DEVELOPMENT OF A NEW CLASS OF DIARYLPENTADIENONE ANALOGUES AS ANTI-DIABETIC AGENTS

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By

MARYAM AISYAH BINTI ABDULLAH

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

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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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September 2019

Chair : Siti Munirah Binti Mohd. Faudzi, PhD
Faculty : Science

Type 2 diabetes mellitus (T2DM) is a chronic disease occurred worldwide and is currently a major cause of morbidity and mortality. Several drugs such as sulfonylureas and biguanides are presently available to reduce hyperglycemia in T2DM patients, however, these medicines possess several side effects and thus searching for a new class of compounds is essential to overcome this problem. Diarylpentadienone is a synthetic compound derived from curcuminoids and chalconoids, which received less extensive studies by researchers, particularly as anti-diabetic agents. In addition, sulfonamide moiety has proven as essential feature for alpha-glucosidase (α-glucosidase) inhibitors and has potential towards dipeptidyl peptidase 4 (DPP-4) inhibitory activity, the two of therapeutic targets for T2DM treatment.

In this study, a series of aminated-1,5-diphenylpenta-2,4-dien-1-ones (compounds **1**-**9**) were synthesized by treating aminoacetophenones with differently substituted cinnamaldehydes *via* Aldol condensation reaction, further completion by sulfonylation reaction with trifluoromethylbenzenesulfonyl chloride to afford the sulfonamide diarylpentadienone analogues (compounds **10**-**18**). The purified intermediate and final compounds were collected and subjected for confirmatory structural elucidation *via* established spectroscopic techniques comprising of ^{1}H- and ^{13}C- high field nuclear magnetic resonance (NMR), direct injection-mass spectroscopy (DI-MS), and Fourier-transform infrared (FTIR) spectroscopy. These new integrated sulfonamide-diarylpentadienone derivatives were screened for their potential anti-diabetic properties through α-glucosidase and DPP-4 *in vitro* assay.

Based on α-glucosidase inhibition results, all sulfonamide-containing analogues (compound **10**-**18**) showed a remarkable suppression activity, in which compound **18** exhibited the highest inhibition with IC_{50} values of 4.93 ± 0.7 μM, followed by compound **17** (IC_{50} = 5.83 ± 0.4 μM), in which both analogues demonstrated good inhibitory activity compared to the standard quercetin (IC_{50} = 6.38 ± 0.4 μM). The structure-activity relationship (SAR) studies revealed that the introduction of the trifluoromethylbenzene

sulfonamide on *para* position of ring A and a lower electron density group (-Cl) on phenyl ring B of diarylpentadienone scaffold enhanced their α-glucosidase inhibition potential. Molecular docking analyses further confirmed the critical role of both sulfonamide and -Cl moieties as they bound to the α-glucosidase active sites, and thus explain their inhibitory activity.

Whereas for DPP-4 inhibition activity, none of the synthesized molecules showed a comparable suppression to the standard drug, sitagliptin, ($IC_{50} = 0.07 \pm 0.1$ μM). However, within the series, compound **15** showed the most active inhibition with IC_{50} of 25.05 ± 0.38 μM. The SAR studies showed that the introduction of the trifluoromethylbenzene sulfonamide on *para* position of ring A and methoxy group on *para* position on ring B seems to exert a positive influence on the DPP-4 inhibition activity of compound **15**. The docking analyses between ligand **15** and DPP-4 receptor (PDB ID:5T4B) showed a hydrogen bonding interaction between sulfonamide moiety with amino acid residues (Tyr574) at the hydrophobic site of the enzyme. Overall results suggest that diarylpentadienone with the sulfonamide moiety could be a new selective potential hit molecule in the search of the novel α-glucosidase inhibitors over anti-DPP-4 agents, for the treatments of T2DM patients.

