AMINOTETRALIN DERIVATIVE FOR THE THERAPY OF CARDIOVASCULAR DISEASES

The present invention relates to the use of 5,6-diisobutyroyloxy-2-methylaminotetralin in the preparation of pharmaceutical compositions for the therapy of cardiac disorders, particularly congestive heart failure.

Notwithstanding the therapeutical progresses of the last years, congestive heart failure is still one of the main death causes.

The symptomatic therapy usually aims at reducing the workload of the decompensed heart and improving the mechanical function.

Recently, cardiac failure was proved to be related with important biochemical and neurohumoral changes involving different factors.

In fact, when cardiac output diminishes, compensatory mechanisms act in the body in order to maintain the circulatory homeostasis.

In heart failure, vasoconstriction associated with the activation of said mechanisms cause an increase in peripheral vascular resistances.

As a consequence, the after-load increases which can in turn further strain the already weakened heart, triggering a vicious circle which leads to a progress of the pathology.

This generalized vasoconstriction is mainly caused by the activation of the sympathetic nervous system consequent to the increase of plasma catecholamines, particularly adrenalin, which is an early signal of

cardiac decompensation.

A close relationship between degree of sympathetic activation and severity of the disease seems to exist, and a direct connection between noradrenalin plasmatic levels and mortality seems moreover established.

Therefore, the therapy of congestive heart failure has to be directed to the improvement of the hemodynamic factors, on one hand, and to the pharmacological modulation of the neurohumoral system on the other.

Dopaminergic drugs appear as candidates to become established as drugs for heart failure in the majority of patients.

In particular, dopamine has peculiar characteristics, compared with the other medicaments, since it stimulates both dopaminergic and alpha and beta-adrenergic receptors.

Two types of dopaminergic receptors exist: those located on the smooth muscle of the vascular system (DA_1 receptors) which mediate vasodilation in the renal, mesenteric, cerebral and coronary districts, and those in pre-synaptic position (DA_2 receptors), which inhibit noradrenalin release from post-ganglionic sympathetic nerve endings to blood vessels and heart.

The usefulness of dopamine in the treatment of heart failure is however restricted by it being inactive orally.

Analogously dobutamine, a synthetic analogue of dopamine, can be used only intravenously.

Aminotetralin derivatives have been studied for a long time as dopamine structural analogues for any uses as medicaments.

However, none of these compounds has up to now been introduced in therapy.

One of them, 5,6-dihydroxy 2-methylaminotetralin hydrobromide, was disclosed as coronary vasodilator in the US patent n. 4,134,997 in the name of Joseph G. Cannon.

Cannon administered the compound to dogs at a rate of approximately 10 µg/kg animal weitht per minute (rante 8.5-13.9) by a continuous intravenous infusion and demonstrated a substantial increase in coronary blood flow.

5,6-Diisobutyroyloxy-2-methylaminotetralin, hereinafter referred to as CHF 1035, has been described first in GB Pat. 2123410 among a series of aminotetralin derivatives disclosed as potential antibronchospastic due to their activity on adrenergic receptors.

Both 5,6-dihydroxy-2-methylaminotetralin (hereinafter indicated with the experimental abbreviation CHF 1024) and CHF 1035 have been formerly characterized as compounds having previling selective activity on β_2 adrenergic receptors.

Now it has been surprisingly found that CHF 1024 and CHF 1035, in addition to the already known β_2 agonist activity, have remarkable peripheral DA_2 and α_2 presynaptic activities leading to a reduction of the sympathetic tone, which is elevated in heart failure patients.

Studies carried out in the animal proved that CHF 1024 and CHF 1035 have a vasodilating activity due the combination of their effects on α_2, β_2 and DA_1/DA_2 receptors as well as a cardiac inotropic activity.

They are effective at a very low doses, even by oral route.

The peripheral α_2 adrenergic and peripheral DA_2 dopaminergic activities of the aminotetralin derivatives of the present invention have never been described until now.

On the contrary, it was previously affirmed by Hilditch A. and Drew G. M. in European Journal of Pharmacology vol. 72, pages 287-296, 1981 that the compound 5,6-dihydroxy 2-methylaminotetralin was inactive as dopamine receptor agonist in relaxing the splenic artery strips.

