**UNIVERSITI PUTRA MALAYSIA**

# *SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW PYRAZOLINE DERIVATIVES OF DIARYLPENTADIENONE*

**ADAM FARUK AUWAL**

**FS 2021 9**

# SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW PYRAZOLINE DERIVATIVES OF DIARYLPENTADIENONE

By

**ADAM FARUK AUWAL**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science**

**July 2020**

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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**July 2020**

**Chairman : Siti Munirah binti Mohd. Faudzi, PhD**
**Faculty : Science**

Diarylpentadienone and pyrazoline analogues were reported to have excellent pharmacological activities including antioxidant, anti-inflammation, and anti-cancer with extremely low toxicity. A number of synthetic phenolic antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxy anisole (BHA) have been widely used in the food industry, cosmetics, and the therapeutic industry, however, have been reported to be dangerous to humans due to their high volatility, instability at elevated temperature and its carcinogenic nature. Thus, led to the growing needs for new antioxidant agents for an alternative safe treatment. A series of the diarylpentadienones (**1**-**10**) are firstly prepared using Claisen-Schmidt condensation reaction, before further reacted with hydrazine hydrate under reflux to obtain the new series of pyrazoline analogues (**11**-**19**). The structures of the synthesized compounds were confirmed via $^{1}$H-, $^{13}$C- and 2-dimensional Nuclear Magnetic resonance (NMR) as well as Fourier Transform Spectroscopy (FTIR) and Direct injection-Mass Spectroscopy (DIMS) analyses. Following that, the antioxidant capacity of the synthesized molecules is determine using 2,2-diphenyl-1-picrylhydrazine (DPPH) radical and nitric oxide (NO) scavenging assays while quercetin is use as the positive control. The results disclose that compounds 1-(2,4-dimethoxyphenyl)-5-(4-methoxyphenyl)penta-2,4-dien-1-one (**4**) and 1-(3-(3-fluorophenyl)-5-(4-methoxystyryl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethenone (**16**) show good activity in the DPPH free radical scavenging activity with $IC_{50}$ values of 1.32±0.015 µg/mL and 1.55±0.029 µg/mL when compared to standard quercetin ($IC_{50}$ : 1.61±0.010 µg/mL); and significant NO scavenging activity with $IC_{50}$ values of 6.13±0.089 µg/mL and 5.97±0.081 µg/mL in comparison to the standard quercetin and gallic acid with $IC_{50}$ values of 1.91±0.006 µg/mL and 0.88±0.010 µg/mL, respectively. Meanwhile, other compounds demonstrate moderate to lower DPPH and NO scavenging activity. Simple SAR study reveal that remarkable antioxidant properties depends on the presence of 2,4-dimethoxy phenyl ring on diarylpentadienone and 3-flouro phenyl ring on the pyrazoline derivatives. It is also proposed to prevent the use of high electron-

donating group on pyrazoline if aimed to be having a potential antioxidant. Additionally, the compounds are also tested against selected acne-causing bacteria [*Propionibacterium acnes* (*P. acne*), *Staphylococcus epidermidis* (*S. epidermidis*) and *Staphylococcus aureus (S. aureus)*] and *Candida albicans* (*C. albicans*), through disc diffusion assay (DDA). However, it is noticeable that all molecules are ineffective towards the antibacterial and anti-candida assays. Therefore, it is conceivably concluded that diarylpentadienone and pyrazoline derivatives are potent families as antioxidant agents.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