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

PEMBANGUNAN KELAS BAHARU ANALOG-ANALOG DIARILPENTADIENON SEBAGAI EJEN ANTI-DIABETIK

Oleh

MARYAM AISYAH BINTI ABDULLAH

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Diabetis jenis 2 (T2DM) adalah penyakit kronik yang berlaku di seluruh dunia dan kini merupakan punca utama morbiditi dan kematian. Beberapa ubat-ubatan seperti sulfonilurea dan biguanida disediakan untuk mengurangkan hiperglisemia pesakit T2DM. Walau bagaimanapun, ubat-ubatan ini mempunyai beberapa kesan sampingan dan sekali gus pencarian kelas sebatian baharu adalah penting untuk mengatasi masalah ini. Diarilpentadienon merupakan sebatian sintetik berasal dari kurkuminoid dan kalkonoid, kurang dikaji secara meluas oleh para penyelidik, terutamanya sebagai agen anti-diabetis. Di samping itu, kumpulan sulfonamida telah terbukti mempunyai ciri-ciri penting bagi perencat alfa-glukosidase (α-glukosidase) dan mempunyai potensi ke arah perencatan aktiviti dipeptidil peptidase 4 (DPP-4), kedua-duanya sasaran terapeutik untuk rawatan T2DM.

Dalam kajian ini, satu siri amino-1,5-difenilpenta-2,4-dien-1-on (sebatian **1**-**9**) disintesis dengan aminoasetofenon bertindakbalas dengan sinamaldehid berbeza gantian melalui tindak balas pemeluwapan Aldol, diikuti dengan tindakbalas sulfonilasi dengan trifluorometilbenzenasulfonil klorida bagi menambah sulfonamida ke atas diarilpentadienon (sebatian **10**-**18**). Sebatian tulen pertengahan dan akhir dikumpulkan dan disubjek bagi penjelasan gejala strukturnya melalui teknik-teknik spektroskopi yang merangkumi ^{1}H- dan ^{13}C- resonans nuklear magnetik (NMR) bermedan tinggi, spektroskopi jisim-suntikan terus (DI-MS), dan spektroskopi inframerah-penjelmaan Fourier (FTIR). Derivatif bersepadu sulfonamida-diarilpentadienon baru ini kemudian diskrinkan bagi menyiasat ciri-ciri potensi anti kencing manisnya melalui α-glukosidase dan DPP-4 dalam pengujian *in-vitro*.

Berdasarkan keputusan perencatan α-glukosidase, kesemua analog yang mengandungi sulfonamida (sebatian **10**-**18**) menunjukkan aktiviti perencatan yang luar biasa, di mana sebatian **18** menunjukkan kesan yang tertinggi dengan nilai IC_{50} 4.93 ± 0.7 μM, diikuti oleh sebatian **17** (IC_{50} 5.83 ± 0.4 μM), di mana kedua-duanya menunjukkan aktiviti rencatan yang baik berbanding dengan standard kuarsetin (IC_{50} = 6.38 ± 0.4 μM). Kajian

hubungan struktur-aktiviti (SAR) mendedahkan bahawa pengenalan sulfonamida trifluorometilbenzena pada kedudukan *para* di gelang A dan kumpulan ketumpatan elektron lebih rendah (-Cl) pada gelang fenil B diarilpentadienon meningkatkan potensi perencatan α-glucosidase. Analisis pengedokan molekul mengesahkan secara lanjut peranan kritikal bahagian sulfonamida mahupun -Cl melalui interaksi dengan tapak aktif α-glukosidase, lantas menjelaskan aktiviti perencatan tersebut.

