between
23 DITPA and placebo treatments then were compared. P values by two-tailed testing
less than 0.05 were considered to be significant.

24

1 Table I summarizes the clinical variables following DITPA administrations in
 2 normal volunteers. As noted above, seven normal volunteers received DITPA at two
 3 dosage levels for two and four weeks.

TABLE I

	At Baseline	After 2 weeks of treatment	P Value*	After 4 weeks of treatment	P Value ⁺
Age	44.3±3.3				
Weight (kg)	84.2±2.6	83.5±2.6	0.08	83.6±2.6	0.13
Heart Rate (beats/min)	55.4±2.9	58.1±3.2	0.93	64.3±3.4	0.15
Systolic Blood Pressure (mm Hg)	121.3±4.4	122.0±5.4	0.86	116.3±6.1	0.20
Diastolic Blood Pressure (mm Hg)	77.1±3.5	76.1±2.9	0.81	71.6±3.8	0.31

17 Data are means ± SE.

18 * P values for t-test of baseline vs. 2 week values.

19 ⁺ P values for t-test of baseline vs. 4 week values.

20 Table II summarizes thyroid hormone measurements after two and four weeks
 21 of treatment with DITPA in normal volunteers.

22

23

24

1 TABLE II

2	3	At Baseline	After 2 weeks of treatment	P Values*	After 4 weeks of treatment	P Values†
4	5	Thyrotropin (mu/L)	3.53±1.00	0.69±.38	0.04	0.44±.29
6	7	Total T ₄ (μ g/dL)	8.73±.85	5.76±.39	0.02	5.89±.44
8	9	Free T ₄ (ng/dL)	1.04±.04	0.95±.07	0.30	1.05±.06
10	11	Total T ₃ (ng/dL)	1.06±.06	ND	ND	ND
		rT ₃ (ng/dL)	23.23±1.71	47.41±7.11	0.02	69.56±9.93
						0.004

11 Data are means \pm SEM for 7 normal volunteers.

12 ND = Not done

13 * P values for t-test of baseline vs. 2 week values.

14 + P values for t-test of baseline vs. 4 week values.

15 Serum concentrations of thyrotropin, free T₄, and rT₃ were normal at baseline.

16 After two weeks of administration of the lower dose of the drug (1.875 mg/kg)

17 thyrotropin (P = 0.04) and total T₄ (P = 0.02) were significantly decreased whereas

18 free T₄ was unchanged. Serum reverse T₃ was significantly increased (P = 0.02).

19 Total T₃ was not measured after starting the drug because DITPA cross-reacted in the
immunoassay.

20 After two additional weeks of administration at the higher dose (3.75 mg/kg)
21 there was a further decrease in average values for thyrotropin to 0.44±0.29 μ U/ml (P
22 = 0.03). These values were at the lower limit of the normal range (0.48 to 4.0 μ U/ml)
23 for the laboratory. All subjects continued their usual activities while receiving the
24 drug and no adverse effects were noted.

25 The initial phase of Applicants' preliminary study indicated that
26 administration of DITPA to normal volunteers was well tolerated and caused no
27 significant changes in blood pressure and pulse rate at either dose of the drug. In

1 these subjects, echocardiographic parameters were not changed significantly.
2 Thyrotropin levels were decreased at both doses of DITPA administered but plasma
3 T₄ remained within the normal range. Total T₃ could not be measured during drug
4 administration because DITPA cross-reacted with the anti-T₃ antibody. Reverse T₃
5 increased substantially, however. The mechanism for the increase in rT₃ is unknown,
6 but may represent competitive inhibition by DITPA of the enzyme 5'-
7 monodeiodinase, which catalyzes the breakdown of rT₃ as well as the conversion of
8 T₄ to T₃. Since no adverse effects were observed in normal volunteers Applicants
9 proceeded with administration of DITPA to a group of individuals with moderately
10 severe heart failure.

11 After the safety of DITPA was established, clinical trials then demonstrated
12 the efficacy of DITPA to treat chronic heart failure. Patients were eligible for
13 enrollment in these clinical studies if they had symptoms of heart failure and an
14 ejection fraction of less than 35%. Patients were required to be in sinus rhythm.
15 Treatment with digitalis, angiotensin converting enzyme inhibitors, and diuretics were
16 allowed, but β -adrenergic blocking agents were not permitted.

