SYNTHESIS OF HETEROCYCLIC CHALCONES AND THEIR NOVEL PYRAZOLINE DERIVATIVES

LIEW SUK MING

UNIVERSITI TEKNOLOGI MALAYSIA

SYNTHESIS OF HETEROCYCLIC CHALCONES AND THEIR NOVEL PYRAZOLINE DERIVATIVES

LIEW SUK MING

A dissertation submitted in partial fulfilment
of the requirements for the award of the
degree of Master of Science (Chemistry)

Faculty of Science
Universiti Teknologi Malaysia

APRIL 2015

To my beloved mother and father.

ACKNOWLEDGEMENT

First and foremost, I would like to express my utmost gratitude to my esteemed supervisor, Dr. Joazaizulfazli Jamalis for his generosity, patience, guidance and support throughout my research.

Thank you also to my fellow postgraduate students, Zakiah and Aishah, for their help and guidance.

My appreciation to the staff of the Chemistry Department for their aid and useful advice, particularly Mr. Rasyidi, Mr. Azmi and Mr. Mohd Amin for teaching me how to operate the NMR and FTIR instruments.

Last but not least, I wish to express my gratitude and appreciation to my family and friends for their support and encouragement during hard times. Thank you very much.

ABSTRACT

Chalcones are open-chain flavanoids possessing a basic scaffold of two aromatic rings linked by a three carbon *α,β*-unsaturated carbonyl system. Synthetic and naturally occurring chalcones display a wide range of biological activities such as antibacterial, anticancer and antioxidant activity because of their *α,β*-unsaturated carbonyl moiety. Modifications to their scaffold at the aromatic rings or the *α,β*-unsaturated carbonyl moiety have been found to either enhance or decrease the chalcones' efficiency. Heterocyclic chalcones are chalcones produced by changing one or both of the aromatic rings to a heterocyclic core such as thiophene, furan, pyridine or pyrazine. Four heterocyclic chalcones and their *N*-acetylated pyrazoline derivatives have been synthesized with a thiophene scaffold as the base combined with pyridine, furan or pyrazine. The synthesis of the heterocyclic chalcones was carried out *via* the Claisen-Schmidt condensation reaction between the respective aldehydes and ketones with sodium hydroxide as the basic catalyst. The pyrazoline, oxazine, thiazine and pyrimidine derivatives of chalcones can be produced through the condensation of their *α,β*-unsaturated carbonyl moiety. The heterocyclic chalcones were refluxed with hydrazine hydrate and anhydrous sodium acetate in glacial acetic acid to obtain their *N*-acetylated pyrazoline derivatives. Structural characterization using ATR-FTIR, ^{1}H NMR, ^{13}C NMR and HMQC has confirmed their structures and the products were obtained with moderate yields.

ABSTRAK

Kalkon merupakan flavanoid rantaian terbuka yang memiliki struktur asas yang terdiri daripada dua gelang aromatik disambungkan oleh satu sistem tiga karbon *α,β*-keton tak tepu. Kalkon sintetik dan semula jadi memiliki pelbagai aktiviti biologi seperti antibakteria, antikanser dan antioksida disebabkan sistem *α,β*-keton tak tepu tersebut. Modifikasi terhadap struktur asas kalkon pada gelang aromatik atau sistem *α,β*-keton tak tepu telah dikenalpasti akan menambahbaik atau mengurangkan keberkesanan kalkon. Kalkon heterosiklik merupakan kalkon yang terhasil apabila satu atau kedua-dua gelang aromatik ditukarkan kepada gelang heteroaromatik seperti tiofena, furan, piridina dan pirazina. Empat kalkon heterosiklik dan terbitan *N*-asetil pirazolina telah dihasilkan dengan struktur tiofena sebagai asas yang digabungkan dengan piridina, furan atau pirazina. Kalkon heterosiklik dihasilkan melalui tindakbalas kondensasi Claisen-Schmidt di antara aldehid dan keton dengan natrium hidroksida sebagai mangkin bes. Terbitan kalkon pirazolina, oksazina, tiazina dan pirimidina boleh diperolehi dengan tindak balas kondensasi pada sistem *α,β*-keton tak tepu. Kalkon heterosiklik direfluks dengan hidrazina hidrat dan natrium asetat kontang dalam asid asetik glasial untuk memperolehi terbitan *N*-asetil pirazolina. Pencirian struktur dengan menggunakan ATR-FTIR, ^{1}H NMR, ^{13}C NMR dan HMQC telah mengesahkan struktur dan semua produk telah diperolehi dengan hasil yang sederhana.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