Manakala bagi aktiviti perencatan DPP-4, tiada satu pun daripada sebatian yang telah disintesis menunjukkan perencatan yang setanding ubat standard, sitagliptin, (IC_{50} = 0.07 ± 0.1 μM). Walau bagaimanapun, dalam rangkuman siri ini, sebatian **15** menunjukkan kesan paling aktif dengan IC_{50} = 25.05 ± 0.38 μM. Kajian SAR menunjukkan bahawa pengenalan sulfonamida trifluorometilbenzena pada kedudukan *para* pada gelang A dan kumpulan metoksi pada kedudukan *para* gelang B memberikan kesan yang positif ke atas aktiviti perencatan DPP-4 sebatian **15**. Analisis antara pengedokan ligan **15** dan penerima DPP-4 (PDB ID:5T4B) menunjukkan interaksi ikatan hidrogen antara kumpulan sulfonamida dan asid amino (Tyr574) di tapak hidrofobik enzim. Secara keseluruhannya keputusan mencadangkan bahawa diarilpentadienon dengan kumpulan sulfonamida boleh menjadi pilihan baru molekul *hit* yang berpotensi dalam pencarian perencat α-glukosidase baharu daripada sebagai ejen anti-DPP-4 bagi rawatan pesakit T2DM.

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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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Supervisory Committee : Muhammad Alif Bin Mohammad Latif

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LIST OF ABBREVIATIONS

%	Percentage
α	Alpha
β	Beta
λ	Wavelength
λ_{Ab}	Absorbance wavelength
λ_{Em}	Emission wavelength
λ_{Ex}	Excitation wavelength
δ	Chemical shift in ppm
^{1}H NMR	^{1}H-Nuclear Magnetic Resonance spectroscopy
approx.	Approximate
br	Broad
^{13}C	Carbon-13
COSY	Correlation Spectroscopy
d	Doublet
dd	Double doublet
DMSO	Dimethyl sulfoxide
DPP-4	Dipeptidyl peptidase 4
E1cB	Elimination Unimolecular conjugate Base
EtOH	Ethanol
EtOAc	Ethyl Acetate
FT-IR	Fourier Transform- Infrared spectroscopy
GC-MS	Gas Chromatograph- Mass Spectrometry
^{1}H	Proton-1
hrs / h	Hours/Hour
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Mutliple Quantum Coherence
IC_{50}	Half maximal inhibitory concentration
m	Multiplet
m	*Meta*
M^{+}	Molecular ion
Me	Methyl
min	Minute
MP	Melting Point
m/z	Mass-to-charge ratio
NCBI	National Center for Biotechnology Information
NMR	Nuclear Magnetic Resonance
o	*Ortho*
oop	Out of Plane Bending
p	*Para*
PDB	Protein data bank
Ph	Phenyl
ppm	Parts per million
RT	Room Temperature
s	Singlet
SAR	Structure-activity relationship
t	Triplet
TLC	Thin Layer Chromatography

TMS	Tetramethylsilanol
UATR	Universal Attenuated Total Reflection
UV	Ultraviolet

CHAPTER 1

INTRODUCTION

Diabetes mellitus or diabetes has become an increasing problem worldwide, both in rich and poor countries. It is a chronic and progressive disease associated with elevated glucose levels in blood or hyperglycaemia over a prolonged time. Over time, diabetes can lead to complications such as heart attack, stroke, kidney failure, leg amputation, vision loss, and nerve damage (WHO, 2016).

The World Health Organization (WHO) recognizes three major types of diabetes, which are type 1, type 2, and gestational diabetes. Type 1 diabetes happens when there is a deficiency in insulin production by the body and is usually diagnosed in young adults. Type 2 diabetes occurs when the body has ineffective insulin or insulin resistance, combined with reduced insulin secretion and hyperglycaemia. Obese persons have a higher risk to get this disease. Meanwhile, pregnant women may temporarily contract gestational diabetes; if it is prolonged after delivery, the person might carry a risk of getting type 2 diabetes (Bellamy *et al*., 2009). Insulin is a peptide hormone secreted by the pancreas. When food is consumed, insulin causes glucose uptake into liver, muscle, and fat cells to be stored as glycogen (Havale *et al*., 2009). Insulin is essential for blood sugar level regulation and energy metabolism. Maintenance of glucose homeostasis is achieved by the hormonal regulation of glucose uptake and endogenous glucose production, primarily by muscle and liver cells. A change in normal glucose homeostasis occurs because of a combination of factors which include impaired insulin secretion, unconcealed hepatic gluconeogenesis, and reduced uptake of glucose by skeletal muscle, adipose tissues, and liver, resulting in hyperglycaemia or diabetes (Damazio *et al.*, 2009).