17 Three patients in the placebo group and one patient receiving DITPA were
18 taking an HMG-CoA reductase inhibitor. Patients were excluded from the study if
19 they were receiving amiodarone, had unstable angina, myocardial infarction within 6
20 months, significant aortic stenosis, hepatic or renal insufficiency, anemia (hematocrit
21 <30%), pre-existent thyroid disease, sensitivity to iodine, active cancer or any other
22 life-threatening disease.

23 All patients were hospitalized before initiating treatment and a right heart
24 catheterization, radionuclide ejection fraction and echocardiogram were performed.
25 Serum samples were drawn for measurement of thyrotropin, total T₄, free T₄, and
26 reverse T₃.

27 DITPA cross-reacted with antibodies for detection of T₃, which consequently
28 was not measured. Renal and hepatic function tests also were performed. Patients
29 were randomly assigned in double-blind fashion to receive either DITPA at a dosage
30 of 1.875 mg/kg daily or placebo in two or three divided doses. For the first four days
31 of drug administration patients were monitored on a telemetry unit. Thereafter,

1 weekly electrocardiograms were performed and patients were examined for changes
2 in thyroid or cardiac status or evidence of drug toxicity.

3 At the end of two weeks an echocardiogram was obtained. If there was no
4 clinical evidence of progression of heart failure or development of an arrhythmia the
5 dose of DITPA was increased to 3.75 mg/kg daily. After an additional two weeks of
6 treatment with the higher dosage of the drug patients were readmitted to the hospital
and the tests performed in the initial evaluation were repeated.

7 M-mode, two-dimensional, and Doppler echocardiograms were obtained with
8 an ultrasonographic system equipped with a 2.5-mHz transducer (GE VingMed,
Milwaukee, WI) according to the recommendation of the American Society of
9 Echocardiography. Ejection fraction was measured by gated radionuclide myocardial
imaging.

10 Right heart catheterization was performed after the patient had been fasted
overnight; no premedication was given. Pulmonary artery, pulmonary capillary
11 wedge and right heart pressures were measured with a 7 Fr Swan-Ganz catheter
12 introduced into the right femoral vein. Blood pressures were recorded with an
13 automated arm cuff system. After an initial stabilization period of 20 to 30 minutes,
14 the resting hemodynamic measurements were obtained. Thermodilution cardiac
output measurements were averaged from five recordings after discarding the highest
15 and lowest values. All blood tests were performed in the Clinical Pathology
16 Laboratory at the Southern Arizona Veterans Administration Health Care System.

17 Twenty-two patients underwent the initial right heart catheterization and were
randomized to receive the subject drug or placebo. Nineteen patients completed the
18 study (mean age 61.6, range 47 to 76). Patient functional classes, according to the
19 New York Heart Association classification were II (n = 12), III (n = 7). One patient
20 had dilated cardiomyopathy. The remaining patients had coronary artery disease,
21 which was considered to be the most likely etiology of congestive heart failure. There
22 was one death in a patient receiving placebo. One patient in the DITPA group was
withdrawn because of abdominal pain and subsequently found to have cholelithiasis.

23 The remaining patients either voluntarily withdrew from the study or were
noncompliant. Baseline variables for the two groups were similar, except for ejection
24

1 fraction, which was lower in the DITPA group. The clinical effects of treatment are
 2 shown in Table III.

TABLE III

	At Baseline		P Value*	After 2 weeks of treatment		After 4 weeks of treatment		P Value ⁺
	Placebo	DITPA		Placebo	DITPA	Placebo	DITPA	
Age	61.6±2.8	61.8±3.3	0.97					
Weight (kg)	85.8±3.6	98.7±6.6	0.09	86.8±10.1	98.2±19.3	89.4±9.7	94.7±18.8	0.059
NY Heart Association functional class	2.2±0.1	2.5±0.2	0.20	2.2±0.1	2.4±0.2	2.1±0.1	2.5±0.2	1.00
Radionuclide Ejection Fraction (%)	28.7±1.9	18.1±2.4	0.003			29.1±2.8	20.6±3.2	0.72 ⁺⁺
Heart Rate (beats/min)	76.9±3.4	81.3±4.4	0.10	72.0±5.1	83.4±6.5	73.9±4.9	82.2±4.7	0.33
Systolic Blood Pressure (mm Hg)	114.7±5.0	122.8±4.9	0.27	112.0±4.3	116.2±7.4	122.8±6.7	119.1±6.1	0.60
Diastolic Blood Pressure (mm Hg)	73.5±3.9	75.8±4.2	0.69	66.6±3.1	65.7±3.3	73.5±5.4	66.4±3.6	0.11