**SINTESIS DAN PENILAIAN BIOLOGI TERBITAN BARU PIRAZOLIN DARIPADA DIARILPENTADIENON**

Oleh

**ADAM FARUK AUWAL**

**Julai 2020**

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Analog diarilpentadienon dan pirazolin dilaporkan mempunyai aktiviti farmakologi yang sangat baik termasuk antioksidan, anti-radang dan anti-kanser dengan tahap toksik yang sangat rendah. Sejumlah antioksidan fenolik sintetik seperti hidroksitoluena terbutilasi (BHT) dan hidroksianisol terbutilasi (BHA) telah banyak digunakan dalam industri makanan, kosmetik dan terapeutik, bagaimanapun, dilaporkan berbahaya bagi manusia kerana kemeruwapan yang tinggi, ketidakstabilan pada suhu tinggi dan sifat karsinogeniknya. Hal ini mendorong kepada meningkatnya keperluan untuk mencari agen antioksidan baru sebagai rawatan alternatif yang selamat. Satu siri diarilpentadienon (**1-10**) dihasilkan menggunakan tindak balas kondensasi Claisen-Schmidt, kemudiannya bertindak balas dengan hidrazin hidrat untuk mendapatkan siri analog pirazolin baru (**11-19**). Struktur sebatian yang disintesis disahkan melalui $^{1}$H-, $^{13}$C- dan dua dimensi resonans magnetik nuklear (NMR) serta spektroskopi inframerah transformasi Fourier (FT-IR) dan spektrometri jisim suntikan langsung (DI-MS). Kemudian, keupayaan antioksidan molekul yang disintesis diuji menggunakan ujian radikal 2,2'-difenil-1-pikrilhidrazil (DPPH) dan nitrik oksida (NO) sementara kuersetin digunakan sebagai kawalan positif. Keputusan mendedahkan sebatian 1-(2,4-dimetoksifenil)-5-(4-metoksifenil)penta-2,4-dien-1-on (**4**) dan 1-(3-(3-fluorofenil)-5-(4-metoksistiril)-4,5-dihidro-1*H*-pirazol-1-il)ethenon (**16**) menunjukkan aktiviti yang baik dalam aktiviti perencatan radikal bebas DPPH dengan nilai $IC_{50}$ 1.32±0.015 µg/mL dan 1.55±0.029 µg/mL jika dibandingkan dengan standard kuersetin ($IC_{50}$ : 1.61±0.010 µg/mL); dan aktiviti perecatan NO yang signifikan dengan nilai $IC_{50}$ 6.13±0.089 µg/mL dan 5.97±0.081 µg/mL berbanding dengan standard kuersetin dan asid gallik dengan nilai $IC_{50}$ 1.91±0.006 µg/mL dan 0.88±0.010 µg/mL, masing-masing. Sementara itu, sebatian lain menunjukkan aktiviti DPPH dan NO dari sederhana hingga rendah. Kajian SAR menunjukkan bahawa sifat antioksidan yang baik bergantung pada kehadiran cincin 2,4-dimetoksifenil pada diarilpentadienon dan cincin 3-flourofenil pada terbitan pirazolin. Kajian ini menyarankan pencegahan penggunaan kumpulan yang melepaskan elektron tinggi

pada pirazolin untuk memiliki potensi antioksidan yang lebih baik. Selain itu, sebatian-sebatian tersebut juga diuji terhadap bakteria penyebab jerawat terpilih [*Propionibacterium acnes* (*P. acnes*), *Staphylococcus epidermidis* (*S. epidermidis*) dan *Staphylococcus aureus* (*S. aureus*)] dan kulat *Candida albicans* (*C. albicans*), melalui ujian penyebaran cakera (DDA). Walau bagaimanapun, semua sebatian tidak berkesan sebagai antibakteria dan antikulat. Oleh itu, dapat disimpulkan bahawa terbitan diarilpentadienon dan pirazolin adalah kumpulan yang kuat sebagai agen antioksidan.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Name of Member of Supervisory Committee: Dr. Nadiah binti Mad Nasir

