



Synthesis of Sulfonamide Chalcones as α -Glucosidase Inhibitors

I Putu Sukanadi, Ade Danova and Warinthorn Chavasiri*

Center of Excellence in Natural Products Chemistry, Department of Chemistry, Faculty of Science,
Chulalongkorn University, Pathumwan, Bangkok, Thailand

*Corresponding author, E-mail: warinthorn.c@chula.ac.th

Abstract

Diabetes is a major problem that has reached an alarming level, nearly half a billion people live with diabetes worldwide and estimated to increase to 51% by 2045. Diabetes mellitus is a complex chronic illness associated with a state of elevated levels of blood glucose or hyperglycemia. One of the therapeutic strategies to suppress postprandial hyperglycemia is namely inhibiting glucose absorption through inhibition of bio-catalysts involved in the digestion of carbohydrates such as α -amylase and α -glucosidase. In this paper, thirteen sulfonamide chalcones **3a-3m** were synthesized using the Claisen-Schmidt condensation reaction by reacting sulfonyl aminoacetophenones with benzaldehydes and tested for their activity as α -glucosidase inhibitors. The results showed that the *para* position of secondary amine (**3c**) greatly influenced the inhibition results, likewise the effect of the electron-donating groups (**3e**). **3c** provides very strong inhibitory activity with $IC_{50} 1.04 \pm 0.19 \mu M$. The finding proves that the sulfonamide chalcone has enormous potential as an α -glucosidase inhibitor and opens up opportunities to find new compounds that have better activity.

Keywords: diabetes, α -glucosidase, chalcone, sulfonamide chalcone

1. Introduction

Diabetes is a health problem that has reached an alarming level where nearly half a billion people live with diabetes worldwide. The International Diabetes Federation (IDF) reported 463 million people with diabetes in 2019 and predicted an increase of up to 51 % (700 million) individuals with diabetes by 2045. Diabetes mellitus is a complex chronic illness associated with a state of elevated levels of blood glucose or hyperglycemia. Diabetes mellitus is occurring from deficiencies in insulin secretion, which leads over time to a high risk for complications, including elevated risk for cardiovascular diseases (Chaudhury *et al.*, 2017).

Diabetes mellitus type 2 contributes to more than 90% of all cases worldwide than diabetes mellitus type 1 and gestational diabetes. Diabetes mellitus type 2 is characterized by dysregulation of carbohydrate, lipid, protein metabolism, and results from impaired insulin secretion, or insulin resistance (DeFronzo *et al.*, 2015). One of the therapeutic strategies for suppressing postprandial hyperglycemia by retarding the absorption of glucose through the inhibition of the bio-catalyzers involved in carbohydrate digestion, namely α -amylase and α -glucosidase (Rocha *et al.*, 2019).

The α -glucosidase inhibitors seem to be the most effective in reducing postprandial hyperglycemia. Some α -glucosidase inhibitors have been clinically used, such as acarbose, miglitol, and voglibose, but they have adverse effects (*e.g.* gastrointestinal symptoms) (Cai *et al.*, 2017). Therefore, it is very important to find new compounds possessing potential anti-diabetes Mellitus, especially α -glucosidase inhibitors. In addition, chalcone and sulfonamide are reported to have biological activities including antidiabetic.

Chalcone is a secondary metabolite of plants and precursors of flavonoid biosynthesis. This compound is described with a 1,3-diarylprop-2-en-1-one framework (**Figure 1**). Its derivatives demonstrate a variety of promising biological activity such as NF- κ B inhibition (Srinivasan *et al.*, 2009), anti-inflammatory (Wu *et al.*, 2011), anti-diabetic (Hisieh *et al.*, 2012), and α -glucosidase (Cai *et al.*, 2017). To increase its biological activity, the modification of chalcone is easily conducted in either ring A or B. One approach is sulfonamide chalcone that has been reported to possess potent biological activities such as antibacterial (Mehta & Parikh, 1979), α -glucosidase inhibitors (Seo *et al.*, 2005), anti-cancer (Ghorab *et al.*, 2015), and therapeutic agent against *Brugia malayi* (Bahekar *et al.*, 2016).

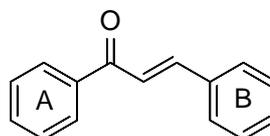


Figure 1 Core structure of chalcone

Seo *et al.* (2005) presented the chalcone with a 4-*p*-tosylamino substituent in ring A and a hydroxy substituent in ring B as an α -glucosidase inhibitor with IC_{50} 0.40 μ M for 3,4-dihydroxy substituent and IC_{50} 0.98 μ M for 4-hydroxy substituent. This sulfonamide chalcone has increased the activity of α -glucosidase inhibition. However, this study did not demonstrate the structure-activity relationship. Thus, sulfonamide chalcones as α -glucosidase inhibitors would be an attractive direction for finding a new therapy for diabetes. In this study, the sulfonamide chalcones were synthesized with various substituents such as methoxy, nitro, and halogen, and then characterized and evaluated the activity as α -glucosidase inhibitors.

2. Objectives

- 1) To study the effect of amino position on the A-ring as an α -glucosidase inhibitor
- 2) To investigate the effect of monosubstituents on B-ring as an α -glucosidase inhibitor
- 3) To see the effect of modification chalcone position on the inhibition of α -glucosidase

3. Materials and Methods

3.1 Materials

All reagents were purchased from Tokyo Chemical Industry (TCI) and Sigma-Aldrich with a grade > 98%, and the solvents were purchased from RCI Labscan Ltd with a grade > 99.9%. The NMR spectra were recorded in DMSO- d_6 using JEOL JNM-EC500R / S1 NMR. The mass spectrum (MS) was measured on micro OTOF-Q II 10335-ESI-Qq-TOF. TLC analysis was used to determine the reaction under UV light. Column chromatography was carried out using hexane: ethyl acetate as eluent, and silica gel (7734, Merck), or re-crystallization using methanol. The α -glucosidase inhibition assay was performed using the ALLSHENG AMR-100 microplate reader.