Majority of people with diabetes are affected by type 2 diabetes mellitus (T2DM) (Alberti *et al.*, 1998). As reported by the International Diabetes Federation, T2DM comprises approximately 90% of all cases of diabetes and to date, an estimation of 15 million peoples are affected globally. Previously, T2DM has only been diagnosed in older adults, but surprisingly, current statistics show that T2DM is becoming more prevalent among children and adolescent, due to escalating obesity and overweight incidence among the youth (WHO, 2016). Thus, overweight and obesity, together with physical inactivity, are estimated to cause a large proportion of the global diabetes burden (Forouzanfar *et al*., 2016). Previously known as non-insulin-dependent diabetes mellitus (NIDDM) and late-onset diabetes mellitus, T2DM is described as a metabolic disorder often coupled with insulin resistance that affects the way the body metabolises its important source of fuel, glucose.

Insulin resistance in T2DM causes insulin to become increasingly ineffective at managing the body's glucose level. As a result, the pancreas produces excessive insulin in an attempt to balance blood glucose level. This insulin overproduction, if occurs over a prolonged period, will consume the insulin-producing beta (β)-cells. By the time a person is diagnosed with T2DM, they have already lost 50%–70% of the cells. Thus,

T2DM is the combination of ineffective and insufficient insulin (Diabetes Australia, 2007).

For people with T2DM, blood glucose level can be managed by good dietary habits and exercise to prevent the development and progression of the disease. However, many patients still need medications or insulin therapy for their treatment. Currently, medications for T2DM are aimed at suppressing hepatic glucose output, stimulating insulin release, mitigating glucose absorption, and increasing peripheral glucose utilisation (Rines *et al*., 2016). While current T2DM therapies involving the increase of insulin secretion have shown therapeutically beneficial effects, these are often accompanied with undesirable side effects such as hypoglycaemia and weight gain. Besides a classical insulin-based treatment for the management of T2DM, other alternative oral medications include sulfonylureas (glyburide, glimepiride), biguanides (metformin), alpha-glucosidase inhibitors (acarbose), and thiazolidinediones (rosiglitazone). Due to their adverse side effects, most of these treatments are unsatisfactory in terms of prevention of complications and preservation of quality of life (Havale & Pal, 2009). Thus, there is a significant unmet medical need for the discovery of effective antidiabetic drugs to treat T2DM.

Alpha-glucosidase (α-glucosidase) is an enzyme that catalyses the final steps in the digestion of carbohydrate; hence, α-glucosidase inhibitors could retard the catabolism of dietary carbohydrate to suppress postprandial hyperglycaemia. There are those who argue that α-glucosidase inhibitors such as acarbose (Glucobay) and miglitol (Glyset), although effective in decreasing the absorption of glucose by interfering with the action of α-glucosidases in the small intestinal mucosa, are often associated with abdominal bloating, diarrhoea, and flatulence (2009). α-Glucosidase inhibitors also raise post-meal levels of glucagon-like peptide-1 (GLP-1), an incretin hormone secreted by the intestine following ingestion of various nutrients to stimulate insulin secretion and inhibit glucagon release, which slows the gastric emptying process and suppresses appetite (Lee *et al.*, 2015). This means that they do not increase the likelihood of weight gain, unlike sulfonylureas and thiazolidinediones.

