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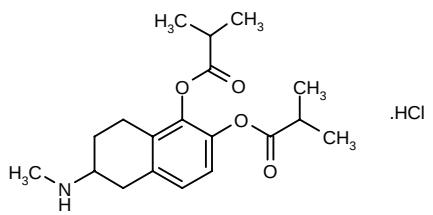
# Nolomirole Hydrochloride

Prop INNM

*Treatment of Heart Failure*
*Dopamine $D_2$ Agonist*
*$\alpha_2$-Adrenoceptor Agonist*

CHF-1035

(±)-5,6-Diisobutyryloxy-2-(methylamino)-1,2,3,4-tetrahydronaphthalene hydrochloride




$C_{19}H_{27}NO_4.HCl$ Mol wt: 369.8862

CAS: 138531-51-8
CAS: 090060-42-7 (as free base)

EN: 235902

## Synthesis

Nolomirole is synthesized by acylation of (±)-6-(methylamino)-5,6,7,8-tetrahydronaphthalene-1,2-diol, CHF-1024 (I) with isobutyryl chloride (II) in THF (1). Scheme 1.

CHF-1024 (I) is obtained by several related ways:

1) Reductocondensation of 5,6-dimethoxy-2-tetralone (III) wth methylamine (IV) by means of $LiBH_4$ or $NaBH_4$ gives *N*-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-methylamine (V), which is treated with 48% HBr at 110 °C (1).

2) The condensation of 2,3-dimethoxybenzaldehyde (VI) with pyruvic acid (VII) by means of KOH in ethanol/water gives 4-(2,3-dimethoxyphenyl)-2-oxo-3-butenoic acid (VIII), which is reductocondensed with methylamine (IV) by means of $H_2$ over Pd/C in ethanol/acetic acid to yield 4-(2,3-dimethoxyphenyl)-2-methylamino)butyric acid (IX). Reaction of acid (IX) with benzyl chloroformate (X) and NaOH in water affords the carbamate (XI), which is treated with refluxing $SOCl_2$ to provide 4-[2-(2,3-dimethoxyphenyl)ethyl]-3-methyloxazolidine-2,5-dione (XII). Reaction of oxazolidinone (XII) with $AlCl_3$ in dichloromethane provides 5,6-dimethoxy-2-(methylamino)-1,2,3,4-tetrahydronaphthalen-1-one (XIII), which is reduced with $H_2$ over Pd/C in ethanol containing some methanolic HCl in an autoclave at 80 °C to yield *N*-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-methylamine (V). Finally, this compound is demethylated by treatment with $AlCl_3$ in hot toluene (2). Scheme 2.

3) Alternatively, 5,6-dimethoxy-2-(methylamino)-1,2,3,4-tetrahydronaphthalen-1-one (XIII) can first be demethylated with 48% HBr to give 5,6-dihydroxy-2-(methylamino)-1,2,3,4-tetrahydronaphthalen-1-one (XIV), which is then reduced by means of $H_2$ over Pd/C in an autoclave as before (2). Scheme 2.

4) Condensation of 4-(2,3-dimethoxyphenyl)-2-oxo-3-butenoic acid (VIII) with methyl carbamate (XV) by means of TsOH in refluxing toluene gives the substituted furanone (XVI), which is hydrogenated with $H_2$ over Pd/C in hot ethanol to yield 4-(2,3-dimethoxyphenyl)-2-(methoxycarbonylamino)butyric acid (XVII). Cyclization of acid (XVII) by means of polyphosphoric acid (PPA) at 60 °C affords tetralone (XVIII), which is reduced with $H_2$ over Pd/C in an autoclave as before to provide *N*-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)carbamic acid methyl ester (XIX). Finally, the carbamoyl group of (XIX) is reduced with $LiAlH_4$ in hot THF to yield *N*-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-methylamine (V) (2). Scheme 3.