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| $^{13}C$ | Carbon 13 |
| $^{1}H$ | Proton |
| *A. niger* | *Aspergillus niger* |
| ATCC | America Type Culture Collection |
| BHA | Butylated hydroxy anisole |
| BHT | Butylated hydroxytoluene |
| *C. albicans* | *Candida albicans* |
| *C. glabrata* | *Candida krusei* |
| *C. krusei* | *Candida krusei* |
| *C. parapsilosis* | *Candida parapsilosis* |
| $CDCl_3$ | Deuterated chloroform |
| $CH_3COOH$ | Acetic Acid |
| CHX | Cycloheximide |
| COSY | Correlation Spectroscopy |
| COX | Cyclooxygenase |
| *d* | doublet |
| *dd* | doublet of doublet |
| DI-MS | Direct Injection-Mass Spectrometry |
| DMSO | Dimethyl sulfoxide |
| DPPH | 2,2-diphenyl-1-picrylhydrazyl |
| EtOAc | Ethyl acetate |
| FT-IR | Fourier Transform Infrared Spectroscopy |
| GC-MS | Gas chromatography-mass spectrometry |
| $H_2SO_4$ | Sulphuric acid |
| $H_3PO_4$ | Phosphoric acid |
| HCl | Hydrochloric acid |

| | |
|---|---|
| HMBC | Heteronuclear Multiple Bond Coherence |
| IC | Inhibitory concentration |
| *m* | multiplet |
| MCF-7 | Human breast adenocarcinoma cell lines |
| $MgSO_4$ | Magnesium sulphate |
| MHA | Mueller Hinton Agar |
| MS | Mass spectroscopy |
| NaOH | Sodium hydroxide |
| NO | Nitric oxide |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| *P. acne* | *Propionibacterium acne* |
| *P. aeruginosa* | *Pseudomonas aeruginosa* |
| PBS | Phosphate buffered silane |
| rt | Room temperature |
| *s* | singlet |
| *S. aureus* | *Staphylococcus aureus* |
| *S. epidermidis* | *Staphylococcus epidermidis* |
| *S. saprophyticus* | *Staphylococcus saprophyticus* |
| SDA | Sabouraud dextrose Agar |
| SNP | Sodium Nitroprusside |
| *t* | triplet |
| TLC | Thin layer chromatography |
| TMS | Tetramethyl silane |
| VVC | Vulvovaginal candidiasis |

## LIST OF SYMBOLS

| | |
|---|---|
| µg | Microgram |
| g | Gram |
| Hz | Hertz |
| *J* | Coupling constant |
| kg | Kilogram |
| M | Molarity |
| m/z | Mass to charge ratio |
| MHz | Mega hertz |
| ml | Milliliter |
| ppm | Parts per million |

# CHAPTER 1

# INTRODUCTION

## 1.1 General introduction

Diarylpentanoids are classified as analogues of curcumin, derived from curcumin structure by the lack of ethylene unit from the heptane bridge, as depicted in Figure 1.1. Previous reports indicated this particular class of compounds have received several attentions for their bioavailability and better pharmacological activities such as anti-bacterial (Liang et al., 2008), anti-inflammatory and antioxidant properties (Lam et al., 2012; Tham et al., 2010; Lee et al., 2009) which enable them to be active in treating several chronic diseases such as cancer, diabetes, sepsis and neurodegenerative diseases. Thus, diarypentanoid system is a potential candidate for the development of several functional drugs.