17 Data are means ± SE for 9 patients receiving DITPA and 10 patients receiving
 18 placebo.

19 * P values for t-test of baseline values of DITPA vs. placebo.

20 ⁺ P values are for ANOVA drug-time interaction.

21 ⁺⁺ P values are for difference scores for baseline vs. 4 weeks.

22 In the DITPA group, no change in body weight occurred after two weeks of
 23 treatment. After 4 weeks there was a decrease of 4 kg while in the placebo group
 24 there was an increase in weight, resulting in a borderline statistically significant
 difference (P = 0.059). There were no significant changes in New York Heart

1 Association class or radionuclide ejection fraction. Average systolic and diastolic
 2 pressures were decreased, but did not achieve statistical significance.

Table IV.

	At Baseline		P Value *	After 2 weeks of treatment		After 4 weeks of treatment		P Value ⁺
	Placebo	DITPA		Placebo	DITPA	Placebo	DITPA	
Cardiac size and shape								
7 LV end-systolic dimension (cm)	5.64±0.27	5.72±0.41	0.87	5.57±0.33	5.87±0.30	5.92±0.28	6.01±0.33	0.85
8 LV diastolic dimension (cm)	6.73±0.19	6.84±0.33	0.78	6.81±0.26	6.83±0.35	7.00±0.23	6.96±0.30	0.71
9 LV mass (g)	492.7±73.3	495.8±45.9	0.97	429.4±37.2	474.2±38.2	461.7±32.9	477.9±40.5	0.75
Systolic Function								
10 Fractional shortening (%)	16.7±2.1	17.0±3.5	0.95	18.6±2.5	13.8±2.4	15.5±2.0	13.8±2.5	0.39
10 Shortening velocity (circ/sec)	0.64±0.07	0.69±0.15	0.74	0.67±0.07	0.55±0.09	0.58±0.07	0.57±0.10	0.49
Diastolic Function								
11 Isovolumic relaxation time (msec)	94.0±7.0	92.2±9.5	0.88	107.7±7.8	87.5±9.2 ⁺⁺	109.0±8.2	84.4±8.5	0.045
11 Ratio of early to late filling	1.08±0.16	1.10±0.21	0.97	1.05±0.15	0.89±0.17	1.08±0.18	1.16±0.26	0.56

14 Data are means ± SE for 9 patients receiving DITPA and 10 patients receiving
 placebo.

15 * P values are for t-test of baseline values for DITPA vs. placebo groups.

16 ⁺ P values are for ANOVA drug-time interaction.

17 ⁺⁺ ANOVA contrast for baseline to 2 weeks P = 0.051.

18 Echocardiographic data are shown in Table IV. DITPA produced no
 19 significant changes in ventricular mass or size after two weeks or four weeks of
 20 treatment. Indices of systolic function, such as fractional shortening and the velocity
 21 of circumferential fiber shortening were unchanged. However, isovolumetric
 22 relaxation time, a measure of active diastolic relaxation, was decreased significantly
 23 after two weeks (P = 0.05) and four weeks of treatment (P = 0.045). The ratio of early
 24 to late diastolic ventricular filling was unchanged.