3.2 General synthetic procedure for sulfonamide chalcones

The sulfonylaminoacetophenones (0.5 mmol) and aromatic aldehydes (1 mmol) were dissolved in 10 mL ethanol. Subsequently, NaOH (2 eq) was added and stirred at room temperature. The reaction was monitored by TLC for 24 hours. Furthermore, 10% HCl was added to the reaction mixture to pH 5 and extracted with ethyl acetate (Bahekar *et al.*, 2016). The organic portion was evaporated and purified using a column chromatography method or recrystallization using a suitable solvent to obtained **3a-3m**. All structures were confirmed their identities by spectroscopic means, including NMR, and for new compounds by mass spectra additionally.

3.2.1 *N*-[2-(3-(3,4-dimethoxyphenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3a**)

1 H-NMR (DMSO- d_6 , 500 MHz) δ = 11.26 (s, 1H N-H), 8.06 (dd, J = 1.5 Hz, 1H, ArH), 7.54 (s, 3H), 7.52 (s, 1H), 7.47 (dt, J = 1.0 Hz, 1H, ArH), 7.39 (d, J = 2.0 Hz, 1H, ArH), 7.37 (dd, J = 1.0 Hz, 1H, ArH), 7.27 (dd, J = 2.0 Hz, 1H, ArH), 7.20 (d, J = 8.0 Hz, 2H, ArH), 7.15 (dt, J = 1.0 Hz, 1H, ArH), 6.93 (d, J = 8.0 Hz, 1H, ArH) 3.74 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 2.13 (s, 3H, CH₃) ppm. 13 C-NMR (DMSO- d_6 , 125 MHz): δ = 193.1, 152.2, 149.5, 146.6, 144.5, 139.0, 136.2, 134.7, 132.0, 130.4, 127.7, 127.4, 126.6, 125.1, 124.5, 120.9, 120.8, 112.0, 111.3, 56.3, 56.2, 21.4 ppm. HRMS calculated for C₂₄H₂₃NO₅S [M+Na]⁺ 460.11966.

3.2.2 *N*-[3-(3-(3,4-dimethoxyphenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3b**)

1 H-NMR (DMSO- d_6 , 500 MHz) δ = 10.45 (s, 1H N-H), 7.84 (d, J = 8.0 Hz, 1H, ArH), 7.67 (d, J = 19.0 Hz, 1H, β -H), 7.67 (d, J = 19.0 Hz, 1H, α -H), 7.64 (d, J = 8.5 Hz, 2H, ArH), 7.62 (s, 1H, ArH), 7.46 (d, J = 1.5 Hz, 1H, ArH), 7.41 (t, J = 7.5 Hz, 1H, ArH), 7.34 (dd, J = 1.5 Hz, 2H, ArH), 7.31