α	-	Alpha
AA	-	Ascorbic acid
AcOH	-	Acetic acid
Al_2Cl_3	-	Aluminium trichloride
ATR-FTIR	-	Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy
β	-	Beta
BaOH	-	Barium hydroxide
$BF_3.Et_2O$	-	Boron trifluoride-etherate
^{13}C NMR	-	Carbon-13 Nuclear Magnetic Resonance
$CDCl_3$	-	Deuterated chloroform
δ	-	Chemical shift
d	-	Doublet
dd	-	Doublet of doublets
EtOAc	-	Ethyl acetate
EtOH	-	Ethanol
^1H NMR	-	Proton Nuclear Magnetic Resonance
HCl	-	Hydrogen chloride
HMQC	-	Heteronuclear multiple-quantum correlation spectroscopy
Hz	-	Hertz
J	-	Coupling constant
KOH	-	Potassium hydroxide
K_2CO_3	-	Potassium carbonate
$LiOH.H_2O$	-	Lithium hydroxide monohydrate

$LiNO_3$	-	Lithium nitrate
m	-	Multiplet
MeOH	-	Methanol
mL	-	Milliliter
m.p.	-	Melting point
NaOAc	-	Sodium acetate
NaOH	-	Sodium hydroxide
$N_2H_4.H_2O$	-	Hydrazine hydrate
R_f	-	Retention factor
$RuCl_3$	-	Ruthenium trichloride
s	-	Singlet
$SOCl_2$	-	Thionyl chloride
TBAI	-	Tetrabutylammonium iodide
$TiCl_3$	-	Titanium trichloride
TLC	-	Thin layer chromatography

LIST OF APPENDICES

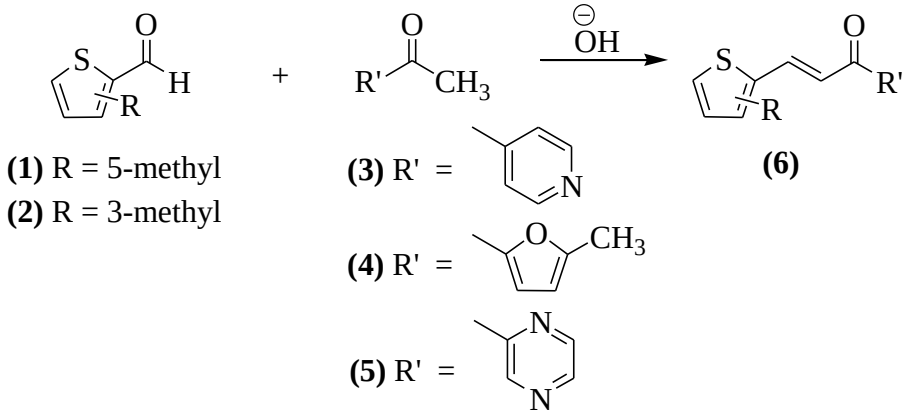
CHAPTER 1

INTRODUCTION

1.1 General Introduction

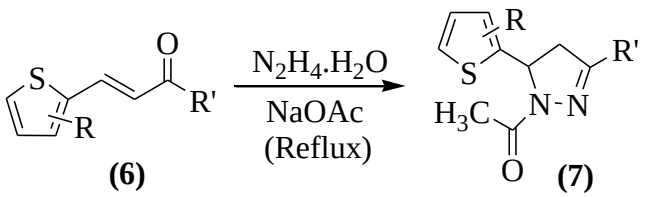
Chalcones, also known as 1,3-diaryl-propene-1-one, are open-chain flavanoids possessing a basic scaffold of two aromatic rings linked by a three carbon *α,β*-unsaturated carbonyl system (Avila *et al.*, 2008) obtained by reacting aromatic aldehydes with aromatic ketones. Synthetic and naturally occurring chalcones have been found to possess a wide range of biological activities such as antibacterial, anticancer, antifungal, anti-inflammatory, antitubercular and antioxidant activity among others (Lin *et al.*, 2002; Nielson *et al.*, 2005; Bandgar *et al.*, 2009; Yadav *et al.*, 2011; Patel *et al.*, 2013), which is credited to the *α,β*-unsaturated ketone moiety. This conclusion is based on previous attempts to modify the chalcone scaffold at the aforementioned part of the compound and the resulting loss or decrease in bioactivity (Abdel-Rahman *et al.*, 2007). Conversely, modifying the aromatic rings has been found to either boost or diminish the bioactivity of chalcones, depending on the type of modification, e.g.: homocyclic or heterocyclic aromatic ring, or the substituent on the aromatic ring (Prasad *et al.*, 2008).

