SYNTHESIS, ANTIFUNGAL AND ANTI-HIV ACTIVITIES OF NEW HETEROCYCLIC COMPOUNDS

HELMI MOHAMMED ABDULGHANI AL-MAQTARI

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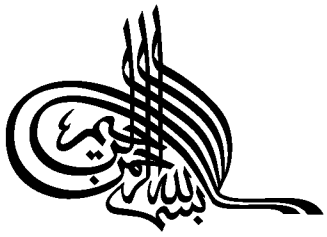

Dedicated to

My beloved parents

My beloved wife

My son, Bakil and My daughter, Azal

My beloved grandmother

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ABSTRACT

Thiophene chalcones, pyrazolines and 1,5-benzodiazepines are important heterocyclic compounds which show broad spectrum of biological activities. Three series of heterocyclic chalcones and their *N*-acetylated pyrazoline derivatives have been synthesized in low to good yields. The first step in this study is the synthesis of 3-acetyl-2,5-dichlorothiophene and 2-acetyl-5-chlorothiophene as heterocyclic ketones using Friedel-Crafts acylation. All thiophene chalcones were synthesized in three separate reactions by Claisen-Schmidt reaction of substituted thiophene aldehydes with ketones. Several acetophenone derivatives (series 2 and 3) were produced by cyclization reaction using hydrazine hydrate to form new and known *N*-acetylated pyrazoline derivatives. A series of substituted 1,5-benzodiazepines were synthesized in moderate to good yields. 4-Methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one was synthesized as starting material by reacting *ortho* phenylenediamine and crotonic acid in the presence of toluene. Cyclization of the starting material with appropriate acid chlorides, unsubstituted and five types of groups (fluoro, chloro, bromo, methyl and methoxy) attached at *ortho*, *para* and *meta* position of phenyl ring in the presence of triethylamine and anhydrous tetrahydrofuran have furnished substituted 1,5-benzodiazepines. The structures of the compounds were confirmed by infrared (IR), ^{1}H NMR and ^{13}C NMR (1D and 2D) nuclear magnetic resonance spectroscopies. Compounds of series 2 and 3 were tested for their antifungal activities against two types of pathogenic strains, namely *Candida albicansa* and *Aspergillus niger* with fluconazole as standard drug. The results for series 2 showed that the presence of bromo and methoxy substitution at *para* position on phenyl ring in chalcone and pyrazoline, respectively, resulted in significant enhancement in potency against both tested fungal strains with MIC value of >64 µg/mL. Compound carrying *para* fluoro on phenyl ring in pyrazoline derivatives exhibited the highest potency with MIC value of >32 µg/mL and 64 µg/mL against *C. albicans* and *A.niger,* respectively, among the series 3. The anti-HIV-1 RT assay of substituted 1,5-benzodiazepines (series 4) showed that the presence of chloro substitution at *meta* and *ortho* position inhibited the activity of HIV-1 RT with IC_{50} values 6.87 and 8.62 µM, respectively.