- (d, $J = 8.0$ Hz, 2H, ArH), 7.00 (d, $J = 8.5$ Hz, 1H, ArH), 3.81 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 2.28 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): $\delta = 189.2, 151.9, 149.5, 145.4, 144.0, 139.3, 139.0, 137.0, 130.3, 130.2, 127.9, 127.2, 124.8, 124.5, 124.4, 120.1, 119.5, 112.1, 111.3, 56.3, 56.2, 21.5$ ppm. HRMS calculated for C₂₄H₂₃NO₅S [M+Na]⁺ 460.11913.
- 3.2.3 *N*-[4-(3-(3,4-dimethoxyphenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3c**)
¹H-NMR (DMSO-d₆, 500 MHz): $\delta = 10.80$ (s, 1H N-H), 8.01 (d, $J = 9.0$ Hz, 2H, ArH), 7.70 (d, $J = 15.5$ Hz, 1H, β -H), 7.70 (d, $J = 8.0$ Hz, 2H, ArH), 7.61 (d, $J = 15.5$ Hz, 1H, α -H), 7.46 (d, $J = 1.5$ Hz, 1H, ArH), 7.34 (d, $J = 8.5$ Hz, 2H, ArH), 7.31 (dd, $J = 2.0$ Hz, 1H, ArH), 7.22 (d, $J = 8.5$ Hz, 2H, ArH), 6.82 (d, $J = 8.5$ Hz, 1H, ArH), 3.81 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 2.29 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): $\delta = 187.9, 151.7, 149.5, 144.5, 144.3, 142.7, 137.0, 133.4, 130.6, 130.4, 128.1, 127.3, 124.4, 119.9, 118.5, 112.1, 111.1, 56.2, 56.1, 21.5$ ppm. HRMS calculated for C₂₄H₂₃NO₅S [M+H]⁺ 438.13720.
- 3.2.4 *N*-[4-(3-(2-methoxyphenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3d**)
¹H-NMR (DMSO-d₆, 500 MHz): $\delta = 10.83$ (s, 1H N-H), 8.00 (d, $J = 8.0$ Hz, 2H, ArH), 7.96 (d, $J = 16.0$ Hz, 1H, β -H), 7.89 (d, $J = 8.0$ Hz, 1H, ArH), 7.78 (d, $J = 16.0$ Hz, 1H, α -H), 7.71 (d, $J = 8.0$ Hz, 2H, ArH), 7.41 (t, $J = 7.5$ Hz, 1H, ArH), 7.34 (d, $J = 8.0$ Hz, 2H, ArH), 7.23 (d, $J = 8.0$ Hz, 2H, ArH), 7.07 (d, $J = 8.5$ Hz, 1H, ArH), 6.99 (t, $J = 7.5$ Hz, 1H, ArH), 3.85 (s, 3H, OCH₃), 2.30 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): $\delta = 187.6, 158.2, 143.7, 142.3, 138.0, 136.4, 132.7, 132.2, 130.1, 129.9, 128.5, 126.8, 122.9, 121.6, 120.7, 118.0, 111.8, 55.7, 21.0$ ppm. HRMS calculated for C₂₃H₂₂NO₄S [M+H]⁺ 408.12658.
- 3.2.5 *N*-[4-(3-(3-methoxyphenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3e**)
¹H-NMR (DMSO-d₆, 500 MHz): $\delta = 10.85$ (s, 1H N-H), 8.04 (d, $J = 9.0$ Hz, 2H, ArH), 7.84 (d, $J = 15.5$ Hz, 1H, β -H), 7.72 (d, $J = 8.5$ Hz, 2H, ArH), 7.63 (d, $J = 15.5$ Hz, 1H, α -H), 7.42 (s, 1H, ArH), 7.37 (d, $J = 9.5$ Hz, 1H, ArH), 7.35 (d, $J = 9.0$ Hz, 2H, ArH), 7.33 (t, $J = 8.0$ Hz, 1H, ArH), 7.24 (d, $J = 9.0$ Hz, 2H, ArH), 6.68 (dd, $J = 3.0$ Hz, 1H, ArH), 3.79 (s, 3H, OCH₃), 2.31 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): $\delta = 187.5, 159.6, 143.7, 143.5, 142.4, 136.4, 136.1, 132.5, 130.2, 129.9, 126.8, 122.1, 121.6, 117.9, 116.6, 113.2, 55.3, 21.0$ ppm. HRMS calculated for C₂₃H₂₂NO₄S [M+H]⁺ 408.12647.
- 3.2.6 *N*-[4-(3-(4-methoxyphenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3f**)
¹H-NMR (DMSO-d₆, 500 MHz): $\delta = 10.83$ (s, 1H N-H), 8.02 (d, $J = 9.0$ Hz, 2H, ArH), 7.80 (d, $J = 9.0$ Hz, 2H, ArH), 7.73 (d, $J = 8.5$ Hz, 2H, ArH), 7.71 (d, $J = 15.5$ Hz, 1H, β -H), 7.65 (d, $J = 15.5$ Hz, 1H, α -H), 7.37 (d, $J = 8.5$ Hz, 2H, ArH), 7.24 (d, $J = 8.5$ Hz, 2H, ArH), 7.00 (d, $J = 9.0$ Hz, 2H, ArH), 3.81 (s, 3H, OCH₃), 2.32 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): $\delta = 187.5, 161.4, 143.8, 143.5, 142.3, 136.5, 132.8, 130.7, 130.1, 129.9, 127.4, 126.8, 119.3, 118.0, 114.4, 55.4, 21.0$ ppm (Kim *et al.*, 2010; Bahekar *et al.*, 2016; Bahekar *et al.*, 2017).
- 3.2.7 *N*-[4-(3-(4-fluorophenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3g**)
¹H-NMR (DMSO-d₆, 500 MHz): $\delta = 10.83$ (s, 1H N-H), 8.00 (d, $J = 8.5$ Hz, 2H, ArH), 7.89 (dd, $J = 6.0$ Hz, 2H, ArH), 7.78 (d, $J = 15.5$ Hz, 1H, β -H), 7.69 (d, $J = 8.0$ Hz, 2H, ArH), 7.64 (d, $J = 15.5$ Hz, 1H, α -H), 7.33 (d, $J = 8.0$ Hz, 2H, ArH), 7.24 (t, $J = 9.0$ Hz, 2H, ArH), 7.20 (d, $J = 9.0$ Hz, 2H, ArH), 2.28 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): $\delta = 187.5, 164.4, 162.4, 143.8, 142.3, 136.4, 132.5, 131.4, 131.2, 131.1, 130.2, 129.9, 126.8, 121.8, 117.9, 116.0, 115.7, 21.0$ ppm (Ghorab *et al.*, 2015; Bahekar *et al.*, 2016; Bahekar *et al.*, 2017).
- 3.2.8 *N*-[4-(3-(4-chlorophenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3h**)
¹H-NMR (DMSO-d₆, 500 MHz): $\delta = 10.85$ (s, 1H N-H), 8.02 (d, $J = 9.0$ Hz, 2H, ArH), 7.86 (d, $J = 8.5$ Hz, 2H, ArH), 7.85 (d, $J = 16.5$ Hz, 1H, β -H), 7.71 (d, $J = 8.0$ Hz, 2H, ArH), 7.64 (d, $J = 15.5$ Hz, 1H, α -H), 7.48 (d, $J = 8.5$ Hz, 2H, ArH), 7.34 (d, $J = 8.0$ Hz, 2H, ArH), 7.22 (d, $J = 9.0$ Hz, 2H, ArH), 2.30 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): $\delta = 187.4, 143.8, 142.5, 142.0, 136.4, 135.0, 133.7, 132.4, 130.5, 130.3, 129.9, 128.9, 126.8, 122.6, 117.9, 21.0$ ppm (Ghorab *et al.*, 2015; Bahekar *et al.*, 2017).