## Introduction

Heart failure, often called congestive heart failure, is a progressive disorder of left ventricular myocardial remodeling that culminates in a clinical syndrome in which impaired cardiac function and circulatory congestion are the defining features (3). The condition occurs when the heart is damaged or overworked and unable to pump out all the blood that returns to it from the systemic circulation. As less blood is pumped out, blood returning to the heart backs up and fluid builds up in other parts of the body. Heart failure also impairs the kidneys' ability to dispose of sodium and water, complicating fluid retention

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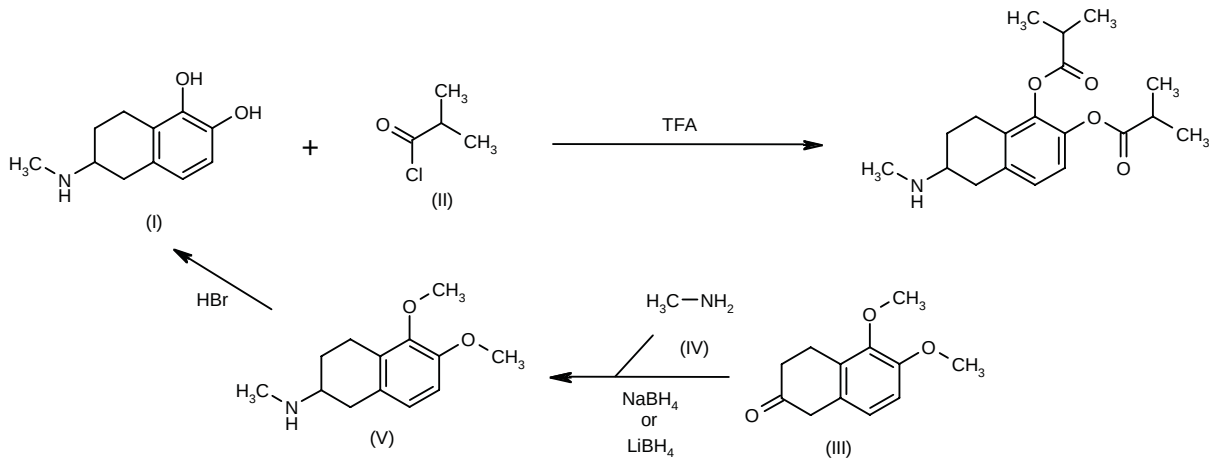
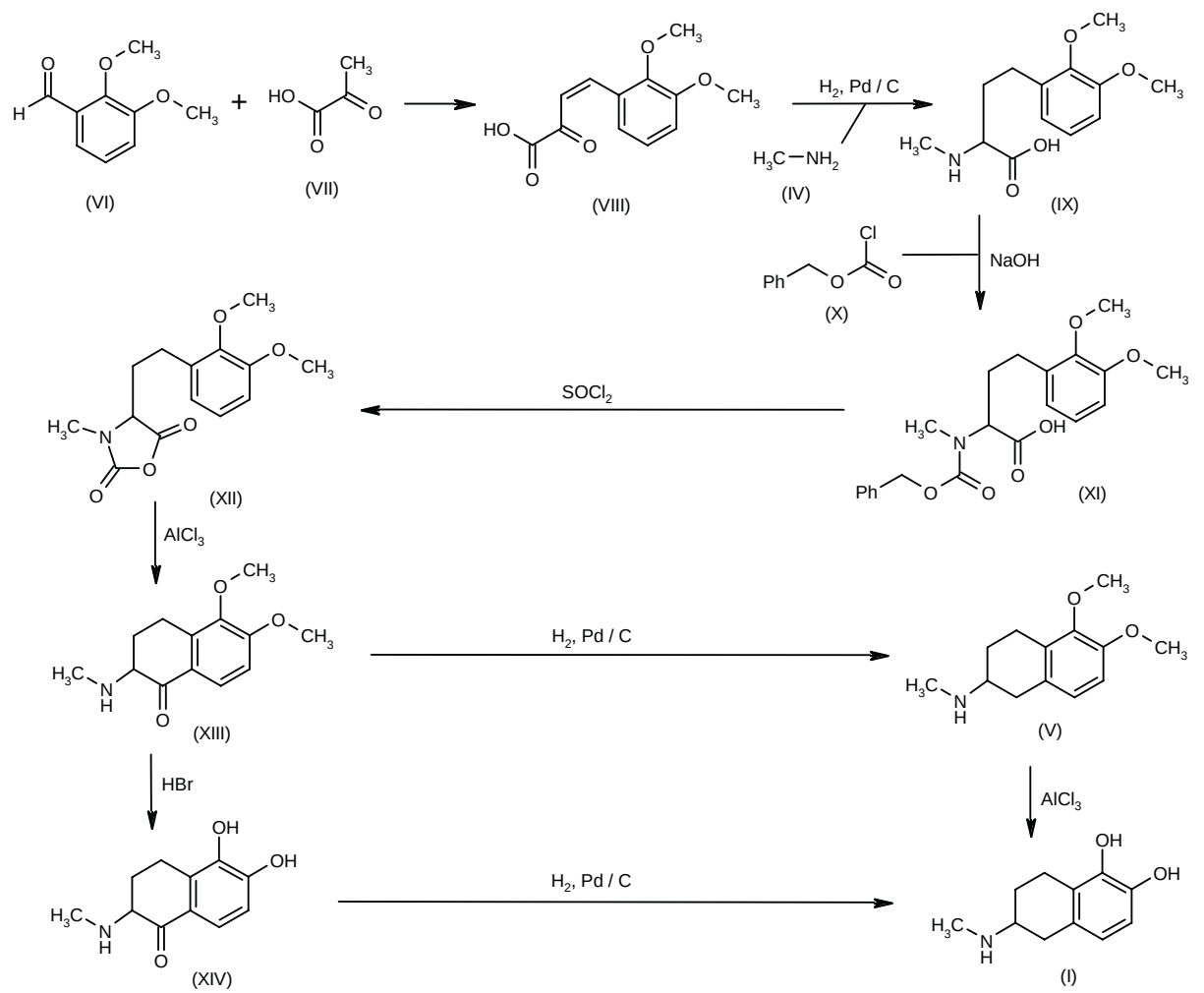
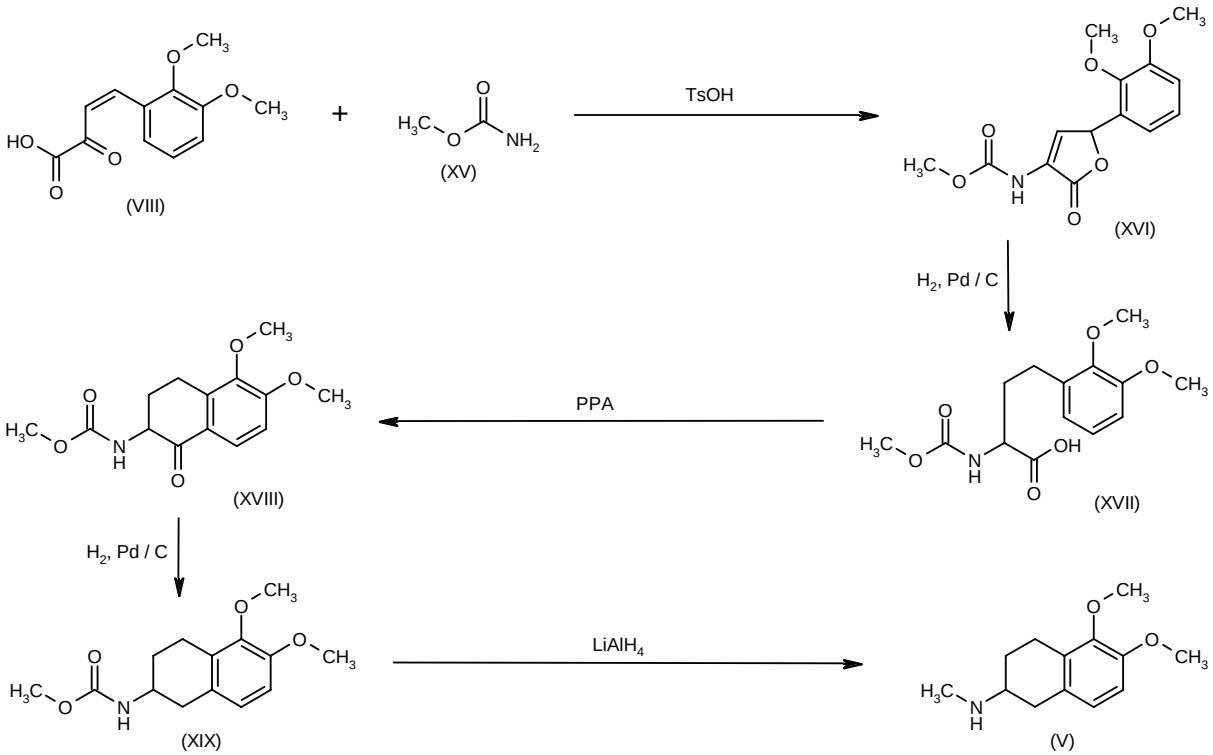
**Scheme 1: Synthesis of Nolomirole**