ABSTRAK

Tiofena kalkon, pirazolina dan 1,5-benzodiazepina adalah sebatian heterosiklik penting yang menunjukkan aktiviti biologi yang pelbagai. Tiga siri heterosiklik kalkon dan terbitan *N*-asetil pirazolina telah disintesis dengan hasil yang rendah hingga hasil yang baik. Langkah pertama dalam kajian ini ialah sintesis 3-asetil-2,5-diklorotiofena dan 2-asetil-5-klorotiofena sebagai keton heterosiklik menggunakan pengasilan Friedel-Crafts. Semua tiofena kalkon disintesis dalam tiga tindak balas berasingan dengan tindak balas Claisen-Schmidt aldehid tiofena tertukar ganti dengan keton. Beberapa terbitan asetofenon (siri 2 dan 3) telah dihasilkan dengan tindak balas pensiklikan menggunakan hidrazina hidrat untuk menghasilkan terbitan pirazolina *N*-asetil yang baharu dan yang diketahui. Satu siri 1,5-benzodiazepina tertukar ganti telah disintesis dengan hasil yang sederhana hingga hasil yang baik. 4-Metil-1,3,4,5-tetrahidro-2*H*-1,5-benzodiazepin-2-on telah dihasilkan sebagai bahan pemula melalui tindak balas *orto* fenilenadiamina dan asid krotonik dengan kehadiran toluena. Pensiklikan bahan pemula itu dengan asid klorida yang sesuai, fenil tanpa penukarganti dan gelang fenil dengan lima jenis kumpulan (fluoro, kloro, bromo, metil dan metoksi) yang terikat pada kedudukan *orto, para* dan *meta* dengan kehadiran trietilamina dan tetrahidrofuran kontang telah menghasilkan 1,5-benzodiazepina tertukar ganti. Struktur sebatian disahkan dengan spektroskopi inframerah (IR) dan resonans magnet nucleus ^{1}H NMR dan ^{13}C NMR (1D dan 2D). Sebatian siri 2 dan 3 telah diuji untuk aktiviti antikulat terhadap dua jenis patogen, iaitu *Candida albicansa* dan *Aspergillus niger* dengan flukonazol digunakan sebagai dadah piawai. Keputusan bagi siri 2 menunjukkan bahawa kehadiran bromin dan metoksi masing-masing pada kedudukan *para* pada gelang fenil dalam kalkon dan pirazolina, menghasilkan peningkatan ketara dalam potensi terhadap kedua-dua strain kulat yang diuji dengan nilai MIC > 64 μg/mL. Sebatian yang mengandungi fluoro *para* pada gelang fenil dalam terbitan pirazolina mempamerkan potensi tertinggi dengan nilai MIC 32 μg/mL dan 64 μg/mL masing-masing terhadap *C. albicans* dan *A.niger* dalam siri 3. Pengujian anti-HIV-1 RT terhadap 1.5-benzodiazepin tertukar ganti (siri 4) menunjukkan bahawa kehadiran kloro pada kedudukan *meta* dan *orto* merencatkan aktiviti HIV-1 RT masing-masing dengan nilai IC_{50} 6.87 dan 8.62 μM.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

CH_3CO_2H	-	Acetic Acid
Ac	-	Acetyl
AIDS	-	Acquired Immunodeficiency Syndrome
α	-	Alpha
Al_2O_3	-	Alumina
$AlCl_3$	-	Aluminum Chloride
ARVs	-	Antiretrovirals
ART	-	Antiretroviral Therapy
aq	-	Aqueous
AA	-	Ascorbic Acid
ATR-IR	-	Attenuated Total Reflectance- Infrared -
AZT	-	Azidothymidine
ABTS	-	2,2′-Azino-bis-(3-ethylbenzothiazoline-6-sulphonic acid)
BDZ	-	Benzodiazepines
β	-	Beta
H_3BO_3	-	Boric Acid
BF_3-Et_2O	-	Boron Trifluoride Ethyl Etherate
BHT	-	Butylated Hydroxytoluene
$CdCl_2$	-	Cadmium Chloride
CSA	-	Camphor Sulphonic Acid
^{13}C	-	Carbon-13
^{13}C NMR	-	Carbon Nuclear Magnetic Resonance
CNS	-	Central Nervous System
CAN	-	Ceric Ammonium Nitrate