We have demonstrated that both CHF 1024 and CHF 1035 have agonist activity on dopaminergic receptors and that they are selective for the presynaptic DA_2 ones.

The α_2 adrenergic and DA_2-dopaminergic acitivities of the compounds have been evaluated in binding tests (example 1 and 3), in isolated neuronally-stimulated rat vas deferens (example 2) and in rabbit rectococcygeus muscle (example 4).

The cardiovascular effects of the compounds have been evaluated in vivo in anesthetized rats both after intravenous and intraduodenal administration (example 5).

Example 1

The affinity of CHF 1024 and CHF 1035 for α_2 adrenergic receptors was tested on human platelets and on rat cerebral cortex.

The antagonist [^{3}H]-rauwolscine was used as marker of the receptor, being its binding reversible, saturable and specific.

CHF 1024 exhibited a significantly higher affinity than dopamine, 9 times in platelets and 15 times in cerebral cortex. The affinity of CHF 1035 was similar to that of dopamine, utilized as reference compound.

The lower affinity of CHF 1035 for the receptor is probably due to the esterification of the molecule.

	CHF 1024	CHF 1035	DOPAMINE
human platelets	3.39×10^{-7} (±0.13)	2.70×10^{-6} (±0.45)	3.04×10^{-6} (±0.38)
rat cerebral cortex	2.62×10^{-7} (±0.58)	2.65×10^{-6} (±0.67)	4.06×10^{-6} (±0.97)

Values are expressed as IC_{50} = molar concentration of drug required for 50% inhibition of [^{3}H]-rauwolscine specific binding.

Example 2

The α_2-adrenergic activity of the aminotetraline derivatives CHF 1024 and CHF 1035 has been evaluated in isolated neuronally-stimulated rat vas deferens in comparison with dopamine.

The results are expressed in the following table as IC_{50} value = molar concentration of drug which induces 50% inhibition of the electrically induced contraction:

	CHF 1024	CHF 1035	DOPAMINE
IC_{50} (M)	2.70×10^{-7}	7.14×10^{-8}	4.91×10^{-6}
C.I.	2.15 - 3.38	5.63 - 9.05	4.19 - 5.75

C.I. = 95% Confidence Interval

The compounds CHF 1024 and CHF 1035 resulted about 20 and 70 times more potent that dopamine, respectively.

Example 3 - peripheral DA_2 dopaminergic activity (binding test)

The affinity of CHF 1024 for peripheral DA_2 dopaminergic receptors was tested on bovine adrenal cortex evaluating its effect on the interaction of [^{3}H]-(-)sulpiride with the specific binding sites of this system.

Dopamine has been employed as reference compound.

The results, expressed as IC_{50} (molar concentration required for 50% inhibition of specific binding) are reported herebelow.

	CHF 1024	DOPAMINE
Bovine adrenal cortex [^{3}H]-sulpiride	2.1×10^{-8}	2.3×10^{-7}

The affinity of CHF 1024 for DA_2 receptors is 11 times higher than that of dopamine.

Example 4 - peripheral DA_2 dopaminergic activity (in vitro test)

The activity of CHF 1024 and CHF 1035 on peripheral DA_2 dopaminergic receptors has been tested in the electrically stimulated rabbit rectococcygeus muscle.

Both compounds determined a dose-dependent inhibition of contraction induced by electrical stimulation and were approximately 3 times more potent than dopamine, utilized as reference compound.

In the table below the IC_{50} values (molar concentration of drug which induces 50% inhibition of the electrically induced contraction) are reported:

	CHF 1024	CHF 1035	DOPAMINE
IC_{50} (M)	3.73×10^{-8}	2.96×10^{-8}	9.93×10^{-8}
C.I. (95% Confidence Interval)	3.16 - 4.36	2.14 - 3.88	4.79 - 18.21

The effects produced by CHF 1024, CHF 1035 and dopamine were competitively antagonized by the selective DA_2-antagonist domperidone.