1 TABLE V

2 Variable	3 At Baseline		P Value*	4 After 4 weeks of treatment		P Value†
	5 Placebo	6 DITPA		7 Placebo	8 DITPA	
9 Heart Rate	10 73.4±5.0	11 84.8±4.9	12 0.12	13 72.0±6.3	14 89.6±5.3	15 0.16
16 Pulmonary artery pressures (mm Hg)						
17 Systolic	18 42.4±4.2	19 45.0±6.2	20 0.72	21 44.9±6.4	22 49.1±5.3	23 0.80
24 Diastolic	25 20.9±3.0	26 25.1±4.1	27 0.41	28 22.2±3.0	29 25.4±2.5	30 0.94
31 Mean	32 28.9±3.3	33 30.1±5.0	34 0.84	35 30.1±3.9	36 33.4±3.2	37 0.61
38 Wedge	39 18.0±2.5	40 24.0±3.9	41 0.20	42 21.1±3.2	43 21.8±2.75	44 0.13
45 Right atrial pressure (mm Hg)	46 9.9±1.7	47 8.1±1.7	48 0.47	49 10.7±1.4	50 10.5±1.8	51 0.36
52 Cardiac Output (liters/min)	53 5.06±0.36	54 4.50±0.36	55 0.30	56 4.98±0.25	57 5.30±0.36	58 0.07
59 Cardiac Index (liters/min/m ²)	60 2.51±0.17	61 2.10±0.14	62 0.09	63 2.44±0.11	64 2.54±0.16	65 0.04
66 Mean Arterial Pressure (mm Hg)	67 91.4±3.3	68 96.2±6.7	69 0.51	70 92.0±4.1	71 92.0±5.7	72 0.44
73 Systemic Vascular Resistance (dynes x sec x cm ⁻⁵)	74 2,685±165	75 3,465±319	76 0.04	77 2,700±159	78 2,644±257	79 0.02

15 Data are means ± SE for 9 patients receiving DITPA and 10 patients receiving
16 placebo.

17 * P values are for t-test of baseline values for DITPA vs. placebo groups.

18 † P values are for difference scores for DITPA vs. placebo groups at 4 weeks.

19 The effects of treatment with DITPA on hemodynamic variables measured
20 invasively are shown in Table V. After four weeks of treatment with DITPA there
21 were no effects on heart rate, pulmonary arterial or right atrial pressures. However,
22 the group averages for resting cardiac outputs and cardiac indices in those receiving
23 DITPA were increased significantly compared to placebo treatment (P = 0.07 and P =
24 0.02, respectively). This was accompanied by a decrease in systemic vascular
resistance index for the DITPA group (P = 0.02). By contrast, cardiac output, cardiac

1 index and peripheral resistance were unchanged after four weeks of placebo
 2 administration.

TABLE VI

	At Baseline		P Value *	After 2 weeks of treatment		After 4 weeks of treatment		P Value†
	Placebo	DITPA		Placebo	DITPA	Placebo	DITPA	
Thyrotropin (mU/L)	1.65±0.2	2.47±0.6	0.17	1.85±0.3	0.04±01 ⁺⁺	2.13±0.3	0.018±0.0004	<0.001
Free T4 (ng/dL)	1.19±0.1	1.19±0.1	0.96	1.18±0.08	1.17±0.1	1.12±0.1	1.17±0.15	0.72
Reverse T3 (ng/dL)	236±23	197±27	0.29	207±15	477±83 ⁺⁺	237±61	559±108	0.002
Cholesterol (mg/dL)	183.0±10.5	198.9±19.7	0.49	198.7±10.4	160.6±14.3 ⁺⁺	181.9±12.3	140.7±16.2	0.013
LDL Cholesterol (mg/dL)	117.9±7.5	115.8±15.8	0.91	122.5±10.3	89.4±12.7	106.1±10.2	80.5±13.7	0.235
HDL Cholesterol (mg/dL)	32.4±2.9	32.8±2.8	0.94	36±3.2	30.6±2.0	34.8±5.0	31.4±3.1	0.055
Triglyceride (mg/dL)	163.4±29.2	248.7±40.4	0.11	218.7±40.2	203.0±30.4 ⁺⁺	204.3±53.9	143.7±21.1	0.005

15 Data are means ± SE for 9 patients receiving DITPA and 10 patients receiving
 placebo.

16 * P values are for t-test of baseline values for DITPA vs. placebo groups.

17 † P values are for ANOVA drug-time interactions.

18 ‡ ANOVA contrasts for baseline values vs. 2 weeks of treatment P<0.05.

