UNIVERSITI PUTRA MALAYSIA

3,19-DIACETYL-14-DEOXY-11,12- DIDEHYDROANDROGRAPHOLIDE (SRS27) ANTAGONISES INFLAMMATORY RESPONSE AND OXIDATIVE STRESS IN *IN VITRO* AND *IN VIVO* ASTHMA MODELS

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By

LIM CHEE WOEI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

3,19-DIACETYL-14-DEOXY-11,12-DIDEHYDROANDROGRAPHOLIDE (SRS27) ANTAGONISES INFLAMMATORY RESPONSE AND OXIDATIVE STRESS IN *IN VITRO* AND *IN VIVO* ASTHMA MODELS

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LIM CHEE WOEI

June 2014

Chairman : Johnson Stanslas, PhD

Faculty : Medicine and Health Sciences

Corticosteroids and non-steroidal anti-inflammatories are the most effective treatments for a variety of inflammatory conditions such as asthma. Steroids act by blocking transcription factors, such as nuclear factor (NF)-κB and activator protein (AP)-1 to down-regulate a vast array of pro-inflammatory genes, whereas NSAIDs specifically target cyclo-oxygenase (COX) activity to reduce prostaglandin production. However, the use of both types of drugs is associated with unwanted side effects, and a significant proportion of patients are steroid resistant. Thus, there is an urgent need to develop novel anti-inflammatory drugs to replace or complement present day therapy.

The bioactive compounds from the famous Asian herb *Andrographis paniculata* (known locally in Malaysia as Hempedu Bumi) have been studied for almost a century. The focus has been placed on the identification of antiinflammatory and anticancer agents. The herb contains two main diterpenoid constituents named andrographolide (AGP) and 14-deoxy-11,12-didehydroandrographolide (DDAG). AGP and DDAG were found to exhibit anti-asthma effects by inhibiting inflammatory responses in an allergic mouse asthma model. As such, both of them could act as novel replacement for current anti-inflammatory drugs. However, due to inadequacies of both compounds in terms of drug-like properties, DDAG analogues were semisynthesised to tackle these shortcomings.

Among the analogues, 3,19-diacetyl-14-deoxy-11,12-didehydroandrographolide (SRS27) was proven to inhibit cysteinyl leukotriene (CysLT) and nitric oxide (NO) synthesis in mouse macrophages, like AGP. However, DDAG on the other hand, failed to exhibit such activity. SRS27 was less toxic compared with AGP, which suggests that a simple chemical modification of DDAG produces a compound with CysLT and NO inhibitory activity similar to AGP but maintained the toxicity profile similar to DDAG. It is interesting to note that other analogues such as SRS28, SRS49, SRS76 and SRS83 with chemical modifications on the same carbon numbers

3 and 19 of DDAG were unable to show inhibition of CysLT and NO synthesis.

Consequently, the potential anti-inflammatory effect of SRS27 was investigated in ovalbumin (OVA)-induced mouse asthma model. The compound was administered in a prophylactic manner and showed a substantial decrease in asthma parameters. SRS27 at 3 mg/kg twice daily for three days consecutively significantly reduced OVA-induced total cell such as macrophages, eosinophils, lymphocytes and neutrophils, as well as inflammatory cytokines such as IL-4, IL-5, IL-13 and eotaxin in bronchoalveolar lavage (BAL) fluid. The compound also suppressed serum IgE production. In addition, SRS27 suppressed mucus hyper-secretion and expression of inflammatory mediators such as TNF-α, MCP-1, Muc5ac, RANTES, IL-33 and iNOS. Mechanistically, the compound inhibited lung NF-κB p65 nuclear translocation. In line with this observation, p65 NF-κB nuclear translocation was also found to be inhibited by the compound in A549 lung cancer cell line. Notably, this inhibition was not a result of cell toxicity as peripheral blood count in normal BALB/C mice treated with 3 mg/kg of SRS27 was not affected. The acute toxicity in mice further supported this idea, which indicated SRS27 is indeed a safe compound, just like DDAG. A pharmacokinetic study in Balb/C mice at 3 mg/kg single dose revealed SRS27 that had a relatively short half-life but was able to achieve a concentration range of 13- 19 μM concentration that could be related to *in vitro* anti-asthma activities. SRS27 is the first known DDAG derivative tested positive in a mouse asthma model and as such this compound could serve as a prototype and template for future improvement as a potential prophylactic agent to control asthma.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