Example 5 - *In vivo cardiovascular effects*

Male albino rats (Sprague Dawley, 350-400 g) were anesthetized by sodium pentobarbital (60 mg/kg) and maintained by i.v. infusion (6 mg/h). The trachea was cannulated to facilitate spontaneous respiration and body temperature was maintained at 37°C Homoeothermic Blanket Control System (Harvard, England).

The right femoral artery was cannulated for arterial blood pressure measurement and left jugular vein or duodenum were cannulated for drug administration. Mean arterial pressure and heart rate were continuously monitored by pressure transducer and medium gain amplifier triggered by the ECG signal, respectively.

After a stabilization period of about 15 min, CHF 1024 (0.23, 0.69 and 2.3 µg/kg/min) was administered by intravenous infusion for 30 min and cardiovascular parameters were recorded for further 30 min after discontinuation.

CHF 1035 was administered intraduodenally (1 mg/kg).

The response to CHF 1035 was determined in the absence and in the presence of the selective $ß_2$-adrenoceptor antagonist ICI 118.551 (0.2 mg/kg i.v.) and the selective DA_2-dopaminergic antagonist domperidone (0.3 mg/kg i.v.) both alone and in combination. The antagonists were administered 10 min before the i.d. drug administration.

Intravenous administration of CHF 1024 induced a dose-dependent reduction in mean arterial pressure which persists even after infusion discontinuation.

Effects induced by intravenous infusion of the compound on mean arterial pressure in anesthetized rat. Mean ± s.e.m. values (expressed as changes from basal value) are reported.

			min after infusion start		min after infusion stop	
	µg/kg/min i.v.	n	5	30	5	30
VEHICLE	---	7	1.7±2.0	3.7±2.9	4.0±2.2	2.0±2.4
CHF 1024	0.23	6	-6.3±2.1	-13.7±4.2	-8.3±3.4	-8.0±3.3
	0.69	6	-24.0±3.8	-25.7±5.4	-12.7±5.2	-6.7±3.3
	2.3	6	-47.7±7.4	-48.7±5.7	-34.0±6.3	-25.3±7.1

n = number of animals

In spite of marked hypotension, no increase in heart rate was observed.

Analogously, intraduodenal administration of CHF 1035 at 1 mg/kg markedly reduced blood pressure without affecting heart rate.

The hypotensive response was characterized by a rapid and marked fall (peak effect of about 45% reduction from basal value at 5 min after administration) followed by a slow recovery (about 20% reduction from basal value is still present 2 hours after administration).

It has been shown that the peak effect is significantly reduced by pretreatment with the β_2-antagonist, while DA_2-antagonist significantly shortened the hypotensive response (the basal value is completely recovered 60 min from administration). The administration of both antagonists combined completely abolished the hypotensive response.

It has been so demonstrated that the compound is active at doses considerably lower than those described by Cannon and that both β_2-adrenergic and DA_2-dopaminergic receptors are involved in the hypotensive activity.

In particular the DA_2 stimulation seems to be responsible of the long-lasting activity of the compound.

In order to investigate the effects of the compound both on the hemodynamic parameters and the neurohumoral pattern, a randomized double-blind study versus placebo was carried out in 18 patients with a moderate congestive heart failure (class NYHA II-III).

Each patient received on 3 consecutive days 2 active doses of CHF 1035 and 1 placebo dose.

The following hemodynamic parameters were evaluated:

- pulmonary capillary wedge pressure (PCWP) (mmHg);
- cardiac index (CI) (L/min/m^2);
- stroke volume index (SVI) (ml/min/m^2);
- systemic vascular resistance (SVR) (dyneseccm^{-5});
- heart rate (HR) (bpm);
- mean blood pressure (BPm) (mmHg).

The evaluations were carried out by catheterization of the right heart (Swan-Ganz catheter), measuring the hemodynamic parameters of the tested medicament before administration or "pre-dose" (PD) and for the 300 subsequent minutes after the administration or "after-dose" (AD), every 20 minutes for the first 2 hours, then every 60 minutes.

To evaluate the effects of the compound on neurohormones, noradrenalin (NE) (pg/ml) and adrenalin (E) (pg/ml) plasmatic levels were further evaluated, before and 140 minutes after the administration of CHF 1035 and placebo, respectively.