δ	-	Chemical Shift
cpz*Ptt*	-	Chimpanzees(*Pan troglodytes troglodytes*)
$CHCl_3$	-	Chloroform
CD_4	-	Cluster of Differentiation 4
CC	-	Column Chromatography
CRIs	-	Co-receptor Inhibitors
COSY	-	Correlation Spectroscopy
J	-	Coupling Constant
COD	-	Cycloocta-1,5-diene
CYA	-	Czapek Yeast Extract Agar
CC_{50}	-	50% Cytotoxic Concentration
DNA	-	Deoxyribonucleic Acid
DD	-	*N*-Desmethyldiazepam
$CDCl_3$	-	Deuterated Chloroform
D	-	Diazepam
1D	-	1 Dimension
2D	-	2 Dimension
DMF	-	N,N'-Dimethylformamide
DMSO	-	Dimethyl Sulfoxide
MTT	-	(3,(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide)
DPPH	-	2,2-Diphenyl-1-picrylhydrazyl
DEPT	-	Distortionless Enhancement by Polarization Transfer
d	-	Doublet
dd	-	Doublet of Doublets
ddd	-	Doublet of Doublet of Doublets
ESI-MS	-	Electrospray Ionization Mass Spectrometry
ELISA	-	Enzyme-Linked Immunosorbent Assay
EtOH	-	Ethanol
EtOAc	-	Ethyl Acetate
FBS	-	Fetal Bovine Serum
FLC	-	Fluconazole
FDA	-	Food and Drug Administration

FIs	-	Fusion Inhibitors
g	-	Gram
CH_3CO_2H	-	Glacial Acetic Acid
Hz	-	Hertz
HMBC	-	Heteronuclear Multiple Bond Correlation
HMQC	-	Heteronuclear Multiple Quantum Coherence
HAART.	-	Highly Active Antiretroviral Therapy
HIV	-	Human Immunodeficiency Viruses
$NH_2NH_2.H_2O$	-	Hydrazine Monohydrate
HCl	-	Hydrochloric Acid
HEPES	-	*N*-(2-Hydroxyethyl)-piperazine-*N*'-(2-ethanesufonic acid)
IR	-	Infrared
IC	-	Inhibition Concentration
IC_{50}	-	Inhibition Concentration at 50 %
IZ	-	Inhibition Zone
INIs	-	Integrase Inhibitors
$LiOH.H_2O$	-	Lithium Hydroxide Monohydrate
L	-	Litre
MHz	-	Megahertz
m.p	-	Melting Point
m	-	*Meta*
MeOH	-	Methanol
µg/mL	-	Microgram Per Millilitre
µL	-	Microliters
µM	-	Micro Molar
MAOS	-	Microwave-Assisted Organic Synthesis
MWI	-	Microwave Irradiation
mL	-	Millilitre
mm	-	Millimetre
MIC	-	Minimum Inhibitory Concentration
min	-	Minute (s)
m	-	Multiplet

ng/g	-	Nanogram/gram
nm	-	Nanometer
NNRTIs	-	Non-nucleoside Reverse Transcriptase Inhibitors
N	-	Normal
NMR	-	Nuclear Magnetic Resonance
NRTIs	-	Nucleoside Reverse Transcriptase Inhibitors
NtRTIs	-	Nucleotide Reverse Transcriptase Inhibitors
NA	-	Nutrient Agar
NB	-	Nutrient Broth
o-	-	*Ortho*
o-PDA	-	*Ortho*-Phenylenediamine
p-	-	*Para*
ppm	-	Part Per Million
$C_6F_5CO_2H$	-	2,3,4,5,6-Pentafluorobenzoic acid
cm^{-1}	-	Per Centimeter
$C_6H_5NHNH_2$. HCl	-	Phenylhydrazine Hydrochloride
$C_6H_5NHNHCONH_2$	-	Phenylsemicarbazide
PEG	-	Polyethylene Glycol
K_2CO_3	-	Potassium Carbonate
KF	-	Potassium Fluoride
KOH	-	Potassium Hydroxide
PIs	-	Protease Inhibitors
^1H	-	Proton
^1H NMR	-	Proton Nuclear Magnetic Resonance
rRT	-	Recombinant Reverse Transcriptase
RNA	-	Ribonucleic Acid
rt	-	Room Temperature
Sm	-	Samarium
$Sc(OTf)_3$	-	Scandium(III) Triflate
sec	-	Second (s)
$H_2CONHNH_2$	-	Semicarbazide
SiO_2	-	Silica Gel
$AgNO_3$	-	Silver Nitrate