3,19-DIACETYL-14-DEOXY-11,12-DIDEHIDROANDROGRAPHOLIDE (SRS27) MENGHALANG RESPON INFLAMASI DAN TEKANAN OKSIDASI DI DALAM MODEL ASMA *IN VITRO* DAN *IN VIVO*

Oleh

LIM CHEE WOEI

Jun 2014

Pengerusi : Johnson Stanslas, PhD

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Kortikosteroid dan drug anti-inflamasi non steroid (DAINS) merupakan rawatan yang paling berkesan untuk pelbagai keadaan radang seperti asma. Steroid bertindak dengan menyekat faktor transkripsi, seperti factor nuklear (NF) κB dan pengaktif protein (AP) -1 untuk merencat pelbagai gen pro-keradangan, manakala DAINS bertindak ke atas aktiviti siklooksigenase (COX) dengan mengurangkan sintesis prostaglandin. Walaubagaimanapun, penggunaan kedua-dua jenis ubat tersebut memberi kesan sampingan yang tidak diingini, dan sebahagian besar daripada pesakit mengalami kerintangan terhadap steroid. Oleh sebab itu, keperluan untuk membangunkan ubat anti-inflamasi yang baharu untuk menggantikan atau sebagai pelengkap bagi terapi yang sedia ada adalah amat kritikal.

Sebatian bioaktif daripada salah herba terkenal di Asia, iaitu *Andrographis paniculata* (Hempedu Bumi) telah dikaji lebih daripada satu abad dengan tumpuan diberikan untuk mengenalpasti ejen anti-inflamasi dan antikanser. Herba ini mengandungi dua komponen utama diterpenoid iaitu andrographolide (AGP) dan 14 - deoxy- 11 ,12- didehidroandrographolide (DDAG). AGP dan DDAG didapati menunjukkan kesan anti asma apabila tindakbalas inflamasi dalam model alahan asma mencit berkurangan selepas diberi diterpenoid tersebut. Oleh itu kedua-dua komponen tersebut dilihat berpotensi menjadi penggantibagi ubat anti-inflamasi semasa yang baharu. Walaubagaimanapun, disebabkan sebatian ini mempunyai ciri-ciri ubat yang tidak sesuai, analog DDAG dihasilkan untuk menangani kelemahan ini dan seterusnya kajian dilakukan untuk menjelaskan hubungan struktur - aktiviti.

Antara analog yang dikaji, 3,19-diacetyl-14-deoxy-11,12-didehidroandrographolide (SRS27) telah dibuktikan dapat merencat sintesis cysteinyl leukotriene (CysLT) dan nitrikoksida (NO) dalam makrofaj mencit, seperti AGP. Namun, DDAG didapati gagal untuk mempamerkan aktiviti sedemikian. SRS27 yang didapati kurang toksik berbanding dengan AGP, menunjukkan pengubahsuaian kimia yang mudah ke atas DDAG menghasilkan sebatian yang mengandungi aktiviti terhadap CysLT dan NO

seperti AGP dan mengekalkan profil ketoksikan seperti DDAG. Menariknya, analog lain seperti SRS28, SRS49, SRS76 dan SRS83 dengan pengubahsuaian kimia pada nombor karbon yang sama iaitu 3 dan 19 dalam DDAG didapati tidak menunjukkan aktiviti perencatan sintesis CysLT dan NO.