Since 2006, dipeptidyl peptidase-4 (DPP-4) inhibitors have become a new class of agent that is proven as an effective treatment of diabetes by improving glycaemic control (McIntosh, 2008). DPP-4 inhibitors target DPP-4, a serine protease enzyme which researchers believe deactivate two potent stimulators of insulin secretion, GLP-1 and glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide or GIP). Like GLP-1, GIP also helps to delay digestion and decrease appetite. However, both hormones are rapidly cleaved to their inactive forms by the enzyme DPP-4, thus reducing their potency in preventing diabetes-related complications. Therefore, it is important to note that inhibition of DPP-4 is compulsory to increase levels of endogenous incretin hormones GLP-1 and GIP for the treatment of diabetes (Singh, 2014). Sitagliptin phosphate (Januvia, Merck) was the first agent of DPP-4 inhibitors to gain FDA approval in the United States on 2006 for the treatment of patients with T2DM. Following the active discovery of antidiabetic drugs from this novel class, other bioactive entities have also been established and marketed, including vildagliptin (Novartis), saxagliptin (BMS), linagliptin (Lilly), and alogliptin (Takeda) (Chen *et al.*, 2015).

In comparison to other classes of antidiabetic therapies, these commercially available DPP-4 inhibitors have shown some advantages such as administration of a single daily oral dose to maintain normal glycaemic condition without causing severe hypoglycaemia, altogether with promotion of β-cell regeneration and differentiation to meet the body's insulin requirement (Al-Masri *et al.*, 2009).

Chalcones (Figure 1.1) have shown significant modulatory effect on all major protein targets in T2DM, namely protein-tyrosine phosphatase 1B (PTP1B), peroxisome proliferator-activated receptor gamma (PPAR-γ), α-glucosidase, DPP-4, and aldose reductase (Vignesh, 2017). They demonstrate promising pharmacological activities and are worthy candidates for the management of diabetes (Bak *et al.*, 2011).

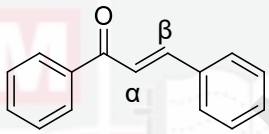


Figure 1.1: General structure of chalcone

The lengthening of the three-carbon spacer of chalcones to a five-carbon chain linker of diarylpentadienones (Figure 1.2) might help in enhancing the therapeutic properties specifically for DPP-4 inhibition of the expected bioactive molecules by strengthening the interaction with specific active sites in the pocket of DPP-4 and reducing its adverse side-effects. Researchers have discovered diarylpentadienone analogues with various pharmacological activities, including promising anti-inflammatory property (Wang *et al*., 2017), significant anticancer effect to leukaemia (Suarez *et al.*, 2010) and breast cancer (Weldon et al., 2014), excellent antimicrobial and antifungal activity (Batovska *et al*., 2009), anti-rhinovirus properties (Conti *et al*., 2005), and also as an antioxidant (Das *et al*., 2014).

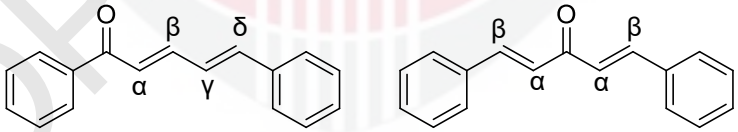


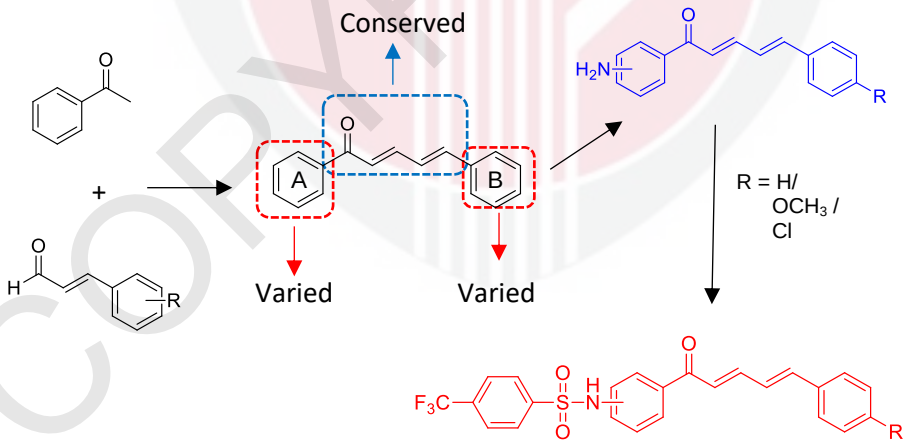
Figure 1.2: General structures of diarylpentadienone