The administration of CHF 1035 at the 3 dose levels, induced changes in the hemodynamic and neurohumoral parameters as shown in the following table:

TABLE

	5 mg		10 mg		15 mg	
	PD	AD	PD	AD	PD	AD
PCWP	22±5	18±4*	20±6	16±9*	21±7	16±6*
CI	3±1	3,4±1*	2,7±1	3,4±1*	3±1	4±1*
SVI	39±12	43±11	38±7	45±10*	40±10	49±11*
SVR	1243±27	1052±265*	1382±45	1009±315*	1359±36	881±257*
HR	74±11	78±11*	70±11	76±12	74±12	80±10*
BPm	85±12	82±12	85±10	77±13*	87±11	79±12*
NE	299±135	301±156	285±244	244±88*	340±162	308±133
E	56±29	42±21*	65±42	62±44	53±25	58±24

*: $p<0.05$

On the contrary, the administration of placebo induced no changes in the same parameters.

The results prove that CHF 1035, at the doses used in the study, induces a significant improvement in hemodynamic parameters and is characterized by a particularly favourable pharmacological profile.

Whilst a dose-related reduction in the peripheral vascular resistances is observed (respectively -15.4%; -27.0%; -35.2% for the 3 dose levels), only a relative increase in heart rate occurs, which is not clinically significant.

The reduction in ventricular after-load, which is the expression of the decrease in the peripheral vascular resistances, induces a significant increase in the cardiac index.

Moreover the significant reduction in the pulmonary capillary wedge pressure should be stressed, which means that the medicament also induces venous vasodilation, with a consequent reduction in the left ventricle pre-load.

Therefore, the general hemodynamic effect CHF 1035 can be ascribed to the peripheral vasodilating activity of the medicament, both arterial and venous.

This evident activity on peripheral receptors could have induced a neurohumoral hyper-reactivity, with a consequent increase in noradrenalin and adrenalin plasmatic levels, which is an undesired reaction in a pathological subject.

On the contrary, the results reported above prove that CHF 1035 is capable of inducing systemic vasodilation without inducing any reflected increase in

catecholamines plasmatic levels.

The vasodilating activity of the compound derives from its receptor properties, particularly from the activity on pre-synaptic DA_2 and α_2 receptors, the stimulation of which can inhibit the catecholamine release, as it is well known.

As said before, congestive heart failure is one of the most common causes of death and disability in industrialized nations and is among the syndromes most commonly encountered in clinical practice, affecting nearly 4 millions persons in the USA and 14 millions individuals in Europe.

The current pharmacological treatment of the condition includes diuretics, angiotensin converting enzyme (ACE) inhibitors and digitalis.

There is a strong impression among the experts that the pharmacologic treatment of patients with heart failure remains suboptimal and more effective treatment is required to prevent complications and thereby reduce morbidity and mortality.

It has been demonstrated that CHF 1035 improves the clinical condition and the exercise capacity of patients with congestive heart failure when used as add-on therapy to baseline therapy with diuretics or with diuretics and ACE-inhibitors and/or with diuretics and digitalis.

It has also been shown that the pharmacodynamic effects last longer than detectable serum levels of the drug. The time course of these effects is independent of the kinetics of the drug in the body.

The effects of CHF 1035 as added therapy have been

evaluated in patients suffering from NYHA class II-III congestive heart failure due to mild hypertension, or coronary disease, or chronic cardiomyopathy, who were on diuretics or diuretics and an angiotensin-converting enzyme inhibitor.

Recruited patients were randomly assigned to added double-blind treatment with placebo or with three different doses of the study drug (5 mg, 10 mg, 15 mg).

The study therapy was started by patients on day 1 and proceeded until day 28 of the study.

The following parameters have been considered to determine the clinical condition of patients:

- pulmonary congestion;
- systemic congestion;
- central haemodynamics;
- regional blood flows

The functional response to the treatments has been evaluated by exertional tests, the 6-minute walking test and the 130-meter walking test.

CHF 1035 improved the functional and clinical condition of patients, compared to placebo.

This improvement was ostensible in terms of the NYHA functional class, exercise performance, and symptoms and signs of pulmonary and systemic congestion, central haemodynamic alterations, and decreased regional/organ blood flows.