Selanjutnya, potensi kesan anti-inflamasi oleh SRS27 dikaji dalam model asma mencit diaruh dengan ovalbumin (OVA). SRS27 yang diberikan secara profilaktik menunjukkan penurunan ketara parameter asma. Sebatian ini yang diberikan secara intraperitonium pada dos 3 mg/kg sebanyak 2 kali sehari selama 3 hari berturut-turut telah mengurangkan jumlah sel yang diaruh oleh OVA seperti makrofaj, eosinofil, limfosit, dan neutrofil, serta sitokin inflamasi seperti IL-4, IL-5, IL-13 dan eotaxin dalam cecair bronchoalveolar (BAL lavage). Sebatian ini juga merencatkan penghasilan IgE. Disamping itu, ia juga dapat merencat rembesan lendir dan ekspresi pengantara inflamasi seperti TNF- α, PKM -1, Muc5ac, RANTES , IL- 33 dan iNOS. Daripada sudut mekanisme, sebatian tersebut menghalang translokasi nukleus NF-κB p65 di dalam paru-paru. Selaras dengan pemerhatian ini, p65 NF-κB nuclear translokasi juga didapati direncatkan oleh sebatian tersebut di dalam sel kanser paru-paru (A549). Perencatan ini bukan terhasil akibat daripada ketoksikan sel dimana kiraan darah periferi dalam mencit BALB/C normal yang dirawat dengan 3 mg/kg SRS27 adalah tidak terjejas. Hasil kajian ketoksikan akut menggunakan model mencit telah menyokong idea ini dengan membuktikan SRS27 sebagai satu sebatian yang selamat seperti DDAG. Kajian farmakokinetik pula menunjukkan bahawa dos tunggal 3 mg/kg SRS27 mempunyai jangka separuh hayat yang agak singkat (4.8 min) tetapi mampu mencapai julat kepekatan maksima darah sebanyak 13 - 19 μM yang boleh dikaitkan dengan aktiviti anti-asma *in vitro*. SRS27 merupakan analog DDAG yang pertama diuji positif dalam model asma mencit dimana ia berpotensi dijadikan sebagai sebatian prototaip dan templat untuk penambahbaikkan sebagai sebatian profilaktik yang berpotensi untuk mengawal asma pada masa hadapan.

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I certify that a Thesis Examination Committee has met on 2 June 2014 to conduct the final examination of Lim Chee Woei on his thesis entitled "3,19-Diacetyl-14-Deoxy-11,12-Didehydroandrographolide (SRS27) Antagonises Inflammatory Response and Oxidative Stress in *In Vitro* and *In Vivo* Asthma Models" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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Signature: _____	Signature: _____
Name of Member of Supervisory Committee: Fred Wong Wai-Shiu	Name of Member of Supervisory Committee: _____

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5-LOX	5-Lipoxygenase
8-OHdG	8-Oxo-2'-deoxyguanosine
A549	Adenocarcinomic human alveolar basal epithelial cells.
AChE	Acetylcholinesterase
AGP	Andrographolide
AHR	Airway hyperresponsiveness
AHU	Animal Holding Unit
AIRIAP	Asthma Insights and Reality in Asia Pacific
AKT	Protein Kinase B
ALT	Alanine transaminase
$Al(OH)_3$	Aluminium hydroxide
AMCase	Acidic mammalian chitinase
AMV	Avian myeloblastosis virus
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AP-1	Activator protein
ASM	Airway smooth muscle
AST	Aspartate transaminase
ATP	Adenosine triphosphate
AUC	Area under curve
B_0	Maximum binding well
BAL	Bronchoalveolar lavage
BALB/C	Albino, laboratory-bred strain mice
Baso	Basophils
BCA	Bicinchoninic acid
Bcl-3	B-cell lymphoma 3-encoded
BEAS-2B	Human lung epithelial cells
BSA	Bovine serum albumin
cAMP	Cyclic adenosine monophosphate
Ca^{2+}	Calcium ion
CARE	Centre for Animal Resources
CD4+	Cluster of differentiation 4
CDER	Centre for Drug Evaluation and Research
Cdyn	Dynamic compliance
CHMP	Committee for Medicinal Products for Human Use
Cl	Clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenases
COX-2	cyclooxygenase 2
CS	Corticosteroids
CVM	Centre for Veterinary Medicine
CXC	α-chemokines
CysLT	Cysteinyl leukotriene
DDAG	14-deoxy-11,12-didehydroandrographolide
DEPC	Diethylpyrocarbonate