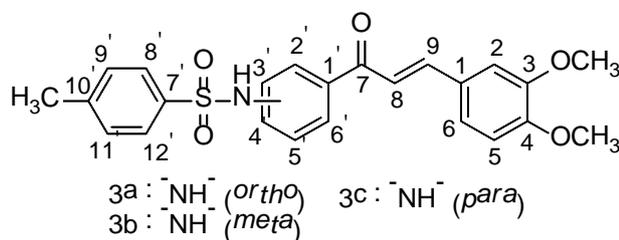
- 3.2.9 *N*-[4-(3-(4-bromophenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3i**)
¹H-NMR (DMSO-d₆, 500 MHz): δ = 10.85 (s, 1H N-H), 8.02 (d, *J* = 8.5 Hz, 2H, ArH), 7.86 (d, *J* = 15.5 Hz, 1H, β-H), 7.79 (d, *J* = 9.0 Hz, 2H, ArH), 7.71 (d, *J* = 8.0 Hz, 2H, ArH), 7.62 (d, *J* = 15.5 Hz, 1H, α-H), 7.62 (d, *J* = 8.5 Hz, 2H, ArH), 7.34 (d, *J* = 8.0 Hz, 2H, ArH), 7.22 (d, *J* = 8.5 Hz, 2H, ArH), 2.30 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): δ = 187.4, 143.8, 142.5, 142.1, 136.4, 134.0, 132.4, 131.9, 130.7, 130.3, 129.9, 126.8, 123.9, 122.7, 117.9, 21.0 ppm (Ghorab *et al.*, 2015; Bahekar *et al.*, 2016; Bahekar *et al.*, 2017).
- 3.2.10 *N*-[4-(3-(4-nitrophenyl)-acryloyl)-phenyl]-4-methylbenzenesulfonamide (**3j**)
¹H-NMR (DMSO-d₆, 500 MHz): δ = 10.88 (s, 1H N-H), 8.26 (d, *J* = 8.5 Hz, 2H, ArH), 8.12 (d, *J* = 9.0 Hz, 2H, ArH), 8.08 (d, *J* = 8.5 Hz, 2H, ArH), 8.04 (d, *J* = 15.5 Hz, 1H, β-H), 7.75 (d, *J* = 15.0 Hz, 1H, α-H), 7.74 (d, *J* = 8.5 Hz, 2H, ArH), 7.37 (d, *J* = 8.5 Hz, 2H, ArH), 7.26 (d, *J* = 9.0 Hz, 2H, ArH), 2.28 (s, 3H, CH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): δ = 187.4, 148.0, 143.8, 142.8, 141.2, 140.6, 136.4, 132.1, 130.5, 129.9, 129.8, 126.8, 125.9, 123.9, 117.9, 21.0 ppm (Mehta & Parikh, 1979).
- 3.2.11 *N*-(phenyl)-4-[1-oxo-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]benzenesulfonamide (**3k**)
¹H-NMR (DMSO-d₆, 500 MHz): δ = 10.46 (s, 1H N-H), 8.23 (d, *J* = 8.0 Hz, 2H, ArH), 7.90 (d, *J* = 8.5 Hz, 2H, ArH), 7.77 (d, *J* = 15.5 Hz, 1H, β-H), 7.71 (d, *J* = 15.5 Hz, 1H, α-H), 7.53 (d, *J* = 1.5 Hz, 1H, ArH), 7.39 (dd, *J* = 1.5 Hz, 1H, ArH), 7.24 (t, *J* = 7.5 Hz, 2H, ArH), 7.11 (d, *J* = 8.0 Hz, 2H, ArH), 7.05 (t, *J* = 8.0 Hz, 1H, ArH), 7.02 (d, *J* = 8.5 Hz, 1H, ArH), 4.67 (s, 3H, OCH₃), 4.64 (s, 3H, OCH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): δ = 188.8, 152.1, 149.5, 146.2, 143.3, 141.6, 137.8, 129.8, 129.7, 127.8, 127.6, 125.0, 121.0, 119.8, 112.1, 111.3, 56.3, 56.2 ppm. HRMS calculated for C₂₃H₂₁NO₅S [M+Na]⁺ 446.10295.
- 3.2.12 *N*-(4-fluorophenyl)-4-[1-oxo-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]benzenesulfonamide (**3l**)
¹H-NMR (DMSO-d₆, 500 MHz): δ = 10.39 (s, 1H N-H), 8.22 (d, *J* = 8.5 Hz, 2H, ArH), 7.84 (d, *J* = 8.5 Hz, 2H, ArH), 7.76 (d, *J* = 15.5 Hz, 1H, β-H), 7.70 (d, *J* = 15.5 Hz, 1H, α-H), 7.51 (d, *J* = 2.0 Hz, 1H, ArH), 7.37 (dd, *J* = 2.0 Hz, 1H, ArH), 7.09 (s, 2H, ArH), 7.08 (d, *J* = 2.0 Hz, 2H, ArH), 7.00 (d, *J* = 8.0 Hz, 1H, ArH), 3.82 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): δ = 188.3, 160.3, 158.3, 151.6, 149.0, 145.8, 142.5, 141.1, 133.5, 129.2, 127.3, 127.1, 124.4, 123.2, 119.3, 116.1, 115.9, 111.6, 110.8, 56.8, 55.6 ppm. HRMS calculated for C₂₃H₂₀FNO₅S [M+Na]⁺ 464.09253.
- 3.2.13 *N*-(4-chlorophenyl)-4-[1-oxo-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]benzenesulfonamide (**3m**)
¹H-NMR (DMSO-d₆, 500 MHz): δ = 10.55 (s, 1H N-H), 8.17 (d, *J* = 8.5 Hz, 2H, ArH), 7.82 (d, *J* = 8.5 Hz, 2H, ArH), 7.70 (d, *J* = 15.5 Hz, 1H, β-H), 7.64 (d, *J* = 15.5 Hz, 1H, α-H), 7.45 (d, *J* = 1.5 Hz, 1H, ArH), 7.31 (dd, *J* = 1.5 Hz, 1H, ArH), 7.23 (d, *J* = 8.5 Hz, 2H, ArH), 7.04 (d, *J* = 9.0 Hz, 2H, ArH), 6.94 (d, *J* = 8.0 Hz, 1H, ArH), 3.76 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃) ppm. ¹³C-NMR (DMSO-d₆, 125 MHz): δ = 188.8, 152.2, 149.5, 146.3, 142.9, 141.7, 136.8, 129.8, 129.1, 127.8, 127.6, 125.0, 122.5, 119.8, 112.1, 111.3, 56.3, 56.2 ppm. HRMS calculated for C₂₃H₂₀ClNO₅S [M+2Na-H]⁺ 502.04479.