In this dissertation, heterocyclic chalcones **(6)** were synthesized from thiophenecarboxaldehyde **(1), (2)** and three different ketones – 4-acetylpyridine **(3)**, 2-acetyl-5-methylfuran **(4)** and 2-acetylpyrazine **(5)** through the base-catalyzed Claisen-Schmidt condensation method. **Scheme 1.1** illustrates the synthesis of the (*E*)-thienyl chalcones **(6)**.



Scheme 1.1 Synthesis of (*E*)-thienyl chalcones **(6)**

Cyclization of the *α,β*-unsaturated ketone moiety to give various heterocyclic systems such as the pyrazoline, oxazine, thiazine and pyrimidine rings seemed to improve the biological activity of the chalcone (Ramiz *et al.*, 2010; Khan *et al.*, 2014; Mathew *et al.,* 2014). The acetylated pyrazolines have been found to be more active than the non-acetylated pyrazolines (Ashraf *et al*., 2013; Rani and Mohamad, 2014). Therefore, cyclization of the heterocyclic chalcones **(6)** obtained in this research to give their *N*-acetylated pyrazoline derivatives **(7)** will also be challenged in the hopes of improving any existing biological activity of the chalcones, as illustrated in **Scheme 1.2**.



Scheme 1.2 Synthesis of the *N*-acetylated pyrazoline derivatives **(7)**

1.2 Problem Statement

Drug resistance is a worldwide problem that is developing rapidly. Some examples of drug resistance are the methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), levofloxacin-resistant *pneumococcus* and the multidrug-resistant *Neisseria gonorrhoeae* (Gonorrhea). The development of new therapeutic agents with different chemical characteristics from the existing drugs, but are nevertheless equal or even more effective in their activities is thus a priority. This can be done by looking at pre-existing bioactive molecules already used in medicine and modifying their scaffolds to obtain novel molecules with the desired biological properties (Turan-Zitouni *et al.*, 2005). Examples are the antibacterial cefoxitin and antifungal tioconazole possessing the thiophene moiety. Thus, undertaking the synthesis of novel thiophene-based compounds is a logical step towards developing potential new drugs to counter drug resistance.

1.3 Significance of Research

With the intention of contributing to the global problem of drug resistance, the synthesis of novel thiophene-based heterocyclic chalcones and their pyrazoline derivatives was undertaken. The bioactive and highly functionalized furan, pyridine and pyrazine rings were adapted to serve this purpose and some degree of biological activity was expected from appending the furan, pyridine or pyrazine moiety to the thiophene scaffold. The successful synthesis of these products could potentially lead to obtaining more effective therapeutic agents to replace the existing drugs that are losing their effectiveness as bacteria become increasingly more resistant to them.

1.4 Research Objectives

The objectives of this study are:

1. To synthesize thiophene-based heterocyclic chalcones *via* the Claisen-Schmidt condensation reaction.

2. To synthesize the *N*-acetylated pyrazoline derivatives of the heterocyclic chalcones.

3. To characterize the heterocyclic chalcones and their pyrazoline derivatives using Fourier Transform Infrared Spectroscopy (ATR-FTIR) and Nuclear Magnetic Resonance (NMR).

1.5 Scope of Research

Thiophene-based heterocyclic chalcones were synthesized *via* the base-catalyzed Claisen-Schmidt condensation reaction and their *N*-acetylated pyrazoline derivatives were also be produced by refluxing with hydrazine hydrate and anhydrous sodium acetate in glacial acetic acid. The molecular structure of the heterocyclic chalcones and their cyclized derivatives was established *via* ATR-FTIR and NMR.