DMEM	Dulbecco's Modified Eagle's medium
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DNAse	Deoxyribonuclease
DPX	Digital Picture Exchange
DTT	Dithiothreitol
ECL	Enhanced chemiluminescence
ECP	Eosinophil cationic proteins
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EPO	Eosinophil peroxidase
Eos	Eosinophils
ERK	Extracellular signal-related kinase
E-selectin	Endothelial selectin
FBS	Foetal bovine serum
FcεR	High affinity IgE receptor
FDA	Food and Drug Administration
FLAP	5-lipoxygenase activating protein
Foxa2	Forkhead box α-2
GATA3	Trans-acting T-cell-specific transcription factor
GCCP	Good cell culture practice
GPCRs	G protein coupled receptors
G-CSF	Granulocyte colony stimulating factor
GINA	Global Initiative for Asthma
GM-CSF	Granulocyte macrophage colony stimulating factor
GR	Glucocorticoid receptors
HCl	Hydrochloride acid
HCT116	Human colon cancer cell line
HDAC2	Histone deacetylase-2
HIV	Human immunodeficiency virus
H_2O_2	Hydrogen peroxide
H_3PO_4	Phosphoric acid
HPLC	High performance liquid chromatography
HRP	Horseradish peroxidase
IACUC	Institutional Animal Care and Use Committee
ICAM-1	Intercellular Adhesion Molecule 1
ICS	Inhaled corticosteroids
IFN	Interferon
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IGF	Insulin-like growth factor
IκB	Inhibitor κB
IKK-α	Inhibitor of kappaB kinase alpha
IKK-β	Inhibitor of kappaB kinase beta
IL	Interleukin
iNOS	Inducible nitric oxide synthase
i.p.	Intraperitoneal

JAK	Janus kinase
JNK	c-Jun N-terminal kinases
kDA	Kilo Dalton
K_{el}	Elimination rate constant
LABA	Long-acting β2-adrenoceptor agonists
L-NAME	L-NG-Nitroarginine Methyl Ester
Log P	Compound lipophilicity
LPS	Lipopolysaccharide
LT	Leukotriene
LTC_4	Leukotriene C4
LTD_4	Leukotriene D4
LTE_4	Leukotriene E4
Lym	Lymphocytes
Mac	Macrophages
MAPK	Mitogen activated protein kinase
MBP	Major basic protein
MCF7	Human breast cancer cell line
Mch	Acetyl-β-methylcholine chloride
MCP-1	Monocyte chemotactic protein-1
MMP	Matrix metalloproteinase
Mono	Monocytes
MHC	Major histocompatibility complex
MUC	Mucin
Muc5ac	Gel-forming mucin
Muc5b	Gel-forming mucin
MTT	3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide
NAG	Neoandrographolide
NDGA	Nordihydroguaiaretic acid
NEMO	NF-kappa-B essential modulator
Neu	Neutrophils
NF-kB	Nuclear factor kappa B
NLS	Nuclear localisation signal
NO	Nitric oxide
NOS	Nitric oxide synthase
NSB	Non-specific binding
NUS	National University of Singapore
ONOO-	Peroxynitrite
O_2-	Superoxide anion
OVA	Ovalbumin
P	1-octanol/water partition coefficient
$\Delta P/V$	Pressure driving respiration divided by airflow
PAGE	Polyacrylamide gel electrophoresis
PBS	Phosphate buffered saline
PBS-T	PBS containing 0.1% Tween 20
PC3	Human prostate cancer cell line
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositol 3-kinase
PKAc	Protein Kinase A catalytic subunit
PKC	Protein kinase C

