

CONTENTS

	Page
ABSTRACT (Thai)	iii
ABSTRACT (English)	
v	
ACKNOWLEDGEMENTS	vii
CONTENTS	viii
LIST OF ABBREVIATIONS	
ix	
LIST OF TABLES	xiii
LIST OF FIGURES	xiv
CHAPTER	
1. INTRODUCTION	1
2. REVIEW OF LITERATURE	
4	
3. MATERIALS AND METHODS	69
4. RESULTS	91
5. DISCUSSION	120
BIBLIOGRAPHY	129
VITAE	171

LIST OF ABBREVIATIONS

%	=	percent
<	=	less than
≤	=	less than or equal to
μl	=	microliters
μM	=	micromolar
μm	=	micrometer (micron)
μg	=	microgram
ACN	=	acetonitrile
Ad libitum	=	at needed or desired
A.M.	=	ante meridiem means “before noon”
ANOVA	=	analysis of variance
b.i.d	=	twice a day
BP	=	blood pressure
BW	=	body weight
°C	=	degree celsius (centigrade)
Ca ²⁺	=	calcium ions
cc	=	cubic centimeter
CI	=	Confidence Interval
CNS	=	central nervous system
CO ₂	=	carbon dioxide
cocaine HCL	=	cocaine hydrochloride
Conc.	=	concentrate
Cont.	=	continue
CV	=	coefficient of variance
CVS	=	cardiovascular system

DA	=	dopamine
$[D]_{\max 50}$	=	the molar concentration of agonist producing response which is 50 percent of maximum response
$[D]_{\max 50}$ ratio	=	the degree of supersensitivity
ECG	=	electrocardiogram
ER	=	emergency room
e.g.	=	exempli gratia means "for example"
EP	=	epinephrine
et al	=	and co-workers
Fig	=	figure
g	=	gram
HR	=	heart rate
K_d	=	dissociation constant
kg	=	kilogram
Krebs' solution	=	Krebs-Henseleit solution
L	=	liter
LOD	=	limit of detection (limit of determination)
LOQ	=	limit of quantification (lowest detectable quantity)
MeOH	=	methanol
mg	=	milligram
min	=	minute
mmHg	=	millimeter of mercury
M.W	=	molecular weight
ND	=	not detectable
ng	=	nanogram
nm	=	nanometer
HPLC	=	high performance liquid chromatography
hr	=	hour

i.p.	=	intraperitoneally
i.e.	=	i.e. (id est) means "that is" or "in other words"
i.v.	=	intravenously
I.D.	=	internal diameter
ISO	=	isoproterenol
M	=	molar
ml	=	milliliter
MI	=	myocardial infarction
Min	=	Minute
mM	=	millimolar
MP	=	mobile phase
NaCl	=	sodium chloride
N	=	number
NE	=	norepinephrine
ng	=	nanogram
nm	=	nanometer
NSS	=	normal saline
<i>p</i>	=	<i>p</i> value
PA	=	peak area
pA_2	=	the measurement of the activity of an antagonist as a log
pD_2	=	negative logarithm of the molar concentration of agonist producing response which is a 50 percent of maximum response
pH	=	the negative logarithm of the hydrogen ion concentration
pKa	=	the negative logarithm of the dissociation constant
P.M.	=	post meridiem means "after noon."
psi	=	a unit of pressure
r	=	correlation coefficient

r^2	=	coefficient determination
rpm	=	round per minute
RSD	=	relative standard deviation
SAL	=	salbutamol
S.D.	=	standard deviation of the response
S.E.M	=	standard error of mean
sec	=	second
UV	=	ultraviolet spectrum
w/v	=	weight/volume

LIST OF TABLES

TABLES		Page
1.	Pharmacokinetic of Cocaine according to the Route of Administration	14
2.	Physical and Psychological Effects of Cocaine	25
3.	Biological responses mediated by α -Adrenergic Receptors	40
4.	Comparison of Adrenoceptor Subtypes	44
5.	The Validation Parameters of Cocaine Concentrations in Plasma	87
6.	The Validation Parameters of Cocaine Concentrations in Atria	88
7.	The Validation Parameters of Cocaine Concentrations in Ventricle	89
8.	The Validation Parameters of Cocaine Concentrations in Trachea	90
9.	The $D_{\max 50}$ and pD_2 Values of the Positive Inotropic, Chronotropic and Tracheal Relaxing Effects of Epinephrine and Salbutamol in Isolated Guinea-Pigs Atria and Trachea	115
10.	The pA_2 Values for Propranolol on the Inhibition of the Responsiveness of Positive Inotropic, Positive Chronotropic and Relaxing Effects of Exogenous Epinephrine on the Isolated Atria and Trachea of Cocaine and Saline-Treated Guinea-Pigs	116
11.	Comparison of the $D_{\max 50}$ ratio of Positive Inotropic, Positive Chronotropic and Tracheal Relaxing Effects of Epinephrine (EP) and Salbutamol(SAL) and Cocaine Concentration in Plasma, Cardiac, and Tracheal Tissues taken at 24 hr after Cocaine Cessation of 2.5 mg/kg of Cocaine-Treated Guinea-Pigs	117
12.	Concentration of Cocaine in Plasma following 2.5 mg/kg of Cocaine Administration at 24 hr after Cessation	118
13.	Concentration of Cocaine in Tracheal Smooth Muscle following 2.5 mg/kg of Cocaine Administration at 24 hr after Cessation	119