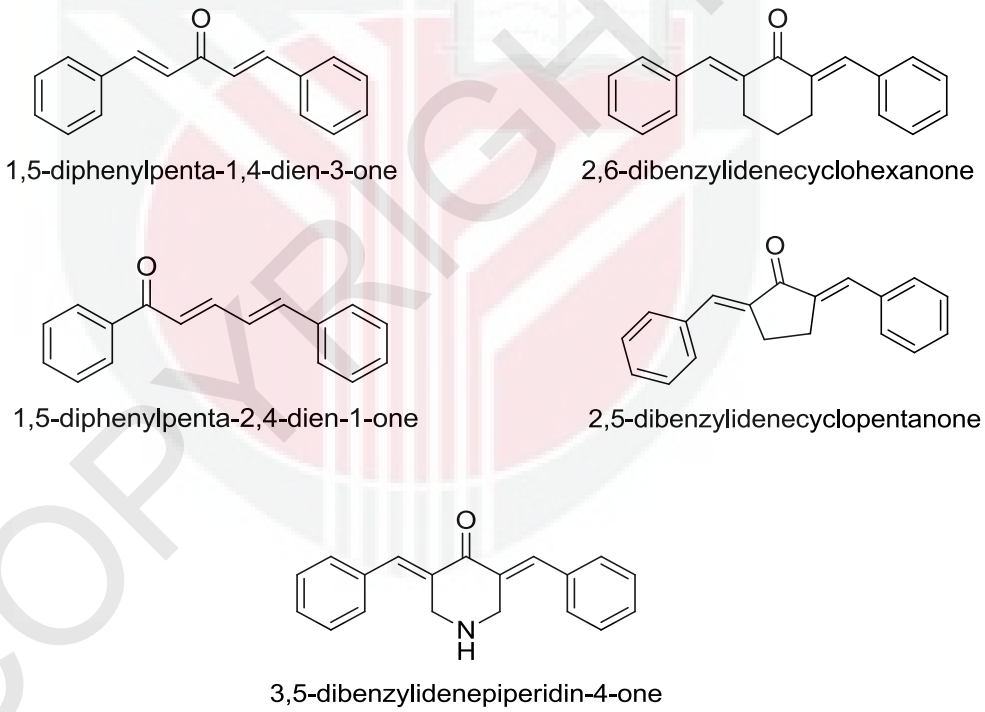
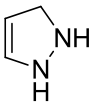



**Figure 1.1 : Diarylpentanoid analogues**

Meanwhile, pyrazolines are five membered ring heterocyclic compounds having two adjacent double nitrogen atoms within the ring, as shown in Figure 1.2. It contains only one endocyclic double bond and is basic in nature (Sethi et al., 2015). Pyrazoline exhibits significant biological activities such as anti-microbial (Naik et al., 2013), anti-bacterial (Baluja and Chandra, 2012), anti-depressant (Jayaprakash et al., 2008), anti-inflammation (Burguete et al., 2007) and anti-oxidant (Babu et al., 2007).




2,3-dihydro-1*H*-pyrazole


4,5-dihydro-1*H*-pyrazole


4,5-dihydro-3*H*-pyrazole

**Figure 1.2 : Structures of pyrazolines**

Antioxidants are molecules that in small quantities are able to prevent or greatly retard the oxidation of easily oxidizable materials, or any substance when present in low concentrations compared to those of an oxidizable substrate significantly delays or prevents oxidation of those substances (Moharram & Youssef, 2014). Antioxidants are responsible for the defense mechanism of the organism against the pathologies associated to the attack of free radicals. Thus, the intake of antioxidant is involved in the prevention of degenerative diseases caused oxidative stress such as cancer, Parkinson, Alzheimer or atherosclerosis (Droge, 2002; Lee et al., 2004; Valko et al., 2007; Pisoschi & Negulescu, 2012). These agents can be classified into three main categories by their mechanism: (1) primary antioxidants, which function essentially as free radical terminators (scavengers); (2) secondary antioxidants, which are important preventive antioxidants that function by retarding chain initiation; and (3) tertiary antioxidants, which are concerned with the repair of damaged biomolecules (Daramola & Adegoke, 2011).

Antioxidants are generally divided into two groups by source; including natural and synthetic antioxidants (Gülçin et al., 2007). There are number of synthetic phenolic antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxy anisole (BHA) which have been widely used as antioxidants in the food industry, cosmetic, and the therapeutic industry. These synthetic antioxidants, however, have been reported to be dangerous to humans due to their high volatility, instability at elevated temperature and its carcinogenic nature. Thus, led to growing needs for new antioxidant agents as an alternative safe treatment (Sindhi et al., 2013).