Sulfonamide, which consist of a sulfur atom singly-bonded to a nitrogen atom with two sets of double bonds bonded to oxygen atoms, has received a lot of attention and is used as an intermediate functional group of many clinically approved therapeutic drugs such as trimethoprim and sulphamethoxazole (anti-microbial), acetazolamide (diuretics), methazolamide (antiepileptic), carbutamide and chlorpropamide (anti-diabetics) (Custodio *et al.*, 2017 and Lavanya, 2017). Many studies show several synthetic pharmacological agents that consist of sulfonamide group possess antibacterial (Prlina *et al.*, 1958), antimalarial (Ryan, 1975), diuretic (Douglas *et al.*, 1961), antirheumatic (Markham, 2017; Penning *et al.*, 1997), and antiretroviral properties (Adkins & Faulds,

1998). Previous studies also reported that sulfonamide-containing compounds are essential for DPP-4 inhibitory activity (Chen *et al.*, 2015). Recently, sulfonamide chalcones have also been reported to possess striking α-glucosidase-inhibiting property (Mahapatra, 2015).

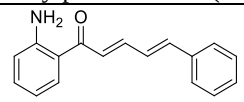
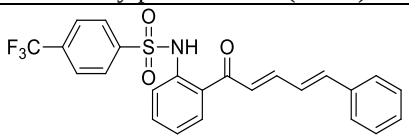
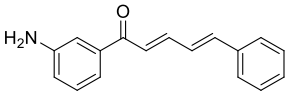
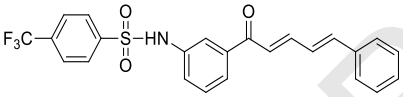
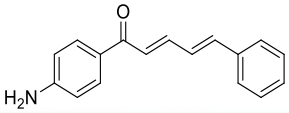
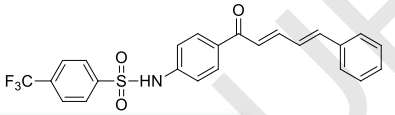
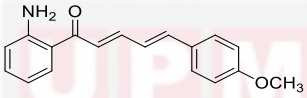
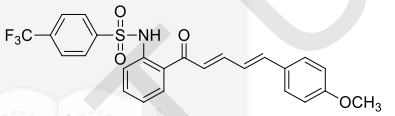
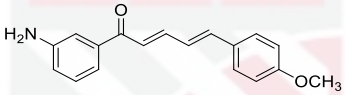
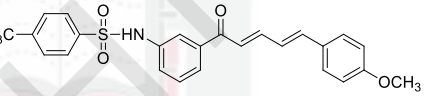
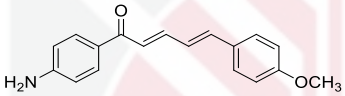
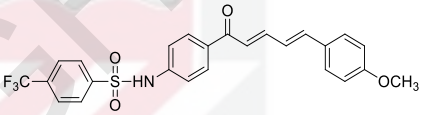
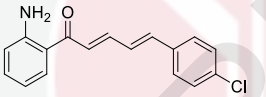
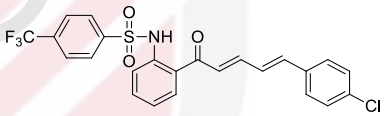
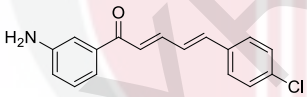
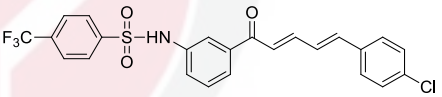
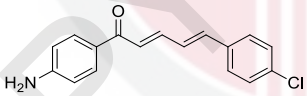
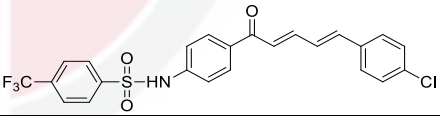
From this perspective, we predicted that the 2-carbon elongated chalcone derivative, diarylpentadienones (Figure 1.2) incorporated with sulfonamide group will retain or enhance the inhibition of α-glucosidase and DPP-4. Considering the significant clinical implication of α-glucosidase and DPP-4 inhibitors and the therapeutic potential of sulfonamides and diarylpentadienones, we herein report the design, synthesis, and biological evaluation of a new series of integrated sulfonamide-containing diarylpentadienones as potential inhibitors of α-glucosidase and DPP-4 for the treatment of T2DM.