PVDF	Polyvinylidene difluoride
RANTES	Regulated on Activation, Normal T Cell Expressed and Secreted
RAW 264.7	Mouse leukaemic monocyte macrophage cell line
RBM	Reticular basement membrane
RBL-2H3	Rat basophilic leukaemia
RI	Airway resistance
RNA	Ribonucleic acid
RNasin	Ribonuclease inhibitor
RNAse	Ribonuclease
RNS	Reactive nitrate species
RSD	Relative standard deviation
RT	Retention time
RT-PCR	Reverse transcriptase polymerase chain reaction
RTV	Real-Time Viewing
ROS	Reactive oxygen species
ROW	Relative organ weight
rpm	Revolutions per minute
RPMI	Roswell Park Memorial Institute medium
SABA	Short-acting beta2-agonists
SCG	Sodium cromoglicate
SD	Standard deviation
SDS	Sodium dodecyl sulphate
SIT	Allergen immunotherapy
SPSS	Statistical Package for Social Sciences
SOD	Superoxide dismutase
SRS27	3,19-Diacetyl-14-deoxy-11,12-didehydroandrographolide
SRS28	19-Acetyl-14-dexoy-11,12-didehydroandrographolide
SRS49	3,19-Dipropionyl-14-deoxy-11,12-didehydroandrographolide
SRS76	3,19-Benzylidene-14-deoxy-11,12-didehydroandrographolide
SRS83	3,19-(4-Chlorobenzylidene)-14-deoxy-11,12-didehydroandrographolide
SRS88	3,19-(4-Acetamidobenzylidene)andrographolide
STAT	Signal transducer and activator of transcription
$T_{1/2}$	Half-life
TA	Total activity well
TAE	Tris-acetate-EDTA
T-bet	T box transcription factor
TDZD-8	4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione
TEMED	N, N, N', N'- tetramethylethylenediamine
TGF-β	Transforming growth factor beta
Th0	Naïve T-Helper cells
Th1	T-helper cells 1
Th2	T-helper cells 2
T_{max}	Time to achieve C_{max}
TMB	3,3',5,5'-tetramethylbenzidine
TNF- α	Tumour necrosis factor alpha
TNF-R	Tumour necrosis factor receptor
TRCP	β-transducin repeat-containing protein
T_{regs}	Regulatory T cells

TSLP	Thymic stromal lymphopoietin
TTBS	Tris-Buffered Saline and Tween 20
Tween 20	Polyoxyethylene sorbitan monolaurate
URTI	Acute upper respiratory tract infection
US	United States of America
USD	United States Dollar
UV	Ultraviolet
ΔV/ΔP	Change in volume of the lung produced by a change in pressure across the lung
V	Volt
VCAM-1	Vascular cell adhesion protein 1
V_d	Volume of distribution
VEGF	Vascular endothelial growth factor
VERO	African green monkey kidney epithelial cells
VLA	Very late antigen
WBC	White blood cells
Ym-2	Chitinase 3-like 4
YKL-40	Chitinase 3-like 1

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Asthma is one of the most common chronic diseases, affecting both children and adults worldwide, with increasing prevalence over the past 40 years. The reasons for this dramatic increase in asthma are not yet clear and are likely to include multiple contributing factors. There are currently 300 million people worldwide estimated to be affected by asthma (Masoli *et al.*, 2004). For decades, the number of asthmatic cases has been increasing significantly. Considering population growth and increased urbanisation, the number of asthmatic patients is expected to rise to 400 million by the year 2025. It is estimated that 1 out of 250 deaths worldwide is due to asthma attacks (Peters *et al.*, 2006).