SIVcpz	-	Simian Immunodeficiency Viruses Found in Chimpanzees
s	-	Singlet
CH_3COONa	-	Sodium Acetate
NaOH	-	Sodium Hydroxide
S.D	-	Standard Drug
SAR	-	Structure Activity Relationship
$4\text{-}(H_2N)C_6H_4SO_3H$	-	Sulfanilic Acid
H_2SO_4	-	Sulphuric Acid
TBAB	-	Tetrabutylammonium Bromide
THF	-	Tetrahydrofuran
TLC	-	Thin Layer Chromatography
$NH_2CSNHNH_2$	-	Thiosemicarbazide
TCID	-	Tissue Culture Infectious Dose
$TiCl_4$	-	Titanium (IV) Chloride
TCT	-	2,4,6-Trichloro-1,3,5-triazine
Et_3N	-	Triethylamine
TEAA	-	Triethylammonium Acetate
t	-	Triplet
US	-	Ultrasound Irradiation
UV	-	Ultraviolet
UNAIDS	-	United Nations Programme on HIV/AIDS
H_2O	-	Water
WHO	-	World Health Organization
$Yb(OTf)_3$	-	Ytterbium(III) Triflate
ZnO	-	Zinc Oxide
ZOI	-	Zone of Inhibition

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Organic chemistry has a wide range of applications in various fields such as biology, medicine and pharmacology, polymer technology, agriculture and petroleum engineering (Carey and Sundberg, 2000).

Heterocyclic chemistry is one of the branches in organic chemistry. The heterocyclic compounds contain atom either one or more atom in addition to carbon, such as nitrogen, oxygen or sulphur (Morrison and Boyd, 2002). The heterocyclic compounds provide a wide range of biological activities especially in medicine or pharmaceutical chemistry and industrial applications such as construction and agriculture. In addition heterocyclic chemistry plays important role in our life (Katritzky *et al.*, 2010).

Chalcones and heterocyclic chalcone derivatives play important roles against diverse human diseases like as anti-inflammatory (Won *et al.*, 2005); (Vogel *et al.*, 2010); anti-leishmanial (Kayser and Kiderlen, 2001); (Aponte *et al.*, 2010); (De Mello *et al.*, 2014); anti-malarial (Wu *et al.*, 2002); (Tadigoppula *et al.*, 2012); anti-fungal(Ameta *et al.*, 2011); anti-oxidant (Ahmad *et al.*, 2011); (Doan and Tran, 2011); anti-cancer (Bandgar *et al.*, 2010); (Syam *et al.*, 2012); anti-AIDS agents (Wu

et al., 2003); (Cheenpracha *et al.*, 2006) and anti-bacterial(Asiri and Khan, 2011); (Nowakowska *et al.*, 2008).

Chalcones are synthesized by condensation between aldehydes and ketones. Chalcone is one of important intermediate in synthesis of five, six and seven membered ring (Kaur and Kishore, 2013) such as isoxazole, pyrazole (five member ring) and thiazine, oxazine (six member ring) (Kalirajan *et al.*, 2009) and benzodiazepine (seven member ring) (Bhatia *et al.*, 2008). In addition chalcones can be used as an intermediate in the biosynthesis of flavonoids (Ávila *et al.*, 2008).

In this work, three series of thiophene chalcones were synthesized from different heterocyclic ketones or aromatic ketones and different heterocyclic aldehydes via base catalyzed Claisen-Schmidt reaction. The thiophene chalcones were subjected to cyclocondensation reaction by using hydrazine hydrate in glacial acetic acid to give three series of *N*-acetylated pyrazoline derivatives.