Despite the numerous bioactivities of diarylpentadienone derivatives, to the best of our knowledge, none of them have been investigated for their effects as an anti-diabetic drug. The general structures and reaction scheme of the targeted compound incorporating diarylpentadienones and sulfonamide are shown in Scheme 1.1, while the structures of all new eighteen compounds are tabulated in Table 1.1. The design of the compounds is based on steric and electronic properties of substituents [(CF_3-containing sulfonamide on ring A and –H, –Cl (electron-withdrawing group), or –OCH_3 (electron-donating group) on ring B)]. The selected functional groups were appended on *ortho-*, *meta-*, and *para-* positions of both ring A and ring B to examine their important influence towards α-glucosidase and DPP-4 inhibitory activity, respectively.



Scheme 1.1: General conversion of aminated-precursor to sulfonamide–diarylpentadienones

Table 1.1: List of new synthesized compounds

Aminated-diarylpentadienone (**1-9**)		Sulfonamide-diarylpentadienone (**10-18**)	
1		**10**	
2		**11**	
3		**12**	
4		**13**	
5		**14**	
6		**15**	
7		**16**	
8		**17**	
9		**18**	

1.1 Problem statements

Prevention and control of diabetes with diet, weight control and physical activity alone are difficult tasks; therefore, some patients might be prescribed with antidiabetic medications in controlling this disease. Treatments of T2DM are centred mainly on increasing blood insulin levels (either by direct insulin administration or oral drugs that promote insulin secretion), decreasing insulin resistance, or reducing the rate of carbohydrate absorption from the gastrointestinal tract (Li *et al.*, 2015). To date, major drug classes presently used to treat T2DM have been reported to possess several side effects, especially for patients with liver and renal disorders (Hsieh *et al.*, 2012). Therefore, developing a new drug candidate for the handling of diabetes is a goal for improving the treatment of diabetic patients.

As regards, we hypothesize a conjugation of diarylpentadienone scaffold with sulfonamide as new drug candidates might offers the enrichment on some pharmacokinetic and pharmacodynamic properties including bioavailability factor, in comparison to the current available drugs.

1.2 Objectives of the study

Due to the broad biological spectrum of diarylpentadienones, including their antidiabetic properties, we aimed to synthesize a series of diarylpentadienone derivatives and examine their effects as α-glucosidase and DPP-4 inhibitors, specifically. Therefore, the objectives of this research are:

1) To synthesize and characterize a series of aminated- and sulfonamide-containing diarylpentadienones.
2) To investigate the potency and structure–activity relationship (SAR) of diarylpentadienone analogues with respect to their *in-vitro* α-glucosidase and DPP-4 inhibitory activities.
3) To determine the possible binding interaction responsible for specific inhibition activity using docking tools.

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