**Scheme 2: Synthesis of CHF-1024 (I)**



**Scheme 3: Synthesis of Intermediate (V)**



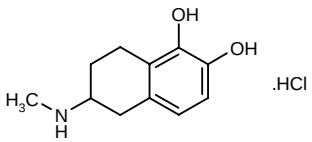

further. Heart failure is characterized by autonomic dysfunction, neurohumoral activation and overproduction of cytokines, which contribute to progressive circulatory failure.

The American Heart Association estimates that approximately 4.7 million Americans have congestive heart failure. As many as 550,000 new cases of heart failure are diagnosed each year. The condition is increasing in prevalence as a result of the aging world population and due to improved survival following acute myocardial infarction.

Chronic heart failure is currently the most costly cardiovascular illness in the United States, resulting in annual expenditures of more than US $40 billion. Hospital-related costs alone account for US $19.4 billion (4). In the U.S., as well as most European countries, heart failure consumes between 1% and 2% of the national annual healthcare budget (5).

There is no definitive cure for heart failure. However, several classes of drugs are available that improve cardiac function and relieve symptoms, significantly prolonging life and improving quality of life for patients. Identification and treatment of underlying conditions such as hypertension is an important component of the therapeutic regimen for heart failure. A large number of drugs are marketed for the treatment of heart failure, including thiazide and thiazide-like diuretics, loop diuretics, potassium-sparing diuretics, carbonic anhydrase inhibitors, cardioselective $\beta_1$-adrenoceptor antagonists, $\alpha_1$-adrenoceptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, calcium sensitizers, phosphodiesterase type 3 (PDE3) inhibitors, dopamine agonists, guanylate cyclase activators, adenylate cyclase activators, vasodilators, positive inotropic agents and metabolic cardiotonic agents.

Heart failure has been traditionally considered to be a hemodynamic disorder and treatment strategies have been designed to correct the hemodynamic status of patients. While hemodynamic abnormalities may explain the symptoms of heart failure, they are not sufficient to explain the progression of the disease. Thus, alternative mechanisms involved in heart failure progression, apart from this hemodynamic hypothesis, have been sought. Several lines of evidence suggested that neurohormonal mechanisms play a central role in the progression of heart failure (6). Activation of the sympathetic nervous system and the renin-angiotensin system exerts a direct deleterious effect on the heart that is independent of the hemodynamic actions of these endogenous mechanisms. Therapeutic interventions that block these neurohormonal systems, *i.e.*, the β-adrenergic (7), renin-angiotensin (8, 9) and endothelin (10) systems, favorably alter the natural history of heart failure. Pharmacological inhibition of pathological adrenergic drive by dopamine $D_2$ and $\alpha_2$-adrenoceptor agonists has proven beneficial in the setting of pressure overload (11, 12) that concurs with




[I]

neurohormonal activation in the pathophysiology of heart failure.