3.3 α-Glucosidase inhibition assay

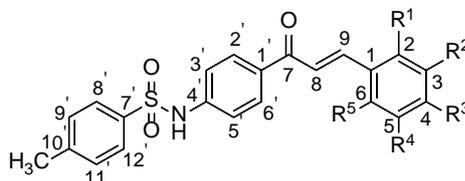
α-Glucosidase (0.1 U/mL) and the substrate (1 mM *p*-nitrophenyl-α-*D*-glucopyranoside) were dissolved in 0.1 M phosphate buffer (pH 6.9). 10 μL the test sample was added with 40 μL α-glucosidase and incubated at 37°C for 10 minutes. 50 μL of the substrate solution was added and incubated at 37°C for 20 minutes, then, it was ended by adding 1 solution of Na₂CO₃ (100 μL). Enzymatic activity was measured with the ALLSHENG AMR-100 microplate reader, by measuring the absorbance at 405 nm (Ramadhan & Phuwapraisirisan, 2015). The percentage of activity inhibition is calculated as follows:

$$\% \text{ Inhibition} = \frac{(A_0 - A_1)}{A_0} \times 100 \%$$

A₀ = absorbance without the sample, A₁ = absorbance with the sample

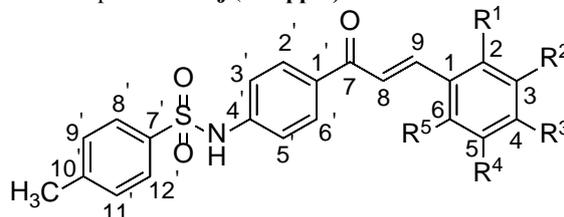
**Table 1** ^1H and ^{13}C NMR spectral data for compounds **3a-3c** (δ in ppm)

Position	3a (DMSO-d ₆)		3b (DMSO-d ₆)		3c (DMSO-d ₆)	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1'	-	132.0	-	139.0	-	130.4
2'	7.06, dd $J = 1.5$ Hz	126.6	7.62, s	112.1	7.70, d $J = 8.0$ Hz	133.4
3'	7.17, dt $J = 1.0$ Hz	125.1	-	137.0	7.22, d $J = 8.5$ Hz	118.5
4'	7.47, dt $J = 1.0$ Hz	134.7	7.34, dd $J = 1.5$ Hz	124.8	-	144.3
5'	7.37, dd $J = 1.0$ Hz	120.9	7.41, t $J = 7.5$ Hz	130.2	7.22, d $J = 8.5$ Hz	118.5
6'	-	146.6	7.84, d $J = 8.0$ Hz	124.5	7.70, d $J = 8.0$ Hz	133.4
7'	-	136.2	-	137.0	-	137.0
8'	7.54, s	130.4	7.64, d $J = 8.5$ Hz	127.2	8.01, d $J = 9.0$ Hz	127.3
9'	7.20, d $J = 8.0$ Hz	127.7	7.31, d $J = 8.0$ Hz	130.3	7.34, d $J = 8.5$ Hz	130.6
10'	-	139.0	-	144.0	-	142.7
11'	7.20, d $J = 8.0$ Hz	130.4	7.31, d $J = 8.0$ Hz	130.3	7.34, d $J = 8.5$ Hz	130.6
12'	7.54, s	127.7	7.64, d $J = 8.5$ Hz	127.2	8.01, d $J = 9.0$ Hz	127.3
1	-	127.4	-	127.9	-	128.1
2	7.39, d $J = 2.0$ Hz	111.3	7.46, d $J = 1.5$ Hz	111.3	7.46, d $J = 1.5$ Hz	111.1
3	-	152.2	-	151.9	-	151.8
4	-	149.5	-	149.5	-	149.5
5	6.93, d $J = 8.0$ Hz	112.0	7.00, d $J = 8.5$ Hz	119.5	6.97, d $J = 8.5$ Hz	112.1
6	7.27, dd $J = 2.0$ Hz	124.5	7.34, dd $J = 1.5$ Hz	124.4	7.31, dd $J = 2.0$ Hz	124.4
7	-	193.1	-	189.2	-	187.9
8	7.52, s	120.8	7.67, d $J = 19.0$ Hz	120.1	7.61, d $J = 15.5$ Hz	119.9
9	7.54, s	144.5	7.67, d $J = 19.0$ Hz	145.4	7.70, d $J = 15.5$ Hz	144.5
-NH	11.26, s	-	10.45, s	-	10.80	-
3-OCH ₃	3.74, s	56.2	3.81, s	56.2	3.81	56.1
4-OCH ₃	3.72, s	56.3	3.78, s	56.3	3.77	56.2
-CH ₃	2.13, s	21.4	2.28, s	21.5	2.29	21.5

