كلية الصيدلة

Alkoxyphenylthiazoles with broad-spectrum activity against multi-drug resistant gram-positive pathogens.

Thesis
submitted by
Moustafa ElAwamy Mohamed (BSc.)

Bachelor Degree of Pharmaceutical Sciences,
Faculty of Pharmacy, MSA University (2013).

In Partial Fulfillment of the Requirements of the
Master Degree
In Pharmaceutical Sciences.
"Pharmaceutical Chemistry".

Under supervision of

Prof. Dr. Khaled Abouzid Mohamed
Professor of Pharmaceutical Chemistry,
Faculty of Pharmacy, Ain Shams University and
Dean of the faculty of Pharmacy, University of Sadat City.
Dr. Rabah Ahmed Taha
Associate Professor of Pharmaceutical Chemistry
and Deputy Head of the Pharmaceutical Chemistry Department
Faculty of Pharmacy, Ain Shams University
Dr. Abdelrhman Salah Mayhoub
Associate Professor of Organic Chemistry
Faculty of Pharmacy, Al Azhar University

Ain-Shams University
Cairo- Egypt
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Besides the work presented in this thesis, the candidate successfully passed the Master's general and special postgraduate courses in Pharmaceutical Chemistry in the academic year 2017/2018 with the following grades;

1) Comprehensive Organic Chemistry A^-
2) Computer Aided Drug Design B^-
3) Methods of Drug Screening A^-
4) Structure Elucidation of Chemical Entities B^+
5) Pharmaceutical Chemistry B^-
6) Stereochemistry C
7) Biostatistics C^+
8) Scientific Writing and Research Ethics C^+
9) Instrumental Analysis B
10) Bioinformatics C

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AACs	Aminoglycoside acetyltransferases
ABC	ATP-binding cassette family
AIDS	Acquired immune deficiency syndrome
AMEs	Aminoglycoside modifying enzymes
AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
CDC	Center for disease prevention and control
CFR	Chloramphenicol–florfenicol resistance
CFUs	Colony forming units
CIMS	Chemical ionization mass spectrometry
CDC	Centre for disease control and prevention
DCM	Dichloromethane
DHFR	Dihydrofolate reductase
DMF	Dimethylformamide
DMF-DMA	Dimethylformamide-dimethyl acetal
EARSS	European antimicrobial resistance surveillance system
ECDC	European center for disease prevention and control
ERM	Erythromycin ribosome methylase
ESIMS	Electrospray ionization mass spectroscopy
FIC	Factory inhibitory concentration
GAIN	Generating antibiotic incentives now
HaCaT	Human keratinocytes
HGT	Horizontal gene transfer
HRMS	High resolution mass spectroscopy
HTS	High throughput screening
IC_{50}	Sample concentration which causes 50% inhibition
ICUs	Intensive care units
IMS	Intercontinental marketing services
IDSA	Infectious disease society of America

LPAD	Limited-population antibiotic drug
LR	Lawesson's reagent
MATE	Multidrug and toxic compound extrusion family
MCPBA	*m*-chloroperbenzoic acid
MDR	Multidrug resistant
MDRP	Multidrug-resistant pathogens
MeOH	Methanol
MGEs	Mobile genetic elements
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
MSSA	Methicillin sensitive *Staphylococcus aureus*
MFS	Major facilitator superfamily
NAPCAB	National action plan for combating antibiotic-resistant bacteria
NIH	National institutes of health
NPV	Net present value
PBP	Penicillin-binding protein
POC	Point-of-care
RDTs	Rapid diagnostic tests
RND	Resistance-nodulation-cell-division family
SMR	Small multidrug resistance family
SSTIs	Skin and soft-tissue infections
TMP-SMX	Trimethoprim-Sulfamethoxazole
UppP	Undecaprenyl pyrophosphate phosphatase
UppS	Undecaprenyl pyrophosphate synthase
VISA	Vancomycin-intermediate *Staphylococcus aureus*
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant *Staphylococcus aureus*

Abstract:

Title of thesis:

"Alkoxyphenylthiazoles with broad-spectrum activity against multidrug-resistant gram-positive bacterial pathogens"

Name of candidate:

Moustafa ElAwamy Mohamed (BSc.)

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Professor of Pharmaceutical Chemistry,

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Dr. Rabah Ahmed Taha

Associate Professor of Pharmaceutical Chemistry

and Deputy Head of the Pharmaceutical Chemistry Department

Faculty of Pharmacy, Ain Shams University

Dr. Abdelrhman Salah Mayhoub

Associate Professor of Organic Chemistry

Faculty of Pharmacy, Al Azhar University

With the continued rise of antibiotic resistance and reduced susceptibility to almost all front-line antibiotics, multidrug-resistant Gram-positive bacterial infections represent an incessant threat to healthcare providers. Antibiotic resistance kills an estimated 700,000 people each year worldwide, and some experts predict that number to reach 10 million by 2050 if efforts are not made to curtail resistance or develop new antibiotics. Although the development of second- and third antibacterial generations from the existing classes of antibiotics has improved the overall activity, bacterial resistance to these known drugs is on an exponential rise.

Previously, phenylthiazoles have been identified as a new scaffold with a notable efficacy against highly mutlidrug-resistant Gram-positive pathogens by using HTS on a wide variety of methicillin and vancomycin-resistant *Staphylococcus aureus* strains. Unfortunately, the promising activity of this novel class of antibiotics was hampered by their short half-life due to rapid hepatic metabolism. The lead compound **1a**, as a representative example, was cleared by liver microsomes at a rate of 80.3 μL/min-mg.

According to SAR analysis, Phenylthiazole scaffold has to carry two important structural features: basic guanidine moiety and lipophilic tail. Starting from the lead compound **1a**, a ligand-based drug design approach has been adopted in order to improve the antibacterial potency of the lead structure. A second generation phenylthiazole derivatives have been developed by replacing the rapidly hydrolysable Schiff-base moiety of the lead compound **1a** with cyclic unhydrolyzable bioisosteres; i.e. pyrimidine ring. And a series of 5-pyrimidophenylthiazoles with different moieties at position-5 has been synthesized and evaluated. As well as the incorporation of different cyclic bioisosteres instead of the *n*-butyl at the *p*-posistion of the phenyl group.

Later, metabolite profiling study determined the benzylic carbon of the lead compound 1a as an easily metabolized soft spot. Rapidly metabolized and cleared in human liver microsomes resulting in a very short half-life (<30 min). Upon replacement this particular methylene with an oxygen atom, the biological life span increased by more than eight-fold while maintaining their potent anti-MRSA activity.