

# بسم الله الرحمن الرحيم





# شبكة المعلومات الجامعية التوثيق الالكتروني والميكرو فيلم





# جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

## قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



## يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار





# بعض الوثائق الأصلية تالفة







بالرسالة صفحات  
لم ترد بالأصل





B 17 V A Y

# Cardiovascular effects of the new nitric oxide synthase inhibitor (4-amino-tetrahydrobiopterin)

## Thesis

Presented by

**Hanan Dawood Saad**

Assistant Lecturer of Pharmacology and Toxicology  
Faculty of Pharmacy, Cairo University

Submitted for the degree  
of Doctor of Philosophy  
In Pharmaceutical sciences  
(Pharmacology and Toxicology)

Under the supervision of

**Prof. Dr. Samira Saleh**

Professor and Head of Pharmacology  
and Toxicology Department  
Faculty of Pharmacy  
Cairo University

**Prof. Dr. B. Mayer**

Professor and Head of Pharmacology  
and Toxicology Department  
Karl Franzens University,  
Graz, Austria

**Assistant Prof. Dr. Laila G. Mahran**

Assistant Professor of Pharmacology  
and Toxicology Department  
Faculty of Pharmacy  
Cairo University

2002

## Approval Sheet

Approved by:

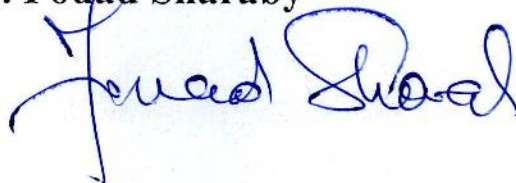
1) Prof. Dr. Samira Saleh



2) Prof. Dr. Mohamed T. Khayyal



3) Prof. Dr. Fouad Sharaby



4) Assistant Prof. Dr. Laila G. Mahran



Committee in charge

Date: 29 / 9 / 2002



## **Approval Sheet**

**Approved by:**

**1) Prof. Dr. Samira Saleh**

**2) Prof. Dr. Mohamed T. El-Khayal**

**3) Prof. Dr. Fouad Sharaby**



**To My**  
**Beloved Mother,**  
**My Husband**  
*and*  
**My Children**

## ACKNOWLEDGEMENT

I would like to express my sincere gratitude and appreciation to **Prof. Dr. Samira Saleh** chairman, Department of Pharmacology and Toxicology, Cairo University for her instructive supervision, fruitful help, continuous advice and valuable guidance throughout the whole work.

I would like to express my deepest gratitude and sincere regards to **Prof. Dr. Bernd Mayer**, chairman, Department of Pharmacology and Toxicology, Graz University for providing all essential research facilities during my thesis work. His suggestions have enabled me to go further on work.

I wish to express my gratitude and deep thanks to **Assistant Prof. Dr. Laila G. Mahran** for her continuous encouragement. I would like to gratefully acknowledge her supervision to this work.

I submit my sincere thanks and respectful regards to **Prof. Dr. Peter Dittrich** for his valuable advice, encouragement and supervision.

I express my great thanks and respects to **Prof. Dr. Sigrid Holzmann** for her timely suggestions and help during the course of my research.

I am sincerely grateful to all my colleagues in the Pharmacology Department, Cairo University and the Institute of Pharmacology and Toxicology, Graz University for their cooperation.

I would like to express my gratitude to the Österreichischer Akademischer Austauschdienst (ÖAD) for a grant in the framework of the channel system that enabled me to complete my practical work in the Institute of Pharmacology and Toxicology, Graz University.



## ABBREVIATIONS

<b>4-ABH<sub>4</sub></b>	4-Amino-tetrahydrobiopterin
<b>DMSO</b>	Dimethylsulfoxide
<b>FAD</b>	Flavine adenine dinucleotide
<b>FMN</b>	Flavine mononucleotide
<b>L-NAME</b>	NG-Nitro-L-Arginine-Methyl ester
<b>L-NNA</b>	NG-Nitro-L-Arginine
<b>NOS</b>	NO-Synthase
<b>nNOS</b>	Neuronal NO-Synthase
<b>eNOS</b>	Endothelial NO-Synthase
<b>iNOS</b>	Inducible NO-Synthase
<b>NO</b>	Nitric oxide
<b>BK</b>	Bradykinin
<b>DEA/NO</b>	2,2-diethyl-1-nitroso-oxyhydrazine sodium salt
<b>NE</b>	Norepinephrine
<b>U<sub>46619</sub></b>	9,11-Dideoxy-9,11-methanoepoxy-prostaglandin F2 $\alpha$
<b>EC<sub>50</sub></b>	Concentration producing half-maximal effect

<b>IC<sub>50</sub></b>	Concentration producing half-maximal inhibition
<b>LPS</b>	Lipopolysaccharide
<b>A<sub>23187</sub></b>	Calcium ionophore
<b>GSNO</b>	Nitrosoglutathione
<b>cGMP</b>	Guanosine 3', 5'-cyclic monophosphate
<b>SIN-1</b>	3-Morpholino sydnonimine