**Table 2** ^1H and ^{13}C NMR spectral data for compounds **3d-3g** (δ in ppm)

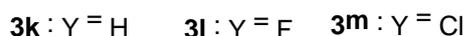
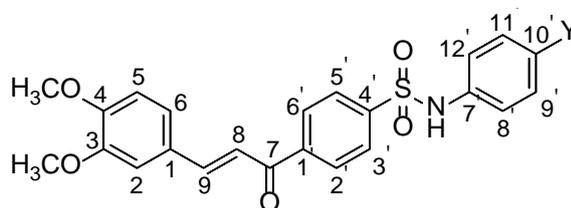
3d : $\text{R}^1 = \text{OCH}_3$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$ **3f** : $\text{R}^3 = \text{OCH}_3$, $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$
3e : $\text{R}^2 = \text{OCH}_3$, $\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$ **3g** : $\text{R}^3 = \text{F}$, $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$

Position	3d (DMSO-d ₆)		3e (DMSO-d ₆)		3f (DMSO-d ₆)		3g (DMSO-d ₆)	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1'	-	126.8	-	122.1	-	127.4	-	121.8
2'	7.71, d $J = 8.0$ Hz	132.2	7.72, d $J = 8.5$ Hz	132.5	7.80, d $J = 9.0$ Hz	132.8	7.69, d $J = 8.0$ Hz	131.4
3'	7.23, d $J = 8.0$ Hz	120.7	7.24, d $J = 9.0$ Hz	121.6	7.24, d $J = 8.5$ Hz	119.3	7.20, d $J = 9.0$ Hz	116.0
4'	-	142.3	-	143.5	-	143.5	-	142.3
5'	7.23, d $J = 8.0$ Hz	120.7	7.24, d $J = 9.0$ Hz	121.6	7.24, d $J = 8.5$ Hz	119.3	7.20, d $J = 9.0$ Hz	116.0
6'	7.71, d $J = 8.0$ Hz	132.2	7.72, d $J = 8.5$ Hz	132.5	7.80, d $J = 9.0$ Hz	132.8	7.69, d $J = 8.0$ Hz	131.4
7'	-	136.4	-	136.4	-	136.5	-	132.5
8'	8.00, d $J = 9.0$ Hz	128.5	8.04, d $J = 9.0$ Hz	126.8	8.00, d $J = 9.0$ Hz	129.9	8.00, d $J = 8.5$ Hz	129.9
9'	7.34, d $J = 8.0$ Hz	130.1	7.35, d $J = 9.0$ Hz	129.9	7.37, d $J = 8.5$ Hz	130.1	7.33, d $J = 8.0$ Hz	130.2
10'	-	138.0	-	142.4	-	142.3	-	136.4
11'	7.34, d $J = 8.0$ Hz	130.1	7.35, d $J = 9.0$ Hz	129.9	7.37, d $J = 8.5$ Hz	130.1	7.33, d $J = 8.0$ Hz	130.2
12'	8.00, d $J = 9.0$ Hz	128.5	8.04, d $J = 9.0$ Hz	126.8	8.00, d $J = 9.0$ Hz	129.9	8.00, d $J = 8.5$ Hz	129.9
1	-	122.9	-	136.1	-	126.8	-	131.2
2	-	158.2	7.42, s	113.2	7.73, d $J = 8.5$ Hz	130.7	7.89, dd $J = 6.0$ Hz	131.1
3	7.07, d $J = 8.5$ Hz	111.8	-	159.6	7.00, d $J = 9.0$ Hz	114.4	7.24, t $J = 9.0$ Hz	115.7
4	7.41, t $J = 7.5$ Hz	129.9	6.68, dd $J = 3.0$ Hz	113.2	-	161.4	-	164.4
5	6.99, t $J = 7.5$ Hz	121.9	7.33, t $J = 8.0$ Hz	130.2	7.00, d $J = 9.0$ Hz	114.4	7.24, t $J = 9.0$ Hz	115.7
6	7.89, d $J = 8.0$ Hz	132.7	7.37, d $J = 9.5$ Hz	116.6	7.73, d $J = 8.5$ Hz	130.7	7.89, dd $J = 6.0$ Hz	131.1
7	-	187.6	-	187.5	-	187.5	-	187.5
8	7.78, d $J = 16.0$ Hz	118.0	7.63, d $J = 15.5$ Hz	117.9	7.65, d $J = 15.5$ Hz	118.0	7.64, d $J = 15.5$ Hz	117.9
9	7.96, d $J = 16.0$ Hz	142.7	7.84, d $J = 15.5$ Hz	143.7	7.71, d $J = 15.5$ Hz	143.8	7.78, d $J = 15.5$ Hz	143.8
-NH	10.83, s	-	10.85, s	-	10.83, s	-	10.83, s	-
2-OCH ₃	3.85, s	55.7	3.79, s	55.3	3.81, s	55.4	-	-
10'-CH ₃	2.30, s	21.0	2.31, s	21.0	2.32, s	21.0	2.28	21.0

**Table 3** ^1H and ^{13}C NMR spectral data for compounds **3h-3j** (δ in ppm)

3h : $\text{R}^3 = \text{Cl}$, $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$ **3j** : $\text{R}^3 = \text{NO}_2$, $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$
3i : $\text{R}^3 = \text{Br}$, $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$