Pyrazoline moiety is a five membered heterocyclic ring associated with a large number of pharmaceutical properties such as anti-inflammatory (Gökhan-Kelekçi *et al.*, 2007), antifungal (Zhang *et al.*, 2010); (Hassan, 2013); (Oliveira *et al.*, 2014), anti malaria (Bekhit *et al.*, 2012); (Cunico *et al.*, 2006), antibacterial (Dabholkar and Ansari, 2009); (Liu *et al.*, 2014); (Hassan, 2013), antioxidant (Jois *et al.*, 2014) and against depression (Das *et al.*, 2012).

According their biological activities, there are a large number of pyrazoline derivatives using diverse synthetic methods reported in literature. These methods include cyclization of chalcones with diazomethane (Lévai, 1997), aminoguanidine hydrochloride (Dos Santos *et al.*, 2017), thiosemicarbazide (Gomha *et al.*, 2017), phenyl hydrazine (Khan *et al.*, 2014) and semicarbazide (Das *et al.*, 2012).

The next project is synthesis of benzodiazepine derivatives. Benzodiazepines moiety is a seven membered heterocyclic ring attracting widespread attention due to variety of applications and biological activities exhibited by derivatives of this

moiety. They are mostly used in treatment of anxiety, insomnia, muscle spasms and epilepsy (Wildmann *et al.*, 1988). Benzodiazepines derivatives also exhibited cytotoxic activity against human cancer like colon cancer, lung cancer, breast cancer and bladder cancer (Nawrocka *et al.*, 2001a), analgesic, anti-inflammatory (Roma *et al.*, 1991), antileukemic (Krezel and Graczyk, 1998) and antimicrobial (Babu *et al.*, 2014) .

1.2 Problem Statement

Fungal infections are considered critical types of health problems infecting humans' health round the world (Turan-Zitouni *et al.*, 2005); (Pilmis *et al.*, 2016); (Campoy and Adrio, 2017); (Revie *et al.*, 2018). There are many available antibiotics for example fluconazole, voriconazole, itraconazole, Posaconazole, micafungin, flucytosine and caspofungin (Nivoix *et al.*, 2008); (Arendrup *et al.*, 2013) that serve in killing, weakening or inhibiting fungi and other microbes. Yet, these drugs lead to the emergence of pathogens that are resistant to pharmaceutical drug (Zervos *et al.*, 1994); (Kathiravan *et al.*, 2012); (Ogundeji *et al.*, 2016); (Campoy and Adrio, 2017); (Revie et al., 2018). Moreover, there are many drugs against fungal but they have side effects such as phlebitis, rash, fever and other gastrointestinal symptoms such as (nausea, vomiting, abdominal and diarrhea) (Torres *et al.*, 2005); (Petrikkos and Skiada, 2007); (Kathiravan et al., 2012) and sometimes inactive against certain kinds of fungal microorganisms (Ogundeji *et al.*, 2016). Similarly, human immunodeficiency virus (HIV) epidemic is regarded a serious health problem that effects humans' health worldwide (Singh and Bodiwala, 2010); (Casano *et al.*, 2010); (Maartens *et al.*, 2014). In addition, drug resistance (Carr and Cooper, 2000); (Hopkins *et al.*, 2006); (Breckenridge, 2009); (Sarafianos *et al.*, 2009); (Adamson and Freed, 2010); (Rizvi *et al.*, 2014) and side effects of anti HIV drugs came into the limelight in the world (Breckenridge, 2009). For instance, there are some side effects associated with the combination therapies such as renal failure, hypokalemia, abdominal pain, vomiting, diarrhea, nausea, decrease appetite, rash, headache, fatigue (Chesney *et al.*, 2000); (Portman, 2018) as well as some CAN symptoms such as depression and suicidal ideation (Cihlar and Fordyce, 2016).

So, the emergence of drug resistance in microorganisms and HIV and side effects of drugs are major challenges that scientists face. Such challenges have led to searching , exploring and modifying molecules to get novel antifungal and anti-HIV agents.