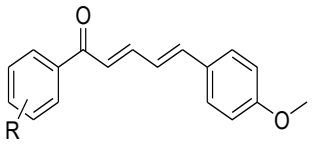
Antibacterial agents are clinically useful compounds in the treatment of bacterial infections which may be derived from natural sources, synthetic or semi-synthetically produced. The activity of bacterial agents can be either bacteriostatic which will only stall the growth of bacterial or bactericidal, which significantly reduces the number of viable bacteria in the culture (Pankey & Sabath, 2004). Bacterial infections are one of the main causes of infectious diseases, Hence, over 50 years of extensive research have been launched to achieving new antimicrobial medicines isolated from different sources. Despite progress in development of antibacterial agents, there are still needs to find new bacterial agents due to development of multidrug resistant bacterial (Wise et al., 1998).

Meanwhile, anticandidal or antifungal are agents that kills fungi or inhibits their growth. Antifungal that kill fungi are called fungicidal while those that merely inhibit their growth are called fungistatic (Kumar & Jha, 2017). Candidiasis is a fungal

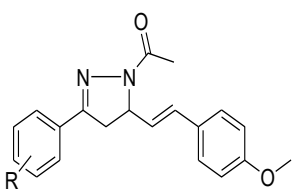
infection due to any species from the yeast *Candida* spp, a genus accounting for more than 85% of known fungemia (Ha et al., 2011). Candidiasis ranges from superficial infection, where *Candida* species can infect the mouth, skin, vagina, stomach and urinary tract (Greenspan & Greenspan, 1996). There are twenty *Candida* species that can cause disease in humans. Of these species, *C. albicans* has been the most implicated in candidiasis. It is the most common fungal pathogen in humans, can cause broad spectrum of diseases including skin, mucosal, and systemic infection (Moran et al., 2012). Antifungal/anticandidal are used to treat fungal infections in people who are at risk, including AIDS patients, cancer patients and individual taking immunosuppressants. In view of scarcity of antibacterial agents acting on cytoplasmic membrane, it is surprising to find some of the most successful groups of anticandidal/antifungal agents, including the polyenes, azole and allylamines (Kumar & Jha, 2017).

The search for new anticandidal/antifungal strategies to overcome *Candida* infections is essential and a matter of public health, due to the high mortality associated to candidiasis (Moraes & Ferreira-Pereira, 2019). The antifungal agent amphotericin B remains the gold standard treatment for candidiasis, but its toxicity underscores the need for alternative safe antifungal. There are also the azoles, a class of chemical compounds used for the treatment of candidiasis. However, *Candida* species are developing resistance to these drugs (Rothstein et al., 2001; Forrest et al., 2008). Candidiasis is costly to the patient; it not only increases patient's mortality rate but also extend patients length of stay in care centers and thus increases the total cost of medical care. Estimates show that each episode of invasive candidiasis costs approximately US$40,000 (Ha et al., 2011).

Therefore, we aimed to study the impact of rigidity of the diarylpentadienone scaffold by incorporating the pyrazoline ring into the system on their biological activities, specifically on antioxidants, antibacterial and anticandidal. Besides, the structure-activity relationship (SAR) of the selected functional groups on both ring A and B on the selected bioactivities will be analyze too. We hypothesized the diarylpentadienones and its respective pyrazolines analogues might be a potential candidate based on the reported strong antioxidant activity (Babu et al., 2007). Consequently, the general structures and reaction scheme of the targeted compound incorporating diarylpentadienone and pyrazoline are shown in Figure 1.3 and Scheme 1.1, respectively. Meanwhile the structure of all nineteen compounds including seven new compounds are tabulated in Table 1.1.