REFERENCES

Abdel-Rahman, A. A. –H., Abdel-Megied, A. E. –S., Hawata, M. A. M., Kasem, E. R. and Shabaan, M. T. (2007). Synthesis and Antimicrobial Evaluation of Some Chalcones and Their Derived Pyrazoles, Pyrazolines, Isoxazolines, and 5,6-Dihydropyrimidine-2-(1*H*)-thiones. *Monatshefte für Chemie*. 138, 889-897.

Abunada, N. M., Hassaneen, H. M., Kandile, N. G. and Miqdad, O. A. (2008). Synthesis and Biological Activity of Some New Pyrazoline and Pyrrole[3,4-c]pyrazole-4,6-dione Derivatives: Reaction of Nitrilimines with Some Dipolarophiles. *Molecules.* 13, 1011-1024.

Ahmad, M. R., Sastry, V. G., Bano, N. Anwer, S. and Kumaraswamy, G. (2011a). Antioxidant and antibacterial activities of some novel chalcone derivatives and their synthesis by conventional and microwave irradiation methods. *Journal of Chemical and Pharmaceutical Research.* 3, 710-717.

Ahmad, M. R., Sastry, V. G. and Bano, N. (2011b). Biological activities of some new 1,3-Diphenyl-2-Propen-1-one derivatives and their synthesis. *Journal of Pharmacy Research.* 4, 2354-2356.

Ashraf, Z., Baseer, M. and Ansari, F. L. (2013). Synthesis, *in vitro* antibacterial and antifungal activity of some *N*-acetylated and non-acetylated pyrazolines. *Pakistan Journal of Pharmaceutical Sciences.* 26, 67-73.

Ávila, H. P., Smânia, E. d. F. A., Monache, F. D. and Júnior, A. S. (2008). Structure-activity relationship of antibacterial chalcones. *Bioinorganic & Medicinal Chemistry*. 16, 9790-9794.

Bag, S., Ramar, E. S. and Degani, M. S. (2009). Synthesis and biological evaluation of *α,β*-unsaturated ketone as potential antifungal agents. *Medicinal Chemistry Research.* 18, 309-316.

Bandgar, B. P., Gawande, S. S., Bodade, R. G., Gawande, N. M. and Khobragade, C. N. (2009). Synthesis and biological evaluation of novel series of pyrazole chalcones as anti-inflammatory, antioxidant and antimicrobial agents. *Bioinorganic & Medicinal Chemistry*. 17, 8168-8173.

Baseer, M. A. and Kendre, M. M. (2013). Synthesis and Evaluation of Some New 3-(2'-hydroxy-phenyl)-5-(4'-substituted-phenyl)-2-Pyrazoline-*N*'-Carboxaldehydes as Antimicrobial Agents. *American Journal of Advanced Drug Delivery.* 1, 387-393.

Batovska, D., Parushev, S., Stamboliyska, B., Tsvetkova, I., Ninova, M and Najdenski, H. (2009). Examination of growth inhibitory properties of synthetic chalcones for which antibacterial activity was predicted. *European Journal of Medicinal Chemistry.* 44, 2211-2218.

Bhoot, D., Khunt, R. C. and Parekh, H. H. (2012). Synthesis and biological evaluation of chalcones and acetyl pyrazoline derivatives comprising furan nucleus as an antitubercular agents. *Medicinal Chemistry Research.* 21, 3233-3239.

Bohm, A. (1998). Introduction to Flavanoids. London: Harwood Academic Pub.

Cetin, A., Cansiz, A. and Digrak, M. (2003). 3-Aryl-5-furylpyrazolines and their Biological Activities. *Heteroatom Chemistry.* 14, 345-347.

Chew, C. Y. (2014). *Synthesis of Chalcone and Pyrazoline Derivatives and Their Antibacterial Activity*. Bachelor of Science, Universiti Teknologi Malaysia, Skudai.

Deng, H., Yu, Z. -Y., Shi, G. -Y., Chen, M. -J., Tao, K. and Hou, T. -P. (2012). Synthesis and *In Vitro* Antifungal Evaluation of 1,3,5-Trisubstituted-2-Pyrazoline Derivatives. *Chemical Biology & Drug Design.* 79, 279-289.

Dhamodaran, M., Kulathooran, S. and Selvakumar, B. (2014) Synthesis and biological activities of novel heterocyclic chalcone derivatives by two different methods using anhydrous potassium carbonate as an efficient catalyst. *Der Pharma Chemica.* 6, 240-249.