Position	3h (DMSO- d_6)		3i (DMSO- d_6)		3j (DMSO- d_6)	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1'	-	126.8	-	126.8	-	126.8
2'	7.71, d $J = 8.0$ Hz	132.4	7.79, d $J = 9.0$ Hz	131.9	7.74, d $J = 8.5$ Hz	132.1
3'	7.22, d $J = 9.0$ Hz	122.6	7.22, d $J = 8.5$ Hz	122.7	7.26, d $J = 9.0$ Hz	130.5
4'	-	142.5	-	142.5	-	142.8
5'	7.22, d $J = 9.0$ Hz	122.6	7.22, d $J = 8.5$ Hz	122.7	7.26, d $J = 9.0$ Hz	130.5
6'	7.71, d $J = 8.0$ Hz	132.4	7.79, d $J = 9.0$ Hz	131.9	7.74, d $J = 8.5$ Hz	132.1
7'	-	136.4	-	134.0	-	136.4
8'	8.02, d $J = 9.0$ Hz	129.9	8.26, d $J = 8.5$ Hz	123.9	8.08, d $J = 8.5$ Hz	125.9
9'	7.34, d $J = 8.0$ Hz	130.5	7.34, d $J = 8.0$ Hz	130.3	7.37, d $J = 8.5$ Hz	129.9
10'	-	142.0	-	136.4	-	140.6
11'	7.34, d $J = 8.0$ Hz	130.5	7.34, d $J = 8.0$ Hz	130.3	7.37, d $J = 8.5$ Hz	125.9
12'	8.02, d $J = 9.0$ Hz	129.9	8.26, d $J = 8.5$ Hz	123.9	8.08, d $J = 8.5$ Hz	129.9
1	-	133.7	-	132.4	-	141.2
2	7.86, d $J = 8.5$ Hz	130.3	7.71, d $J = 8.0$ Hz	129.9	8.12, d $J = 9.0$ Hz	129.8
3	7.48, d $J = 8.5$ Hz	128.9	7.62, d $J = 8.5$ Hz	130.7	8.26, d $J = 8.5$ Hz	123.9
4	-	135.0	-	142.1	-	148.0
5	7.48, d $J = 8.5$ Hz	128.9	7.62, d $J = 8.5$ Hz	130.7	8.26, d $J = 8.5$ Hz	123.9
6	7.86, d $J = 8.5$ Hz	130.3	7.71, d $J = 8.0$ Hz	129.9	8.12, d $J = 9.0$ Hz	129.8
7	-	187.4	-	187.4	-	187.4
8	7.64, d $J = 15.5$ Hz	117.9	7.62, d $J = 15.5$ Hz	117.9	7.75, d $J = 15.5$ Hz	117.9
9	7.85, d $J = 16.5$ Hz	143.8	7.86, d $J = 15.5$ Hz	143.8	8.04, d $J = 15.5$ Hz	143.8
-NH	10.85, s	-	10.85, s	-	10.88, s	-
10'-CH ₃	2.30, s	21.0	2.30, s	21.0	2.28, s	21.0

**Table 4** ^1H and ^{13}C NMR spectral data for compounds **3k-3m** (δ in ppm)

Position	3k (DMSO-d₆)		3l (DMSO-d₆)		3m (DMSO-d₆)	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1'	-	141.6	-	141.1	-	141.7
2'	8.23, d $J = 8.0$ Hz	137.8	8.22, d $J = 8.5$ Hz	129.2	8.17, d $J = 8.5$ Hz	129.8
3'	7.90, d $J = 8.5$ Hz	127.8	7.84, d $J = 8.5$ Hz	127.3	7.82, d $J = 8.5$ Hz	127.8
4'	-	146.2	-	145.8	-	146.3
5'	7.90, d $J = 8.5$ Hz	127.8	7.84, d $J = 8.5$ Hz	127.3	7.82, d $J = 8.5$ Hz	127.8
6'	8.23, d $J = 8.0$ Hz	137.8	8.22, d $J = 8.5$ Hz	129.2	8.17, d $J = 8.5$ Hz	129.8
7'	-	129.7	-	133.5	-	136.8
8'	7.11, d $J = 8.0$ Hz	112.1	7.08, d $J = 2.0$ Hz	123.2	7.04, d $J = 9.0$ Hz	122.5
9'	7.24, t $J = 7.5$ Hz	129.8	7.09, s	116.1	7.23, d $J = 8.5$ Hz	129.1
10'	7.05, t $J = 8.0$ Hz	121.0	-	160.3	-	127.6
11'	7.24, t $J = 7.5$ Hz	129.8	7.09, s	116.1	7.23, d $J = 8.5$ Hz	129.1
12'	7.11, d $J = 8.0$ Hz	112.1	7.08, d $J = 2.0$ Hz	123.2	7.04, d $J = 9.0$ Hz	122.5
1	-	127.6	-	127.1	-	125.0
2	7.53, d $J = 1.5$ Hz	111.3	7.51, d $J = 2.0$ Hz	110.8	7.45, d $J = 1.5$ Hz	112.1
3	-	152.1	-	151.6	-	152.2
4	-	149.5	-	149.0	-	149.5
5	7.02, d $J = 8.5$ Hz	111.3	7.00, d $J = 8.0$ Hz	111.6	6.94, d $J = 8.0$ Hz	111.3
6	7.39, dd $J = 1.5$ Hz	125.0	7.37, dd $J = 2.0$ Hz	124.4	7.31, dd $J = 1.5$ Hz	122.5
7	-	188.8	-	188.3	-	188.8
8	7.71, d $J = 15.5$ Hz	119.8	7.70, d $J = 15.5$ Hz	119.3	7.64, d $J = 15.5$ Hz	119.8
9	7.77, d $J = 15.5$ Hz	143.3	7.76, d $J = 15.5$ Hz	142.5	7.70, d $J = 15.5$ Hz	142.9
-NH	10.46, s	-	10.39, s	-	10.55	-
3-OCH ₃	4.67, s	56.2	3.82, s	55.6	3.76	56.2
4-OCH ₃	4.64, s	56.3	3.79, s	56.8	3.74	56.3



4.2 α -Glucosidase inhibitors

The α -glucosidase inhibitors are one of the steps to treat type 2 diabetes, which are effective in reducing postprandial hyperglycemia. The IC_{50} value was inferred from a plot of % inhibition *versus* test sample concentration with acarbose as the standard control (Ramadhan & Phuwapraisirisan, 2015).