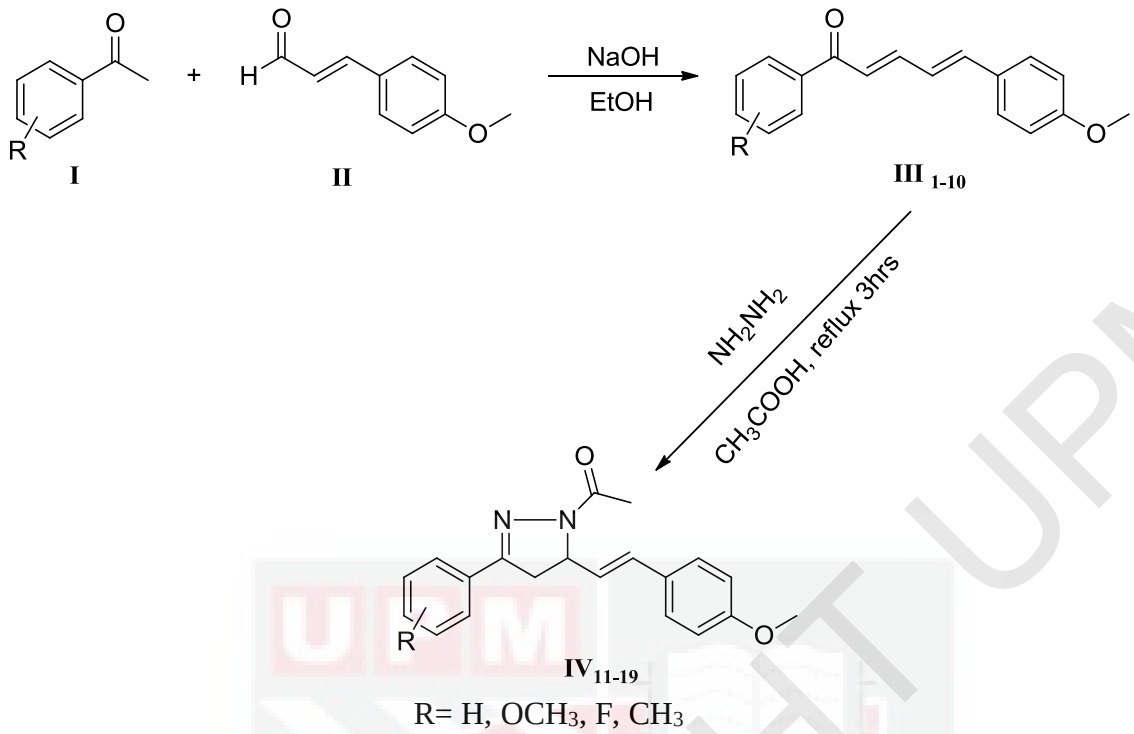



5-(4-methoxyphenyl)-1-phenylpenta-2,4-dien-1-one



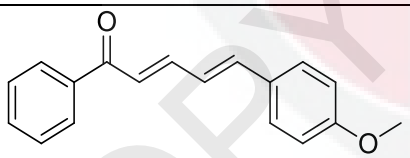
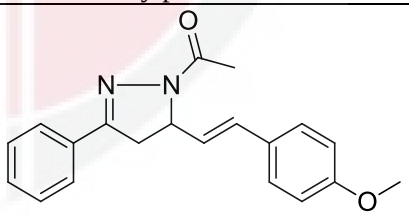
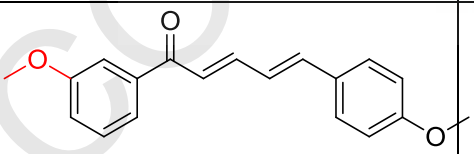
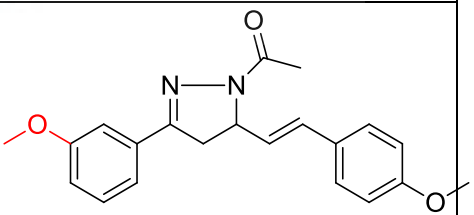
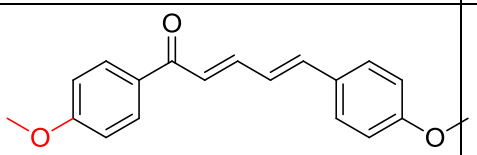
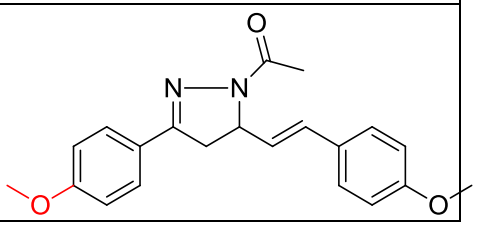