Eddarir, S., Cotelle, N., Bakkour, Y. and Rolando, C. (2003). An efficient synthesis of chalcones based on the Suzuki reaction. *Tetrahedron Letters*. 44, 5359-5363.

Ghosh, P. and Mandal A. (2012). Greener approach towards one pot route to pyrazine synthesis. *Green Chemistry Letters and Reviews.* 5, 127-134.

Gökhan-Kelekçi, N., Yabanoğlu, S., Küpeli, E., Salgin, U., Ozgen, O., Uçar, G., Yeşilada, E., Kendi, E., Yeşilada, A. and Bilgin, A. A. (2007). A new therapeutic approach in Alzheimer disease: some novel pyrazole derivatives as dual MAO-B inhibitors and anti-inflammatory analgesics. *Bioorganic & Medicinal Chemistry Letters.* 15, 5775-5786.

Gothwal, P., Malhotra, G. and Srivastava, Y. K. (2012). Microwave Assisted Synthesis and antimicrobial activities of some 3-[4'-(4"-nitrophenoxy)-phenyl]-5-(substitutedaryl)-2-pyrazoline-1-thiocarboamides. *International Journal of Green and Herbal Chemistry.* 1, 39-45.

Grimm, J. B., Wilson, K. J. and Witter, D. J. (2009). A Divergent Approach to the Synthesis of 3-Substituted-2-pyrazolines: Suzuki Cross-Coupling of 3-Sulfonyloxy-2-pyrazolines. *Journal of Organic Chemistry.* 74, 6390-6393.

Gupta, R., Gupta, N. and Jain, A. (2010). Improved synthesis of chalcones and pyrazolines under ultrasonic irradiation. *Indian Journal of Chemistry.* 49B, 351-355.

Hareesh, M., Mahanti, S., Sailu, B., Subramanyam, D., Sakam, S. R., Tara, B., Balram, B., Vasudha, B. and Ram, B. (2012). Synthesis and Antibacterial Evaluation of Some Novel Pyrazoline Derivatives. *Der Pharma Chemica*. 4, 1637-1643.

Holla, B. S., Mahalinga, M., Poojary, B., Ashok, M. and Akberali, P. M. (2006). Synthesis of pyrazolines promoted by Amberlyst-15 catalyst. *Indian Journal of Chemistry*. 45B, 568-571.

Hussain, M. M. M., Bhat, I. K., Revanasiddappa, B. C., Siddiq, A. and Bharathi, D. R. (2011). Antimicrobial and Cytotoxic Evaluation of (*E*)-Thienyl Chalcones derived from Thiophene-2-carbaldehyde. *Pharmacologyonline*. 3, 880-888.

Johnson, M., Younglove, B., Lee, L., LeBlanc, R., Holt, H. Jr., Hills, P., Mackay, H., Brown, T., Mooberry, S. L. and Lee, M. (2007). Design, synthesis and biological testing of pyrazoline derivatives of combretastatin-A4. *Bioorganic & Medicinal Chemistry Letters.* 21, 5897-5901.

Jyothi, M. V. and Venkatesh, P. (2012). Preparation and Biological Evaluation of Novel Pyrimidines from Novel Chalcones. *Oriental Journal of Chemistry*. 28, 1437-1442.

Jyothi, M. V., Dinda, S. C., Reddy, J. R. and Venkatesh, P. (2012). Synthesis and Antimicrobial Activity Evaluation of Some Novel Pyrazolines. *Journal of Chemical and Pharmaceutical Research.* 4, 2626-2630.

Kalirajan, R., Sivakumar, S. U., Jubie, S., Gowramma, B. and Suresh, B. (2009). Synthesis and Biological evaluation of some heterocyclic derivatives of Chalcones. *International Journal of ChemTech Research.* 1, 27-34.

Karaman, I., Gezegen, H., Gürdere, M., B., Dingil, A. and Ceylan M. (2010). Screening of Biological Activities of a Series of Chalcone Derivatives against Human Pathogenic Microorganisms. *Chemistry & Biodiversity*. 7, 400-408.

Khalil, O. M. (2012). Synthesis and anti-inflammatory activity of 1-acetyl/propanoyl-5-aryl-3-(4-morpholinophenyl)-4,5-dihydro-1*H*-pyrazole derivatives. *Medicinal Chemistry Research.* 21, 3240-3245.