LIST OF FIGURES

FIGURES		Page
1.	The Chemical Structure of Cocaine	5
2.	Cocaine and Metabolites	18
3.	The Mechanism of Cocaine	23
4.	The Adrenoceptor Family	38
5.	Signal Transduction of Adrenoceptors	43
6.	Synthesis of Endogenous Catecholamines	48
7.	Chemical Structure of Salbutamol	53
8.	Chemical Structure of Propranolol	54
9.	The Isolated Guinea-Pig Atrial Preparation	71
10.	The Set up of Isolated Guinea-Pig Atria	72
11.	The Segments of Trachea Dissected from Guinea-Pig (above) And The Preparation of Tracheal Strip (below)	73
12.	The Set up of Isolated Guinea-Pig Trachea	74
13.	The Calibration Curve of Cocaine in Plasma	83
14.	The Calibration Curve of Cocaine in Atria	84
15.	The Calibration Curve of Cocaine in Ventricle	85
16.	The Calibration Curve of Cocaine in Trachea	86
17.	The Representative Tracing of the Positive Inotropic and Positive Chronotropic Effects of the Cumulative Increase in Concentrations of Epinephrine in Isolated Atria of Cocaine -and Saline -Treated Guinea-Pigs	95
18.	The Representative Tracing of the Positive Inotropic and Positive Chronotropic Effects of the Cumulative Increase in Concentrations of Salbutamol in Isolated Atria of Cocaine-and Saline-Treated	96

Guinea-Pigs

LIST OF FIGURES (cont)

FIGURES		Page
19.	The Cumulative Concentration-Effect Curves of Epinephrine (EP) and Salbutamol (SAL) on Force of Contraction of Isolated Atria of Cocaine- and Saline-Treated Guinea-Pigs	97
20.	The Cumulative Concentration-Effect Curves of Epinephrine (EP) and Salbutamol (SAL) on Heart Rate of Isolated Atria of Cocaine- and Saline-Treated Guinea-Pigs	98
21.	The Representative Tracing of Relaxing Effect of the Cumulative Increase in Concentrations of Epinephrine on Carbachol-Induced Contraction of Cocaine- and Saline-Treated Guinea-Pig Tracheas	99
22.	The Representative Tracing of Relaxing Effect of the Cumulative Increase in Concentrations of Salbutamol on Carbachol-Induced Contraction of Cocaine- and Saline-Treated Guinea-Pig Tracheas	100
23.	The Cumulative Concentration-Effect Curves of Epinephrine (EP) and Salbutamol (SAL) on Carbachol-Induced Contraction of Isolated Trachea of Cocaine- and Saline-Treated Guinea-Pigs	101
24.	The Representative Tracing of Positive Inotropic and Positive Chronotropic Effects of the Cumulative Increase in Concentrations of Epinephrine in the Presence of Propranolol of Cocaine-and Saline-Treated Guinea-Pig Atria	102
25.	The Representative Tracing of the Cumulative Increase in	103

Concentrations of Epinephrine in the Presence of Propranolol on
Carbacol-Induced Tracheal Contraction of Cocaine-and Saline-
Treated Guinea-Pig Tracheas

LIST OF FIGURES (cont)

FIGURES		Page
26.	Effects of some Concentrations of Propranolol on the Cumulative-Concentration Stimulation Curves of Epinephrine on Force of Contraction of Isolated Atria of Cocaine-Treated Groups Compared to Those of Saline-Treated Groups	104
27.	Effects of Propranolol (Pro) on the Cumulative-Concentration Response Curves of Positive Inotropic Effects of Epinephrine (EP) on Isolated Atria of Cocaine-Treated and Saline-Treated Guinea-Pigs	105
28.	Effects of some Concentrations of Propranolol on the Cumulative-Concentration Stimulation Curves of Epinephrine on Heart Rate of Isolated Atria of Cocaine-Treated Groups Compared to Those of Saline-Treated Groups	106
29.	Effects of Propranolol (Pro) on the Cumulative-Concentration Response Curves of Positive Chronotropic Effects of Epinephrine (EP) on Isolated Atria of Cocaine-Treated and Saline-Treated Guinea-Pigs	107
30.	Effects of some Concentrations of Propranolol on the	108

- Cumulative-Concentration Stimulation Curves of Epinephrine
on Tracheal Relaxation on Isolated Trachea of Cocaine-Treated
Groups Compared to Those of Saline-Treated Groups
31. Effects of Propranolol (Pro) on the Cumulative-Concentration 109
Response Curves of Tracheal Relaxing Effects of Epinephrine (EP)
on Isolated Trachea of Cocaine- and Saline-Treated Guinea-Pigs

LIST OF FIGURES (cont)

FIGURES		Page
32.	Schild Plot for Determination of pA ₂ Values of the Antagonism of Propranolol on the Positive Inotropic Response to Epinephrine of Cocaine- and Saline-Treated Guinea-Pigs	110
33.	Schild Plot for Determination of pA ₂ Values of the Antagonism of Propranolol on the Positive Chronotropic Response to Epinephrine of Cocaine and Saline-Treated Guinea-Pigs	111
34.	Schild Plot for Determination of pA ₂ Values of the Antagonism of Propranolol on the Tracheal Relaxing Response to Epinephrine of Cocaine- and Saline-Treated Guinea-Pigs	112
35.	The Representative Chromatograms of Cocaine in Plasma, Atrial, Ventricular, and Tracheal Tissues	113