## LIST OF TABLES

	Page
<b>Table (1a) :</b> Effect of 4-ABH <sub>4</sub> and L-NNA on endothelium-dependent relaxation of pig pulmonary artery. Concentration-response curves elicited by bradykinin in pulmonary artery strips precontracted with 1μM NE in the presence of the indicated concentrations of 4-ABH <sub>4</sub> .....	36
<b>Table (1b) :</b> Effect of 4-ABH <sub>4</sub> and L-NNA on endothelium-dependent relaxation of pig pulmonary artery. Concentration-response curves elicited by A <sub>23187</sub> in pulmonary artery strips precontracted with 1μM NE in the presence of the indicated concentrations of 4-ABH <sub>4</sub> .....	38
<b>Table (2a) :</b> Effect of 4-ABH <sub>4</sub> and L-NNA on endothelium-dependent relaxation of pig coronary artery. Concentration-response curves elicited by bradykinin in coronary artery strips precontracted with 0.1μM U <sub>46619</sub> in the presence of the indicated concentrations of 4-ABH <sub>4</sub> .....	40
<b>Table (2b) :</b> Effect of 4-ABH <sub>4</sub> and L-NNA on endothelium-dependent relaxation of pig coronary artery. Concentration-response curves elicited by A <sub>23187</sub> in coronary artery strips precontracted with 0.1μM U <sub>46619</sub> in the presence of the indicated concentrations of 4-ABH <sub>4</sub> .....	42

<b>Table (3) :</b> Effect of 4-ABH <sub>4</sub> on relaxation of pig pulmonary artery to the NO donor DEA/NO. Concentration-response curves elicited by DEA/NO in the absence and presence of 100μM 4-ABH <sub>4</sub> in pulmonary artery strips precontracted with 1μM NE. ....	45
<b>Table (4) :</b> Effect of 4-ABH <sub>4</sub> (10μM) and L-NNA (0.1mM) on time-dependent relaxation of pig coronary artery to LPS. Vascular tone of coronary artery strips precontracted with 0.1μM U <sub>46619</sub> was continuously monitored for 18 hour. ....	48
<b>Table (i) :</b> Potency of 4-ABH <sub>4</sub> to inhibit relaxations of pig pulmonary and coronary artery in response to endothelium-dependent agonists and LPS. ....	51
<b>Table (5a) :</b> Effect of 4-ABH <sub>4</sub> and L-NNA on the contractile response of pig pulmonary artery. Concentration-response curves elicited by norepinephrine in artery strips obtained from blood vessels incubated for 10 hours. ....	52
<b>Table (5b) :</b> Effect of 4-ABH <sub>4</sub> and L-NNA on the contractile response of pig coronary artery. Concentration-response curves elicited by U <sub>46619</sub> in artery strips obtained from blood vessels incubated for 20 hours. ....	54
<b>Table (6) :</b> Concentration-dependent effect of 4-ABH <sub>4</sub> on the contractile response of pig coronary artery to 0.1μM U <sub>46619</sub> . Non-linear curve fitting of the data shown in Figure 5b. ....	56



<b>Table (7) :</b> Effect of sepiapterin on the inhibition by 4-ABH <sub>4</sub> of LPS-triggered hyporesponsiveness of pig pulmonary artery to NE. Concentration-response curves elicited by NE in artery strips obtained from blood vessels incubated for 10 hours.....	59
<b>Table (8a) :</b> Concentration-dependent effect of the non-selective NOS inhibitor L-NNA on bradykinin-induced relaxations of pig pulmonary arteries.....	62
<b>Table (8b) :</b> Concentration-dependent effect of the non-selective NOS inhibitor L-NNA on LPS-triggered hyporeactivity of pig pulmonary arteries.....	64
<b>Table (9) :</b> Effect of hypoxia and reoxygenation on pig coronary arteries precontracted with 0.1 $\mu$ M U <sub>46619</sub> in the absence (control) and in the presence of 200nM glibenclamide, 2 $\mu$ M glibenclamide, 100 $\mu$ M L-NNA and in the presence of L-NNA with 200nM glibenclamide and L-NNA with 2 $\mu$ M glibenclamide. ....	68
<b>Table (10) :</b> Effect of hypoxia and reoxygenation on pig pulmonary arteries precontracted with 1 $\mu$ M NE in the absence (control) and in the presence of 200nM glibenclamide, 2 $\mu$ M glibenclamide, 100 $\mu$ M L-NNA and in the presence of L-NNA with 200nM glibenclamide and L-NNA with 2 $\mu$ M glibenclamide. ....	71
<b>Table (11a) :</b> Time course studies of hypoxia and reoxygenation on cGMP levels for the control strips. ....	74