Khalil, N. A., Ahmend, E. M., El-Nassan, H. B., Ahmed, O. K. and Al-Abd, A. M. (2012). Synthesis and Biological Evaluation of Novel Pyrazoline Derivatives as Anti-Inflammatory and Antioxidant Agents. *Archives of Pharmacal Research.* 35, 995-1002.

Khan, S. A., Asiri, A. M., Kumar, S. and Sharma, K. (2014). Green synthesis, antibacterial activity and computational study of pyrazoline and pyrimidine derivatives from 3-(3,4-dimethoxy-phenyl-1-(2,5-dimethylthiophen-3-yl)-propenone. *European Journal of Chemistry.* 5, 85-90.

Khan, S. A. and Asiri, A. M. (2014). Green synthesis, characterization and biological evaluation of novel chalcones as antibacterial agents. *Arabian Journal of Chemistry*.

Kitawat, B. S., Singh, M. and Kale, R. K. (2013). Solvent free synthesis, characterization, anticancer, antibacterial, antifungal, antioxidant and SAR studies of novel (*E*)-3-aryl-1-(3-alkyl-2-pyrazinyl)2-propenone. *New Journal of Chemistry*. 37, 2541-2550.

Kitawat, B. S. and Singh, M. (2014). Synthesis, characterization, antibacterial, antioxidant, DNA binding and SAR study of a novel pyrazine moiety bearing 2-pyrazoline derivatives. *New Journal of Chemistry.* 38, 4290-4299.

Kumar, H., Saini, D., Jain, S. and Jain, N. (2013). Pyrazole scaffold: A remarkable tool in the development of anticancer agents. *European Journal of Medicinal Chemistry.* 70, 248-258.

Lin, Y. –M., Zhou, Y., Flavin, M. T., Zhou, L. -M., Nie, W. and Chen, F. –C. (2002). Chalcones and Flavanoids as Anti-Tuberculosis Agents. *Bioinorganic & Medicinal Chemistry*. 10, 2795-2802.

Lone, I. H., Khan, K. Z. and Fozdar, B. I. (2014). Synthesis, physicochemical properties, antimicrobial and antioxidant studies of pyrazoline derivatives bearing a pyridyl moiety. *Medicinal Chemistry Research*. 23, 363-369.

Mahé, O., Drath, D., Dez, I., Marsais, F., Levacher, V. and Brière, J, -F. (2009). TBD-organocatalysed synthesis of pyrazolines. *Organic & Biomolecular Chemistry*. 7, 3648-3651

Maleki, B., Azarifar, D., Moghaddam, M. K., Hojati, S. F., Gholizadeh, M. and Salehabadi, H. (2009). Synthesis and characterization of a series of 1,3,4-trisubstituted-2-pyrazolines derivatives using methanoic acid under thermal condition. *Journal of the Serbian Chemical Society*. 74, 1371-1376.

Mathew, B., Suresh, J., Anbazghagan, S., Paulraj, J. and Krishnan, G. K. (2014). Heteroaryl chalcones: Mini review about their therapeutic voyage. *Biomedicine & Preventive Nutrition*. 4, 451-458.

Monga, V., Goyal, K., Steindel, M., Malhotra, M., Rajani, D. P. and Rajani, S. D. (2014). Synthesis and evaluation of new chalcones, derived pyrazoline and cyclohexanone derivatives as potent antimicrobial, antitubercular and antileshimal agents. *Medicinal Chemistry Research*. 23, 2019-2032.

Narender, T. and Reddy, K. P. (2007). A simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate. *Tetrahedron Letters*. 48, 3177-3180.

Nielson, S. F., Larsen, M., Boesen, T., Schønning, K. and Kromann, H. (2005). Cationic Chalcone Antibiotics. Design, Synthesis, and Mechanism of Action. *Journal of Medicinal Chemistry*. 48, 2667-2677.

Özdemir, Z., Kandilci, H. B., Gümüşel, B., Çalış, Ü. and Bilgin, A. (2007a). Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives. *European Journal of Medicinal Chemistry*. 42, 373-379.

Özdemir, A., Turan-Zitouni, G., Kaplancıklı, Z. A., Revial, G. and Güven, K. (2007b). Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives. *European Journal of Medicinal Chemistry*. 42, 403-409.