19 As shown in Table VI, serum concentrations of thyrotropin, free T₄, and rT₃
 20 were not significantly different at baseline in the treatment and control group. Values
 21 for thyrotropin and free T₄ were within the normal range whereas rT₃ values were
 22 elevated at baseline in both groups. After two weeks there was a highly significant
 23 decrease in thyrotropin levels in patients receiving DITPA, which became more
 24 pronounced after four weeks of treatment. In the placebo group, thyrotropin was
 unchanged at both times. Interestingly, treatment with DITPA did not cause

1 significant changes in free T₄. However, rT₃ progressively increased after two and
2 four weeks of treatment.

3 The effects of DITPA and placebo on serum lipid levels also are shown in
4 Table VI. After two weeks of treatment with DITPA there was a significant decrease
5 in value of cholesterol for the group from 185.8±46.9 mg/dL at baseline to 160.6±14.3
6 mg/dL (P < 0.05). After four weeks of DITPA treatment there was a further decrease
7 to 140.7±16.2 mg/dL (P = 0.013). LDL-cholesterol decreased from 107.3±42.8
8 mg/dL at baseline to 89.4±12.7 at two weeks and 80.5±13.7 mg/dL after 4 weeks.
9 Although LDL-cholesterol decreased in 8 of 9 patients treated for 4 weeks there was
10 variability in the magnitude of the response and the ANOVA value did not achieve
11 statistical significance (P=0.235). HDL-cholesterol trended down with DITPA
12 treatment but did not achieve statistical significance. Serum triglycerides were
13 elevated at baseline in the DITPA treatment group and decreased by 11% after two
14 weeks of treatment (P < 0.05) and 35% after four weeks (P = 0.005). None of these
15 changes in serum lipids were observed in patients receiving placebo.

16 Thyroid hormone replacement in hypothyroidism is thought to lower
17 cholesterol by increasing the activity of LDL-cholesterol receptors and lipoprotein
18 lipase. DITPA, however, has never previously been clinically tested for its
19 cholesterol lowering activity. After two weeks in the group receiving DITPA there
20 was an average decrease in cholesterol and LDL-cholesterol of 14% and 17%,
21 respectively. After four weeks of treatment cholesterol and LDL-cholesterol were
22 decreased by 24% and 25%, respectively.

23 Values for serum triglycerides, which were elevated at baseline in both
24 groups, were decreased after two and four weeks of treatment with DITPA. Given the
25 large number of patients with heart failure secondary coronary artery disease, the lipid
lowering effects of DITPA is a potentially useful attribute of the drug.

26 The major hemodynamic effects of DITPA in heart failure patients were an
27 increase in cardiac index and lower systemic vascular resistance. These changes
28 occurred without an increase in resting heart rate. At baseline the gated radionuclide
29 ejection fractions were smaller in the DITPA treatment group than the placebo group
30 and did not change significantly during the study. Judging by the unchanged ejection
31 fraction and echocardiographic parameters of systolic function, LV systolic function

probably was unaffected by treatment with DITPA. However, there was almost uniform improvement in diastolic function as assessed by shortening of isovolumic relaxation time. Interestingly, echocardiographic changes were not seen in normal volunteers suggesting that DITPA treatment improves 5 depressed cardiac function, but does not stimulate cardiac performance in the normal heart.

Because of experimental indications that DITPA cause less metabolic response than thyroid hormone and was well tolerated in normal subjects, patients with ischemic heart disease were enrolled in the present trial. The 10 drug also was well tolerated in this group of patients. No arrhythmias were noted. There was no increase in frequency or severity of anginal attacks and clinical manifestations of hyperthyroidism were not observed.

While the invention has been described in detail herein in accordance with certain preferred embodiments thereof, many modifications and changes 15 therein may be effected by those skilled in the art. Accordingly, it is intended by the appended claims to cover all such modifications and changes as fall within the true spirit and scope of the invention.

In the specification and the claims the term "comprising" shall be understood to have a broad meaning similar to the term "including" and will be 20 understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. This definition also applies to variations on the term "comprising" such as "comprise" and "comprises".