CHF-1035 (nolomirole hydrochloride) is a recently developed, orally active dopamine agonist that activates prejunctional dopamine $D_2$ receptors and $\alpha_2$-adrenoceptors. The drug is rapidly hydrolyzed to its active metabolite CHF-1024 [I] following oral administration.

## Pharmacological Actions

Binding, functional and animal studies demonstrated that the dopamine $D_2$ receptor-agonist activity of nolomirole is mostly due to the (–)-enantiomer, while both enantiomers contribute to the $\alpha$-adrenoceptor-agonist effect. The affinity of the (–)-enantiomer for rat striatal $D_2$ receptors and rat cerebral cortical $\alpha_2$-adrenoceptors ($K_i$ = 120 and 130 nM, respectively) was much higher than the (+)-enantiomer ($K_i$ = 2400 and 1600 nM, respectively). Functional assays using isolated electrically sitmulated rabbit rectococcygeus muscle demonstrated markedly higher potency for the (–)-enantiomer as compared to the (+)-enantiomer for inhibition of the $D_2$ receptor-mediated twitch response ($pD_2$ = 8.3 and 4.2, respectively), whereas the enantiomers were equipotent in inhibitng $\alpha_2$-adrenoceptor-mediated contractions in rat vas deferens ($pD_2$ = 6.8 and 6.2, respectively). Only the (–)-enantiomer was able to inhibit the increase in diastolic blood pressure induced by electrical stimulation of sympathetic outflow in pithed rats, a $D_2$-mediated response, but both enantiomers dose-dependently reduced mean arterial pressure and slightly reduced heart rate in anesthetized normotensive rats, with a 25-40% decrease in blood pressure at 1 μg/kg/min i.v. Studies in conscious spontaneously hypertensive rats (SHR) showed that the (–)-enantiomer was more effective and longer acting than the (+)-enantiomer in decreasing blood pressure when administered s.c. by osmotic minipump, which was associated with a slight decrease in heart rate (13).

Other pharmacological studies have been performed with the active metabolite CHF-1024. A rat model of left ventricular dysfunction following myocardial infarction was used to examine the effects of CHF-1024 on hemodynamics, ventricular remodeling, β-adrenergic drive and cardiac fibrosis. Two months after ligation of the left coronary artery, animals were administered CHF-1024 (0.33 or 1 mg/kg/day) or metoprolol (10 mg/kg/day) by osmotic minipump for 1 month. $\beta_1$-Blockade with metoprolol resulted in a reduction in left ventricular (LV) end-diastolic pressure (LVEDP) but had no effect on cardiac function. Both compounds also significantly reduced collagen deposition in the left ventricle, but only CHF-1024 significantly reduced plasma levels and urinary excretion of norepinephrine. The higher dose of CHF-1024 significantly reduced systolic blood pressure and heart rate, although this dose also decreased diastolic wall stress. According to these findings, CHF-1024 may have beneficial effects in postmyocardial infarction heart failure via a selective effect on norepinephrine outflow and myocardial interstitial collagen (14, 15).