Padarthi, P. K., Sridhar, S., Jagatheesh, K. and Namasivayam, E. (2013). Synthesis and Biological Activity of Imidazole Derived Chalcones and Its Pyrimidine. *International Journal of Research in Ayurveda and Pharmacy.* 4, 355-362.

Patel, A. R., Badmanaban, R., Sen, D. J. and Patel, C. N. (2013). Design, Synthesis and Antimicrobial, Antifungal and Anti-Inflammatory Evaluation of Some (4-Substituted Phenyl)[5-{4- Substituted Phenyl)-3-Phenyl-4,5-Dihydro-1*H*-Pyrazol-1-yl]-Methanone Derivatives. *American Journal of Advanced Drug Delivery*. 2, 113-127.

Pavia, D. L., Lampman, G. M., Kriz, G. S and Vyvyan, J. R. (2010). *Spectroscopy* (4^{th} Edition). Canada: Brooks/Cole, Cengage Learning.

Prasad, Y. R., Kumar, P. R., Smiles, D. J. and Babu, P. A. (2008). QSAR studies on chalcone derivatives as antibacterial agents against Bacillus pumillus. *ARKIVOC*. (xi), 266-276.

Rahman, M. A. and Siddiqui, A. A. (2010). Pyrazoline Derivatives: A Worthy Insight into the Recent Advances and Potential Pharmacological Activities. *International Journal of Pharmaceutical Sciences and Drug Research*. 2, 165-175.

Raj, C. G. D., Sarojini, B. K., Hegde, S., Sreenivasa, S., Ravikumar, Y. S., Bhanuprakash, V., Revanaiah, Y. and Ragavendra, R. (2013). *In vitro* biological activities of new heterocyclic chalcone derivatives. *Medicinal Chemistry Research*. 22, 2079-2087.

Ramesh, B. and Rao, B. S. (2010). Synthesis, spectral studies and anti-inflammatory activity of 2-acetylthiophene. *European Journal of Chemistry*. 7, 433-436.

Ramiz, M. M. M., El-Sayed, W. A., El-Tantawy, A. I. and Abdel-Rahman, A. A.-H. (2010). Antimicrobial Activity of New 4,6-Disubstituted Pyrimidine, Pyrazoline, and Pyran Derivatives. *Archives of Pharmacal Research.* 33, 647-654.

Rani, M., Yusuf, M., Khan, S. A., Sahota, P. P. and Pandove, G. (2011). Synthesis, studies and *in-vitro* antibacterial activity of *N*-substituted 5-(furan-2-yl)-phenyl pyrazolines. *Arabian Journal of Chemistry*.

Rani, M. and Mohamad, Y. (2014). Synthesis, studies and *in vitro* antibacterial activity of some 5-(thiophene-2-yl)-phenyl pyrazoline derivatives. *Journal of Saudi Chemical Society*. 18, 411-417.

Rueping, M., Bootwicha, T., Baars, H. and Sugiono, E. (2011). Continuous-flow hydration-condensation reaction: Synthesis of *α,β*-unsaturated ketones from alkynes and aldehydes by using a heterogeneous solid acid catalyst. *Beilstein Journal of Organic Chemistry*. 7, 1680-1687.

Sailu, B., Hareesh, M., Mahanti, S., Subramanyam, D., Sakam, S. R., Tara, B., Balram, B. Vasudha, B. and Ram, B. (2012). Synthesis and Antibacterial Evaluation of Some Novel Pyrazoline Derivatives. *Der Pharma Chemica*. 4, 1637-1643.

Shandala, M. Y. and Hamdy, A. M. (2008). Synthesis of Some New Substituted 1,3,5-Triaryl Pyrazolines. *National Journal of Chemistry*. 30, 338-342.

Sharma, P., Kumar, S., Ali, F., Anthal, S., Gupta, V. K., Khan, I. A., Singh, S., Sangwan, P. L., Suri, K. A., Gupta, B. D., Dutt, P., Vishwakarma, R. A. and Satti, N. K. (2013). Synthesis and biologic activities of some novel heterocyclic chalcone derivatives. *Medicinal Chemistry Research*. 22, 3969-3983.

Singh, S., Sharma, P. K., Kumar, N. and Dudhe, R. (2011). A Review on a Versatile Molecule: Chalcone. *Asian Journal of Biochemical and Pharmaceutical Research*. 1, 412-418.