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition for treatment of a patient with congestive heart failure, comprising a therapeutically effective amount of 3,5-diiodothyropionic acid in a pharmaceutically acceptable carrier.
2. The composition of claim 1, in the form of a liquid preparation, a solid preparation, a capsule preparation, or an implant preparation.
3. The composition of either claim 1 or 2, and further comprising a stabilizer, an excipient, a solubilizer, an antioxidant, a pain-alleviating agent, and/or an isotonic agent.
4. A composition for lowering cholesterol blood levels of a patient, comprising a therapeutically effective amount of 3,5-diiodothyropionic acid in a pharmaceutically acceptable carrier.
5. The composition of claim 4, in the form of a liquid preparation, a solid preparation, a capsule preparation, or an implant preparation.
6. The composition of either claim 4 or 5, and further comprising a stabilizer, an excipient, a solubilizer, an antioxidant, a pain-alleviating agent, and/or an isotonic agent.
7. A method for synthesizing 3,5-diiodothyropionic acid, comprising the steps of:
 - reacting ethyl-3-(3,5-diiodo-4-hydroxyphenyl)-propionate with dianisoleiodonium trifluoroacetate to form ethyl-3-(4'-methoxy-3,5-diiodothyro)-propionate; and
 - reacting said resulting ethyl-3-(4'-methoxy-3,5-diiodothyro)-propionate with hydrogen iodide and glacial acetic acid to form 3,5-diiodothyropionic acid.
8. The method of claim 7, wherein said ethyl-3-(3,5-diiodo-4-hydroxyphenyl)-propionate starting material is formed by reacting 3-(4-hydroxyphenyl)-propionic acid with iodine to form 3-(3,5-diiodo-4-hydroxyphenyl)-propionic acid; and
- 30 reacting said resulting 3-(3,5-diiodo-4-hydroxyphenyl)-propionic acid with ethanol to form ethyl-3-(3,5-diiodo-4-hydroxyphenyl)-propionate.

9. The method of claim 7, wherein said dianisoleiodonium trifluoroacetate starting material is formed by:

reacting fuming nitric acid, iodine, and trifluoroacetic acid to form iodine(III)trifluoroacetate; and

5 reacting said resulting iodine(III)trifluoroacetate with anisole to form dianisoleiodonium trifluoroacetate.

10. A method for treatment of a patient with congestive heart failure, comprising administering to the patient a therapeutically effective amount of 3,5-diiodothyropionic acid.

10 11. A method for treatment of a patient to lower cholesterol blood levels of said patient, comprising administering to the patient a therapeutically effective amount of 3,5-diiodothyropionic acid.

12. The method of claim 10 or claim 11, wherein 3,5-diiodothyropionic acid is administered as a formulation selected from the group consisting of liquid preparation, a solid preparation, a capsule preparation, or an implant preparation.

15 13. The method of claim 10 of claim 11, wherein such formulation further comprises a pharmaceutically acceptable carrier.

14. The method of any one of claims 10 to 13, wherein said 3,5-diiodothyropionic acid is administered in conjunction with a stabilizer, an excipient, a 20 solubilizer, an antioxidant, a pain-alleviating agent and/or an isotonic agent.

15. The method of claim 10, 11 or 13, wherein said 3,5-diiodothyropionic acid is administered by parenteral injection.

16. The method of claim 10, 11 or 13, wherein said 3,5-diiodothyropionic acid is administered by parenteral intravenous injection.

25 17. The method of claim 10, 11 or 13, wherein said 3,5-diiodothyropionic acid is administered orally.

18. The method of claim 10, 11 or 13, wherein said 3,5-diiodothyropionic acid is administered directly to the pulmonary system of the patient.

30 19. The method of claim 10, 11 or 13, wherein said 3,5-diiodothyropionic acid is administered transdermally.

20. The method of claim 10, 11 or 13, wherein said 3,5-diiodothyropionic acid is administered by implantation.
21. A composition for treatment of a patient with congestive heart failure substantially as herein described with reference to the examples.
- 5 22. A composition for lowering cholesterol levels of a patient substantially as herein described with reference to the examples.
23. A method for treatment of a patient with congestive heart failure, substantially as herein described with reference to the examples.
- 10 24. A method for lowering cholesterol blood levels of a patient substantially as herein described with reference to the examples.
25. A method for synthesizing 3,5-diiodothyropionic acid substantially as herein described with reference to the examples.