A similar study examined the effects of CHF-1024 (0.33 mg/kg/day) or metoprolol (10 mg/kg/day), administered via osmotic minipump, in combination with the ACE inhibitor delapril (6 mg/kg/day) in the drinking water, following the induction of a large myocardial infarction by ligation of the left coronary artery. Delapril alone or together with CHF-1024 or metoprolol exerted no effect on heart rate or systolic blood pressure in conscious animals, whereas combination therapies were associated with significant decreases in heart rate in anesthetized rats. Delapril alone or in combination with CHF-1024 or metoprolol significantly reduced the increase in LV chamber volume following infarction, and the combination of delapril and CHF-1024 appeared to improve LV apical shape. Although delapril alone had no significant effect, combination treatments reduced urinary norepinephrine excretion. Thus, the combination of CHF-1024 and delapril appears to have beneficial effects on LV remodeling after infarction in the absence of significant hemodynamic effects (16).

A model of pressure overload hypertrophy in rats was used to compare the effects of the ACE inhibiotr captopil and CHF-1024 on neuroendocrine activation and cardiac fibrosis. Rats underwent interrenal aortic stenosis and received vehicle, CHF-1024 (0.33, 2 or 6 mg/kg/day) by osmotic minipump or captopril (1 g/l) in the drinking water over 2 months. Compared to vehicle-treated stenotic rats, animals treated with CHF-1024 showed a reduction in blood pressure and a marked, dose-dependent attenuation of urinary norepinephrine excretion and LV perivascular fibrosis. No effect on LV weight was detected. Captopril also reduced perivascular collagen, in addition to heart and body weight, plasma aldosterone levels and dopamine excretion, but it was associated with a marked hypotensive effect. It is concluded that the D2/alpha2 agonist CHF-1024 effectively prevents hypertension, blunts adrenergic drive and reduces cardiac fibrosis in this model of pressure overload (17).

## Metabolism

Following animal and human studies demonstrating that orally administered CHF-1035 is rapidly hydrolyzed by tissue and plasma esterases to the free dihydroxy derivative CHF-1024, the major active metabolite, the metabolism of CHF-1035 was studied in rats administered a dose of 100 mg/kg p.o. Over a 24-h period, no unchanged drug was recovered in the urine. The main metabolite was CHF-1024, and the *N*-dealkylated and

*Table I: Randomized, double-blind, placebo-controlled studies of nolomirole hydrochloride in congestive heart failure NYHA class II-III (Prous Science Integrity database).*

| Study drug | Dose | n | Results | Conclusions | Ref. |
|---|---|---|---|---|---|
| Nolomirole<br>Placebo | 5 mg po bid x 10d | 29 | Increase in heart rate variability+<br>Reduction in plasma norepinephrine levels+:<br>Nolomirole (–76 pg/ml) > placebo (+42 pg/ml)<br>No changes in ventricular premature complexes and runs of ventricular tachycardia<br>No changes in hemodynamic variables | Good tolerability. Reduction in norepinephrine levels and improvement in heart rate variability | 18 |
| Nolomirole<br>Nolomirole<br>Nolomirole<br>Placebo | 5 mg po od x 4d<br>10 mg po od x 4w<br>15 mg po od x 4w | 39 | NYHA class improvement:<br>Nolomirole 5 mg 73%<br>Nolomirole 10 mg** 100%<br>Nolomirole 15 mg** 100%<br>Placebo 20%<br>Improvement in effort dyspnea:<br>Nolomirole* 5 mg, 10 mg and 15 mg > Placebo<br>Improvement during 6 min walking:<br>Nolomirole 5 mg** + 59 m<br>Nolomirole 10 mg + 51 m<br>Nolomirole 15 mg + 21 ml<br>Placebo – 26 ml<br>No changes in ectopic beats and arrhythmias<br>No changes in hemodynamic variables<br>No changes in left ventricular end-diastolic and end-systolic diameters | Improvements in heart failure with doses up to 15 mg/day | 19 |
| Nolomirole<br>Nolomirole<br>Nolomirole<br>Placebo | 2.5 mg po bid x 4w<br>5 mg po bid x 4w<br>10 mg po bid x 4w | 64 | Clinical response: 10 mg ≥ 20 mg > placebo<br>No changes in echocardiographic indicators of left ventricular function<br>No changes in ectopic beats and arrhythmias<br>No changes in hemodynamic variables | Improvement in heart failure with doses up to 10 mg bid | 20 |
| Nolomirole<br>Nolomirole<br>Nolomirole<br>Placebo | 5 mg po<br>10 mg po<br>15 mg po | 18 | Improvement in hemodyanmic parameters*<br>Induces systemic vasodilatation<br>Reduction in plasma catecholamine levels*<br>No changes with placebo | Improvement in hemodynamic parameters and catecholamine levels | 21 |