For the evaluation of clinical condition, more than 60 symptoms or signs were evaluated.

For statistical purposes scores from signs and symptoms (as applicable) were summed to form clinical compound scorings (CCSs) of pathophysiological

importance in congestive heart failure.

Three CCSs were evaluated by adding the scores for certain symptoms and signs; each symptom and sign was used for only one CCS. The central hemodynamics (CH, 0-17), the pulmonary congestion (PC, 0-26), and the systemic congestion (SC, 0-8) CCS were associated with the NYHA functional class ($p=0.013$; $p=0.001$; $p=0.001$) before, and they correlated with it positively ($p=0.001$; $p=0.022$; $p<0.001$) after CHF 1035 add-on therapy.

The pulmonary congestion CCS correlated also with the 130-m mean walking velocity ($p=0.002/p=0.035$) and with the left ventricle end-diastolic ($p=0.026/p=0.019$) and end-systolic internal dimensions before/after CHF 1035 add-on therapy.

The pulmonary congestion appeared as the most important determinant of the functional status in congestive heart failure and was the most sensitive CCS to CHF 1035 add-on therapy.

Furthermore, pharmacological and clinicopharmacological studies showed that CHF 1035 increases diuresis without affect natriuresis and kaliuresis.

CHF 1035 is the diisobutyroyl ester of 5,6-dihydroxy-2-methylaminotetralin, which is referred to as CHF 1024.

Immediately after the administration, CHF 1035 is transformed by the plasma and tissue esterases into the pharmacologically active desesterified form, which is also included within the present invention.

Due to these favourable characteristics, CHF 1035 can be advantageously used as pro-drug for the preparation of pharmaceutical compositions for the

therapy of cardiac disorders and in particular of the congestive cardiac failure.

The daily dose of the active ingredient can vary from 1 to 100 mg and preferably will range from 2.5 to 20 mg.

The administration can be performed by any route, preferably by the oral route.

For the oral administration, the compound can be formulated in solid or liquid preparations, preferably in tablets, using the additives and excipients of common use in pharmaceutical technique.

Another particularly advantageous method for the administration of the compound of the invention are the transdermal systems, which are adhesive matrixes that can be applied to the skin containing a suitable concentration of the active ingredient, which can gradually be released thus entering the blood circulation.

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* C L M S *

CLAIMS

1. The use of 5,6-diisobutyroyloxy-2-methylaminotetralin, or a pharmaceutically acceptable salt thereof, in the preparation of pharmaceutical compositions for the therapy of heart disorders, particularly congestive heart failure.

2. Pharmaceutical compositions for use in the treatment of cardiac disorders, particularly congestive heart failure, containing 5,6-diisobutyroyloxy-2-methylaminotetralin, or a pharmaceutically acceptable salt thereof, in combination with suitable excipients.

3. Pharmaceutical compositions as claimed in claims 1 and 2, characterized in that the daily dose of the active ingredient ranges from 1 to 100 mg, preferably from 2.5 to 20 mg.

4. Pharmaceutical compositions as claimed in claim 2 wherein the treatment is a method of treating cardiac heart failure and the compound is administered, in said treatment, in an amount of 1-100 mg/day and, preferably, in an amount of 2.5-20 mg/day.

5. A method of providing a treatment of cardiac disorders, particularly congestive heart failure, to a human patient, comprising administering a therapeutically effective amount of a pharmaceutical composition, as claimed in any of claims 2-4, to said human patient.

6. The use of 5,6-dihydroxy-2-methylaminotetralin, or a pharmaceutically acceptable salt thereof, as active metabolite of 5,6-diisobutyroyloxy-2-methylaminotetralin in the preparation of pharmaceutical compositions for the treatment of cardiac disorders, particularly congestive heart failure.

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(57) Abstract

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2. The use of 5,6-dihydroxy-2-methylaminotetralin, or a pharmaceutically acceptable salt thereof, as active metabolite of 5,6-diisobutyroyloxy-2-methylaminotetralin in the preparation of pharmaceutical compositions for the treatment of cardiac disorders, particularly congestive heart failure.

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