Thiophene chalcones with its derivatives carrying 2-acetylated pyrazoline and 1,5-benzodiazepine derivatives are reported to have a broad of significant biological activities including antifungal and anti-HIV, respectively. Taking into consideration the importance of the therapeutic uses of these compounds in treatment of fungal and HIV, it is clear that synthesizing and designing new compounds is needed to be explored for their pharmacological properties, namely being against fungal and HIV.

In this study, four series have been synthesized which are thiophene chalcones with its derivatives and benzodiazepine derivatives. The synthesis of novel compounds identified as thiophene chalcones, 2-acetylated pyrazoline derivatives and substituted 1,5-benzodiazepines and their biological activities against fungal and HIV which have not been reported in any previous work so far. Moreover, some thiophene chalcones (series 2 and 3) have been synthesized but no report on the biological activity against fungal has appeared in the scientific database. The present research for new drugs development used as antifungal and anti-HIV is highly significant as it can potentially help to solve the problems related to existing drugs.

1.3 Objectives of Study

The objectives of this research are :

1. To synthesize heterocyclic ketones by using Friedel-Crafts acylation.
2. To synthesize thiophene chalcones, its derivatives carrying 2-acetylated pyrazoline and 1,5-benzodiazepines derivatives.

3. To characterize the synthetical compounds by spectroscopic techniques.
4. To evaluate the bioactivity of the synthetical compounds using antifungal and anti-HIV-1 RT assays.

1.4 Scope of Study

This thesis is divided into four parts. Part one is focusing on the synthesis of 3-acetyl-2,5-dichlorothiophene and 2-acetyl-5-chlorothiophene as starting material for series one by Friedel-Crafts acylation. Then thiophene chalcones were synthesized through Claisen-Schmidt method in the presence of base catalyst. Part two is focusing on the synthesis of *N*-acetylated pyrazoline derivatives using cyclization of thiophene chalcones with hydrazine hydrate in glacial acetic acid by refluxing. Part three focused on synthesizing 4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one as starting material. Then the latter was cyclized with appropriate acid chloride to substituted 1,5-benzodiazepines by refluxing in presence of anhydrous tetrahydrofuran and triethylamine. All these compounds were established using spectroscopic techniques including Nuclear Magnetic Resonance (NMR), Infrared Spectroscopy (IR) and electrospray ionization mass spectrometry (ESI- MS) for series one.

Finally, the biological activities including antifungal of the series (two and three) and anti-HIV-1 RT of 1,5-benzodiazepines derivatives (series four). The antimicrobial activity was evaluated against antifungal by microdilution technique for determination of minimum inhibitory concentration (MIC). Fourteen selected compounds of 1,5-benzodiazepines derivatives were tested against HIV-1 RT, inhibition concentration at 50% (IC_{50}) was calculated using serial dilution method.

1.5 Significance of Study

Many people suffer from some diseases that may result from fungal infections or HIV if they do not take safety and prevention. Multidrug-resistant (fungals and HIV) are well known to have undesirable side effects which can delay recovery and may lead to a relapse of the patient.

Previous studies have been carried out on heterocyclic compounds, especially carrying sulfur as thiophene chalcone (Tomar *et al.*, 2007); (Bag *et al.*, 2009); (Kumar *et al.*, 2013a); (Mazimba, 2015) or a ring containing multiple nitrogen such as pyrazole (Kumar *et al.*, 2013d); (Zayane *et al.*, 2015); (Yusuf and Jain, 2012) or benzodiazepine (Bräse *et al.*, 2002) displayed promising results for fungi or anti-HIV-1 RT. In this study, it was observed that the effect of substituents and type on biological activity either on phenyl ring in series of thiophene chalcones with its derivatives or in a series of benzodiazepines derivatives on benzoyl ring can affect antifungal and anti-HIV activities. A synthesis of these new compounds may lead to bioactive compounds and result into designing other new drugs.

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