*Nolomirole $p < 0.05$ *vs.* baseline; **nolomirole $p < 0.01$ *vs.* baseline; +nolomirole $p < 0.05$ *vs.* placebo.

5-*O*-methylated compounds were also detected. These three metabolites were found to be eliminated mostly as the β-glucuronide conjugates. The 6-*O*-glucuronide of CHF-1024 was the major product, accounting for over half of all metabolites excreted (18).

## Clinical Studies

The results from the few double-blind, randomized, placebo-controlled studies conducted on nolomirole in congestive heart failure patients – one dose-finding study and three trials as add-on therapy to diuretics with or without ACE inhibitors – are summarized in Table I. Overall, nolomirole was associated with hemodynamic and functional improvement, good safety and a lack of effect on arrhythmias at doses of 5-20 mg/day (19-22). The drug is currently in phase III trials (23).

## Manufacturer

Chiesi Farmaceutici SpA (IT).

## References

1. Chiesi, P., Villani, V. (Chiesi Farmaceutici SpA). *1,2,3,4-Tetrahydronaphthaline derivs., process for their preparation and pharmaceutical compsns. containing them.* DE 3320936, FR 2528422, GB 2123410, IT 1218322.

2. Chiesi, P., Ventura, P., Servadio, V., Del Canale, M., De Fanti, R., Amari, G. (Chiesi Farmaceutici SpA). *A process for the preparation of 5,6-dihydroxy-2-amino-1,2,3,4-tetrahydronaphthalene derivs.* WO 9529147.

3. Francis, G.S. *Pathophysiology of chronic heart failure.* Am J Med 2001, 110(Suppl.7A): 37S-46S.

4. American Heart Association. *2001 heart and stroke statistical update.* Dallas, Texas: American Heart Association, 2000.

5. Szucs, T.D. *The growing healthcare burden of CHF.* J Renin-Angiotensin-Aldosterone Syst 2000, 1(Suppl. 1): 2.

6. Packer, M. *The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure*. J Am Coll Cardiol 1992, 20: 248-54.

7. Ostman-Smith, I. *Reduction by oral propranolol treatment of left ventricular hypertrophy secondary to pressure-overload in the rat.* Br J Pharmacol 1995, 116: 2703-9.

8. Weinberg, E.O., Schoen, F.J., George, D., Kagaya, Y., Douglas, P.S., Litwin, S.E., Schunkert, H., Benedict, C.R., Lorell, B.H. *Angiotensin-converting enzyme inhibition prolongs survival and modifies the transition to heart failure in rats with pressure overload hypertrophy due to ascending aortic stenosis.* Circulation 1994, 90: 1410-22.

9. Regan, C.P., Anderson, P.G., Bishop, S.P., Berecek, K.H. *Pressure-independent effects of $AT_1$-receptor antagonism on cardiovascular remodeling in aortic-banded rats.* Am J Physiol 1997, 272(5, Part 2): H2131-8.

10. Hocher, B., George, I., Rebstock, J., Bauch, A., Schwarz, A., Neumayer, H.H., Bauer, C. *Endothelin system-dependent cardiac remodeling in renovascular hypertension.* Hypertension 1999, 33: 816-22.

11. Haeusler, G., Lues, I., Minck, K.O., Schelling, P., Seyfried, C.A. *Pharmacological basis for antihypertensive therapy with a novel dopamine agonist.* Eur Heart J 1992, 13(Suppl. D): 29-35.