1-(5-(4-methoxystyryl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone

**Figure 1.3 : General structure of targeted compounds**




**Scheme 1.1 : General reaction for the synthesis of diarylpentadienones (III) and pyrazoline-diarylpentadienones (IV)**

**Table 1.1 : Structure of diarylpentadienones and pyrazoline-diarylpentadienones**

| | Diarylpentadienone | | Pyrazoline-Diarylpentadienone |
|---|---|---|---|
| 1 |  | 11 |  |
| 2 |  | 12* |  |
| 3 |  | 13 |  |

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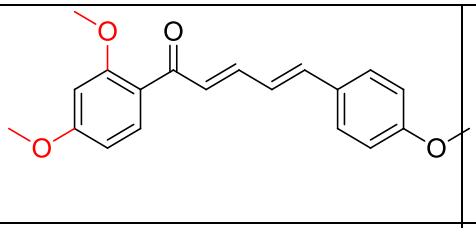
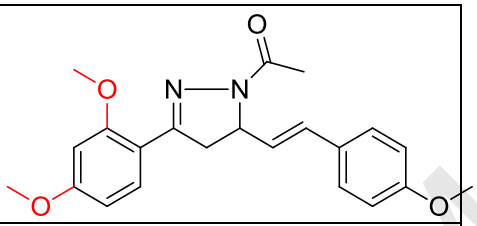
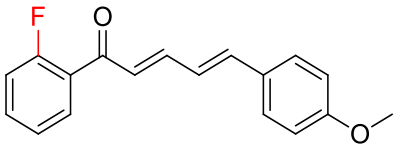
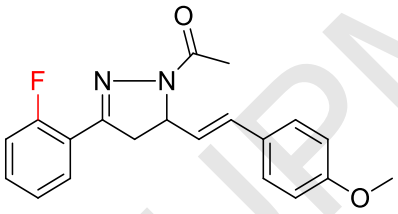
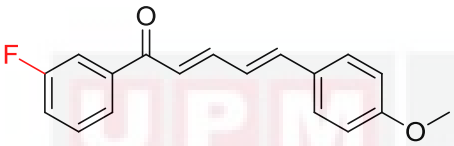
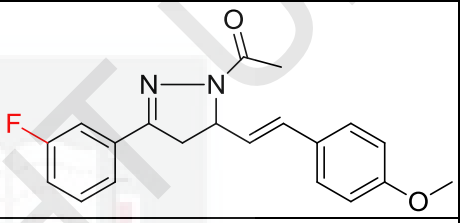
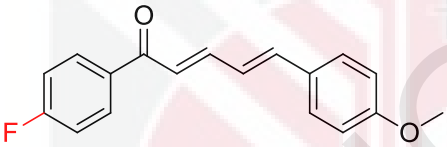
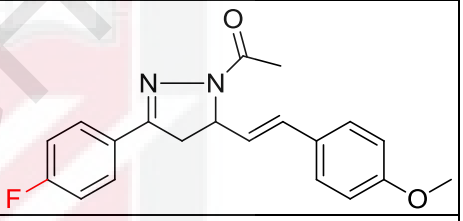
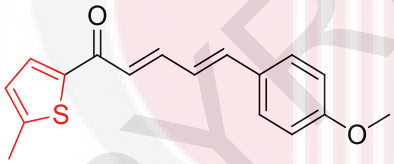
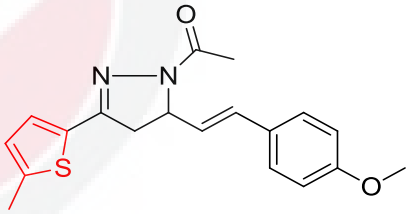
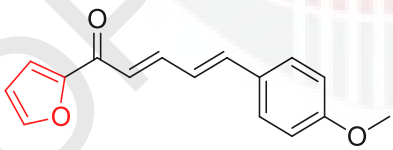
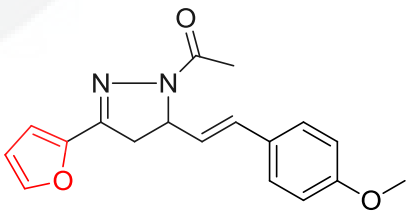
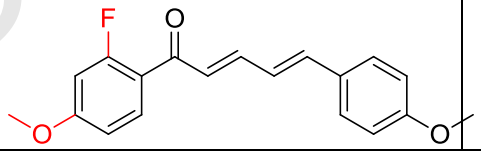
| 4 |  | 14* |  |
| 5 |  | 15* |  |
| 6 |  | 16* |  |
| 7 |  | 17* |  |
| 8 |  | 18* |  |
| 9 |  | 19* |  |
| 10 |  | | |