1.2 Problem Statements

Asthma is underdiagnosed and undertreated, but the symptoms usually respond well and can be controlled with inhaled corticosteroids (CS) and a short- or long-acting β2-agonist (Braman, 2006). Glucocorticoids are the most effective anti-inflammatory drugs available for the treatment of many chronic inflammatory and immune diseases, including asthma, rheumatoid arthritis, inflammatory bowel disease and autoimmune diseases (Barnes, 2010). In Malaysia, the most preferred medications for 'first-line', 'second-line' and 'third-line' treatment for asthma by government doctors were inhaled short-acting beta2-agonists (SABAs), CS, and leukotriene antagonist, respectively, whereas private doctors preferred oral SABAs, inhaled CS, and oral CS, respectively (Loh and Wong, 2005). However, CS suffers from unwanted side effects and a significant proportion of patients are steroid-resistant (Adcock and Lane, 2003; Barnes, 2010). Steroid-resistant patients have symptoms consistent with asthma and show very poor or no response at all to high doses of inhaled or even systemic corticosteroids (Barnes, 2010). In addition to resistance, there has been increasing concern over the adverse effects of CS, such as osteoporosis, glaucoma, growth retardation in children and poor wound healing effects (Schacke *et al.*, 2002). Add-on therapies for asthma such as long-acting reliever inhalers, leukotriene receptor antagonists and theophylline were invented to attenuate asthma *via* other approaches; however, the effects of these treatments are not as efficacious as those of steroids.

There has been a sharp increase in economic burden associated with asthma over the last 40 years, particularly in children. Asthma can involve costs related to health care use and morbidity, including missed work and school days. The large asthma burden and continued adverse outcomes present an on-going public health challenge, including the effort to enhance the uptake of underutilised management strategies to control symptoms (Akinbami *et al.*, 2011). Approximately 300 million people worldwide currently have asthma, and its prevalence increases by 50% every decade. Although asthma is most common in developed (westernised) countries, it is becoming increasingly common in developing countries like Malaysia, which is most likely related to the increased urbanisation of communities. Despite the constant publications and guidelines from the National Asthma Education and Prevention Program to educate the public awareness on

the disease, asthma still remains poorly controlled, with annual estimated costs of up to 56 billion USD (Spangler, 2012).

1.3 Significance of the Study

With the in-depth knowledge of asthma available, many new therapies for asthma have been developed. Current leading therapies for asthma rely mainly on ICS and LABAs. Despite being the most effective treatment for asthma, ICSs cause several systemic side effects. Add-on therapies that have been introduced over the past decade also either pose noticeable side effects (in the case of omalizumab) or have a narrow therapeutic index (in the case of theophylline). Thus, there is always an urgency to discover and develop a more potent and yet safer treatment for asthma. Searching for an alternative for many inflammatory diseases in natural products is the current trend, as many of the plants have yet to be exploited and studied (Lim *et al.*, 2012).

The bioactive compounds from the famous Asian herb *Andrographis paniculata* have been studied for their anticancer and anti-inflammatory properties for more than a decade (Lim *et al.*, 2012). The herb contains two main diterpenoid constituents named andrographolide (AGP) and 14-deoxy-11,12-didehydroandrographolide (DDAG). Both of the compounds were found to exhibit antiasthma effects by inhibiting inflammatory responses in an allergic mouse asthma model (Bao *et al.*, 2009; Guan *et al.*, 2011). In the present investigation, the anti-inflammatory effects and the involved pathways of a DDAG analogue which possess improved drug-like properties compared with the parent compound as new antiasthma agents were investigated.

1.4 HYPOTHESIS

The new semi-synthetic andrographolide derivatives have anti-asthma activity through their inhibitory effect on NF-κB and related pathways.

1.5 OBJECTIVES OF THE STUDY

1.5.1 Main Objective:

The aim of the study is to investigate the potential of DDAG analogues which possess improved drug-like properties compared with the parent compound as new antiasthma agents.

1.5.2 Specific Objectives

a) To determine the inhibition of cysteinyl leukotriene and nitric oxide synthesized *in vitro* by andrographolide derivatives in mouse macrophage models.
b) To determine the effect of SRS27 on cell signalling pathway in A549 cells associated with anti-asthmatic effect.
c) To determine the efficacy of SRS27 in a mouse asthma model.
d) To evaluate toxicity and pharmacokinetics of SRS27 in mice.

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