12. Takechi, S., Nomura, A., Shimono, H., Katoh, K., Kakinoki, S., Jin, E.Z., Akutsu, M., Kitabatake, A. *Recovery of cardiac norepinephrine concentration and tyrosine hydroxylase activity by the central $\alpha_2$-adrenoceptor agonist guanabenz in rats with aortic constriction.* J Cardiovasc Pharmacol 1999, 33: 409-13.

13. Pastore, F., Razzetti, R., Riunno, M., Bergamaschi, M., Caruso, P., Giossi, M., Civelli, M., Bongrani, S. *Pharmacological characterisation of the enantiomers of nolomirole, a selective $D_2$-dopaminergic and $\alpha_2$-adrenergic receptors agonist.* 30th Congr Naz Soc Ital Farmacol (May 30-June 2, Genova) 2001, Abst B53.

14. Latini, R., Jeremic, G., Luvara, G., Fiordaliso, F., Bernasconi, R., Calvillo, L., Torri, M., Razzetti, R., Masson, S. *Reduction of sympathetic drive and collagen deposition with a $DA_2$-agonist in an experimental model of left ventricular dysfunction after myocardial infarction.* Eur Heart J 1997, 18(Suppl.): Abst P2941.

15. Latini, R., Masson, S., Jeremic, G. et al. *Comparative efficacy of a $DA_2/\alpha_2$ agonist and a $\beta$-blocker in reducing adrenergic drive and cardiac fibrosis in an experimental model of left ventricular dysfunction after coronary atery occlusion.* J Cardiovasc Pharmacol 1998, 31: 601-8.

16. Masson, S., Masseroli, M., Fiordaliso, F. et al. *Effects of a $DA_2/\alpha_2$ agonist and a $\beta_1$-blocker in combination with an ACE inhibitor on adrenergic activity and left ventricular remodeling in an experimental model of left ventricular dysfunction after coronary artery occlusion.* J Cardiovasc Pharmacol 1999, 34: 321-6.

17. Masson, S., Chimenti, S., Salio, M. et al. *CHF-1024, a $DA_2/\alpha_2$ agonist, blunts norepinephrine excretion and cardiac fibrosis in pressure overload.* Cardiovasc Drugs Ther 2001, 15: 131-8.

18. Puccini, P., Zanelli, U., Spinabelli, D., Acerbi, D., Redenti, E., Lipreri, M., Delcanale, M., Ventura, P. *In vivo metabolism of CHF 1035, a chiral aminotetralin, in the rat.* Pharmacol Res 1997, 35: 209-10.

19. Crippa, G., Umile, A., Carrara, G.C., Reyes, A.J. *First clinical experience with the new oral dopaminergic CHF 1035 in congestive heart failure.* J Heart Failure 1995, 2(1): Abst 590.

20. Crippa, G., Reyes, A.J., Giogi-Pierfranceschi, M., Meny, M.G., Sverzellati, E. *Pilot clinical study of a new dopaminergic in heart failure.* Eur Heart J 2001, 22(Suppl.): Abst 2745.

21. Morisco, C., Ricciardelli, R., Argenziano, L., Rendina, V., Iaccarino, G., Vecchione, C., Umile, A., Volpe, M., Trimarco, B. *Hemodynamic effects of graded oral doses of a new dopaminergic analogue CHF 1035 in patients with congestive heart failure.* J Am Coll Cardiol 1995, 128A.

22. Tjeerdsma, G., van Wijk, L.M., Molhoek, G.P., Boomsma, F., Haaksma, J., van Vedhuisen, D.J. *Autonomic and hemodynamic effects of a new selective dopamine agonist, CHF1035, in patients with chronic heart failure.* Cardiovasc Drugs Ther 2001, 15: 139-45.

23. R&D Pipeline. Chiesi Group Web Site July 18, 2001.