شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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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

HANAA ALY

Ain Shams University
Faculty of Pharmacy
Pharmaceutical Chemistry Dept.

"Rational Design, Synthesis and Biological Evaluation of Certain Five Membered Ring Heterocycles"

A Thesis

Submitted for the Partial Fulfillment of the Requirements for the

Master degree
In Pharmaceutical Sciences
(Pharmaceutical Chemistry)

Presented by

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Besides the work presented in this thesis, the candidate successfully passed general and special postgraduate courses in pharmaceutical chemistry for one year during academic year 2015/2016 with the following grades

1) Statistics	A
2) Instrumental Analysis	A
3) Computer Sciences	A
4) Physical Chemistry	B+
5) Pharmaceutical Chemistry	B
6) Drug Spectroscopy	A
7) Selected Topics in Pharmaceutical Chemistry	B
8) Drug Stereochemistry	A

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List of abbreviations

A. baumannii	*Acinetobacter baumannii*
AMPT	5-acetyl-4-methyl-2-(3-pyridyl) thiazole
ASPs	Anti-microbial stewardship programs
C. violaceum	*Chromobacterium violaceum*
CDC	Centers for disease control and prevention
HIV	Human immunodeficiency virus
ICUs	Intensive care units
K. pneumonia	*Klebsiella pneumonia*
kDa	Kilodalton
LPS	Lipopolysaccharide
MDR	Multidrug resistant
MRSA	Methicillin resistant *Staphylococcus aureus*
OmpA	Outer membrane protein A
P. aeruginosa	*Pseudomonas aeruginosa*
S. aureus	*Staphylococcus aureus*
S. pneumonia	*Streptococcus pneumonia*
T2SS	Type two secretion system
WHO	World health organization

AceI	Acinetobacter-chlorhexidine-efflux protein
DMF	Dimethyl formamide
CpaA	Glycan-specific-adamalysin-like protease
BapAb	Biofilm associated proteins of *Acinetobacter baumannii*
Csu	Chaperon/usher pilus system
PNAG	Poly-β-1,6-N-acetylglucosamine
FecA	Ferric citrate
IC_{50}	The concentration of inhibitor needed to inhibit enzymatic activity by 50%
Ata	Trimeric autotransporter
Lip	Lipase
T6SS	Type VI secretion system
m.p	Melting point
LCFA	Long chain fatty acid
NBS	N-bromosuccinimide
MUFAs	Monounsaturated fatty acids
SAR	Structure-activity relationship
HEK	Human embryonic kidney cell
DMSO	Dimethyl sulfoxide
CC_{50}	Concentration that reduces the cell viability by 50%

HC_{50}	50% Hazardous concentration
HC_{10}	10% Hazardous concentration
MIC	Minimum inhibitory concentration
OD	Optical density
CAMHB	Cation-adjusted mueller hinton broth
CFU	Colony forming unit
MAD	Mean absolute deviation
DMEM	Dulbecco's modified eagle medium
FBS	Fetal Bovine Serum

Abstract

The resistant of *Acinetobacter baumannii* to almost all the available anti-microbial agents and their susceptibility for the epidemic spread, made an urgent need for discovering new targets for inhibition of virulent *Acinetobacter baumannii*, without stimulation of other resistant. Long chain fatty acid (LCFA) pathway of *A. baumannii* is a vital factor for bacterial physiology, make it an attractive target for drug discovery. Ole1p (Δ9-fatty acid desaturase enzyme) is a key element in LCFA pathway. It responsible for converting saturated fatty acyl-CoA substrates to monounsaturated fatty acids which is critical for membrane permeability, biofilm formation and surface motility. In this study, the main aim is to design novel thiazol-2(3*H*)-imine derivatives targeting Ole1p. The design focused on exploration of the previously exposed SAR studies and bioisosteric modifications of the lead compounds. The structure and purity of each final synthesized compound were confirmed by X-ray crystallography, ^{1}H-NMR, ^{13}C- NMR, EI-MS, and elemental analysis.

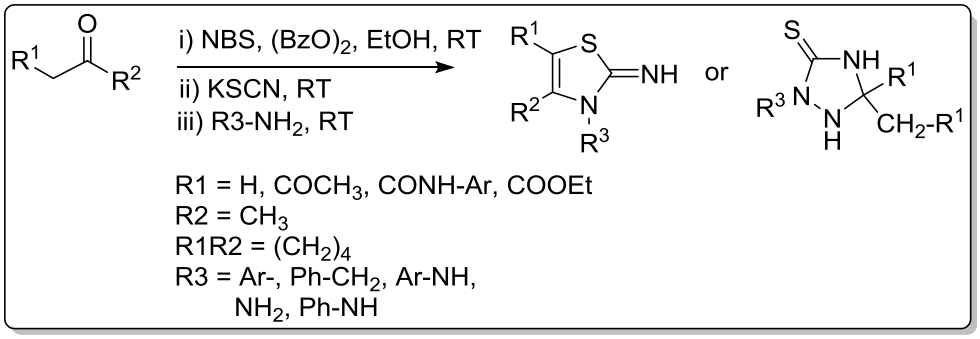

Figure 1: Graphical abstract for the new synthesized compounds described in this work.

This study involves the synthesis of the following new compounds:

1) *N*-(3-Benzyl-4-hydroxy-4-methylthiazolidin-2-ylidene)acetamide (**2)**

2) 4-Methyl-3-(*p*-tolyl)thiazol-2(3*H*)-imine (**5**)

3) 5-Bromo-4-methyl-3-(p-tolyl)thiazol-2(3*H*)-imine (**6**)

4) 3-(o-Tolyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2(3*H*)-imine (**9a**)

5) 3-(*p*-Tolyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-2(3*H*)-imine (**9b**)

6) 4-(2-Imino-4,5,6,7-tetrahydrobenzo[d]thiazol-3(2*H*)-yl)phenol (**9c**)