*Indicates new compound

## 1.2 Problem Statement

Antioxidants are used routinely as a protection against oxidation. Several synthetic phenolic antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) have been widely used in the food industry, cosmetics, and the therapeutic industry. However, these synthetic antioxidants have been reported to be hazardous to humans, due to their high volatility, instability at elevated temperature, and its carcinogenic nature which then have led to the growing needs for new antioxidant agents as an alternative safe treatment (Sindhi et al., 2013).

Diarylpentadienones and pyrazolines analogues might be the potent candidate based on their reported strong antioxidant property (Babu et al., 2007). Hence, in this study we have designed and synthesized a series of pyrazoline analogues of diarylpentadienones. We hypothesize with a different selected functional group on both rings and increase rigidity on the diarylpentadienone scaffold, the selected bioactivities might be enhanced.

To the best of our knowledge, limited number of studies incorporated the α, β, γ, σ-unsaturated ketone moiety in a diarylpentadienone scaffold and pyrazoline analogue of diarylpentadienone in the evaluation of antioxidant, antibacterial and anticandidal properties. Therefore, we are focusing on design strategies of diarylpentadienone and pyrazoline analogue of diarylpentadienone to produce the desired antioxidant, antibacterial and anticandidal properties by studying the effect of various functional group at different positions of diarylpentadienone and pyrazoline analogue of diarylpentadienone on the selected bioactivities. The antioxidant, antibacterial and anticandidal activities were conducted at the Laboratory of Natural Products, Institute of Bioscience, UPM.

## 1.3 Objectives of the study

1. To synthesize the diarylpentadienones and its pyrazoline analogues
2. To structurally characterize the synthesized compounds via spectroscopic methods such as $^{1}H$- and $^{13}C$-NMR, Nuclear Overhouser Effect Spectroscopy (NOESY), Heteronuclear Multiple bond Coherence (HBMC), Correlation Spectroscopy (COSY), Gas Chromatography-Mass Spectroscopy (GC-MS) as well as Fourier Transform Infrared Spectroscopy (FT-IR).
3. To evaluate their antioxidant activity using 2,2-dipheny-1-picrylhydrazine (DPPH) radical and nitric oxide (NO) scavenging assays as well as their antibacterial and anticandidal efficacies using disk diffusion assay.

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