Singh, M. and Kitawat, B. S. (2014). Synthesis, characterization, antibacterial, antioxidant, DNA binding and SAR study of a novel pyrazine moiety bearing 2-pyrazoline derivatives. *New Journal of Chemistry*. 38, 4290-4299.

Solomon, V. R. and Lee, H. (2012). Anti-breast cancer activity of heteroaryl chalcone derivatives. *Biomedicine & Pharmacotheraphy*. 66, 213-220.

Sunduru, N., Agarwal, A., Katiyar, S. B., Nishi, Goya, N., Gupta, S. and Chauhan, P. M. S. (2006). Synthesis of 2,4,6-trisubstituted pyrimidine and triazine heterocyclics as antileishmanial agents. *Bioorganic & Medicinal Chemistry*. 14, 7706-7715.

Tala, S. D., Vekariya, P. B., Ghetiya, R. M., Dodiya, B. L. and Joshi, H. S. (2013). Synthesis and biological study of some chalcone and pyrazole derivatives. *Indian Journal of Chemistry*. 52B, 807-809.

Thanh, T. -D., Nyugen, T. -T. -N., Do, T. -H., Huynh, T. –N. –P., Tran, C. –D. and Thai, K. –M. (2012). Synthesis and Antibacterial Activity of Some Heterocyclic Chalcone Analogues Alone and in Combination with Antibiotic. *Molecules.* 17, 6684-6696.

Turan-Zitouni, G., Özdemir, A. and Guven, K. (2005). Synthesis of Some 1-[(*N, N*-Disubstituted thiocarbamoylthio)acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline Derivatives and Investigation of Their Antibacterial and Antifungal Activities. *Archiv der Pharmazie – Chemistry in Life Sciences*. 338, 96-104.

Usta, A., Yaşar, A., Yilmaz, N., Güleç, C., Yayli, N., Karaoğlu, Ş. A. and Yayli, N. (2007). Synthesis, Configuration and Antimicrobial Properties of Novel Substituted and Cyclized 2',3"-Thiazachalcones. *Helvetica Chimica Acta*. 90, 1482-1490.

Usta, A., Yaşar, A., Yayli, N., Karaoğlu, S. A. and Yayli, N. (2009). Synthesis of methyl (*E*)-2',4"-thiazachalcones and their *N*-alkyl derivatives, photochemistry with theoretical calculations and antimicrobial activities. *Turkish Journal of Chemistry.* 33, 621-632.

Vanagamudi, G., Subramanian, M. and Thirunarayanan, G. (2013). Synthesis, spectral linearity, antimicrobial, antioxidant and insect antifeedant activities of some 2,5-dimethyl-3-thienyl chalcones. *Arabian Journal of Chemistry*.

Wu, X. A., Zhao, Y. M. and Yu, N. J. (2007). A novel analgesic pyrazine derivative from the leaves of *Croton tiglium L*. *Journal of Asian Natural Products Research.* 9, 437-441.

Yadav, V. R., Prasad, S., Sung, B. and Aggarwal, B. B. (2011). The role of chalcones in suppression of NF-κB-mediated inflammation and cancer. *International Immunopharmacology*. 11, 295-309.

Yanagimoto, K., Lee, K. G., Ochi, H. and Shibamoto, T. (2002). Antioxidative activity of heterocyclic compounds found in coffee volatiles produced by Maillard reaction. *Journal of Agricultural and Food Chemistry*. 50, 5480-5485.

Zangade, S., Mokle, S., Vibhute, A. and Vibhute, Y. (2011). An Efficient and Operationally Simple Synthesis of Some New Chalcones by Using Grinding Technique. *Journal of Chemical Sciences.* CSJ-13, 1-5.

Zhaohui, Z., Taotao, W., Jingwu, H., Gengshan, L., Shaozu, Y. and Wenjuan, X. (2003). Tetramethylpyrazine scavenges superoxide anion and decreases nitric oxide production in human polymorphonuclear leukocytes. *Life Sciences*. 72, 2465-2472.

Zheng, C. -J., Jiang, S. -M., Chen, Z. -H., Ye, B. -J. and Piao, H. -R. (2011). Synthesis and Anti-Bacterial Activity of Some Heterocyclic Chalcone

Derivatives Bearing Thiofuran, Furan, and Quinoline Moities. *Archiv der Pharmazie – Chemistry in Life Sciences.* 344, 689-695.