Table 5 Inhibitory effects of amino position on the A-ring against α -glucosidase

o^- or m^- or p^-

Compound	-NH	$IC_{50} \pm SD$ (μM)
3a	<i>o</i> -	76.75 ± 5.99
3b	<i>m</i> -	30.22 ± 4.40
3c	<i>p</i> -	1.04 ± 0.19
Acarbose		93.63 ± 0.49

Note: All compounds were examined in a set of experiments repeated three times; error is the standard deviation (SD); IC_{50} values of compounds represent the concentration that caused 50% enzyme activity loss.

According to Bharatham *et al.* (2008), validated docking results projected that the NH group plays an important role in the binding of sugar/non-sugar derivatives to the active site. **Table 5** shows the IC_{50} value of sulfonamide chalcones synthesized against α -glucosidase based on the difference in the position of amine (-NH-). The secondary amine (-NH-) at the *para* position (**3c**) revealed a very strong inhibition with IC_{50} 1.04 ± 0.19 μM , where this value was 30 and 76 times more intense than that bearing at *meta* (**3b**) and *ortho* (**3a**) positions, respectively. The better activity of **3c** may be due to the amine (-NH-) could form a stronger bond to the enzyme without being weakened by the carbonyl group. Whereas in the *ortho* and *meta* positions, the amine (-NH-) position was closer to the carbonyl group that caused the amine and carbonyl to oppose or weaken each other in forming bonds with the enzyme. Thus, the secondary amine (-NH-) at the *para* position could be used as a guideline for determining the effect of substituents on the B-ring of chalcone.

Table 6 Inhibitory effects of monosubstituents on B-ring against α -glucosidase

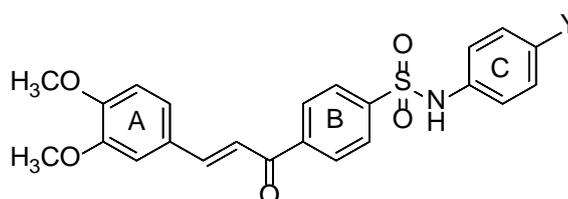
Compound	R ¹	R ²	R ³	R ⁴	R ⁵	$IC_{50} \pm SD$ (μM)
3d	OCH ₃	H	H	H	H	28.66 ± 4.30
3e	H	OCH ₃	H	H	H	4.82 ± 1.08
3f	H	H	OCH ₃	H	H	10.55 ± 0.67
3g	H	H	F	H	H	15.54 ± 0.85
3h	H	H	Cl	H	H	14.67 ± 0.76
3i	H	H	Br	H	H	18.92 ± 0.46
3j	H	H	NO ₂	H	H	80.30 ± 2.59
Acarbose						93.63 ± 0.49

Note: All compounds were examined in a set of experiments repeated three times; error is the standard deviation (SD); IC_{50} values of compounds represent the concentration that caused 50% enzyme activity loss.



Table 6 shows that most sulfonamide chalcones are good α -glucosidase inhibitors. The inhibitory activity was significantly affected by the position of the substituent on the B-ring chalcone: 3-methoxy **3e** (IC_{50} $4.82 \pm 1.08 \mu M$) > 4-methoxy **3f** (IC_{50} $10.55 \pm 0.67 \mu M$) > 2-dimethoxy **3d** (IC_{50} $28.66 \pm 4.30 \mu M$). Besides, the type of substituent also affected the inhibitory activity: 4-methoxy **3f** (IC_{50} $= 10.55 \pm 0.67 \mu M$) > 4-chloro **3h** (IC_{50} $14.67 \pm 0.76 \mu M$) > 4-fluoro **3g** (IC_{50} $15.54 \pm 0.85 \mu M$) > 4-bromo **3i** (IC_{50} $18.92 \pm 0.46 \mu M$) > 4-nitro **3j** (IC_{50} $80.30 \pm 2.59 \mu M$). The methoxy substituents as electron-donating groups revealed greater inhibition potential than electron-withdrawing groups (F, Cl, Br and NO_2).

Table 7 Inhibitory effects of modification chalcone position against α -glucosidase



Compound	Y	$IC_{50} \pm SD (\mu M)$
3k	H	>200
3l	F	135.90 ± 11.06
3m	Cl	> 100
Acarbose		93.63 ± 0.49

Note: All compounds were examined in a set of experiments repeated three times; error is the standard deviation (SD); IC_{50} values of compounds represent the concentration that caused 50% enzyme activity loss.

However, in contrast to the results shown in **Table 7**, the IC_{50} value ($> 100 \mu M$) obtained was above the IC_{50} of acarbose (control). The association of secondary amine to chalcone was found to be very important for the inhibition of α -glucosidase. Besides, the presence of a chalcone group in sulfonyl can weaken the bonds that occur between the sulfonyl group and the enzyme.

5. Conclusion

This strategy allows the efficient synthesis of the sulfonamide chalcones as an α -glucosidase inhibitor, which is effective in reducing postprandial hyperglycemia as a step in the treatment of type 2 diabetes. It was disclosed that the *para* position of secondary amine (**3c**) greatly influenced the inhibition results, as did the effect of the electron-donating groups (**3e**). **3c** provides a very strong inhibitory activity with IC_{50} $1.04 \pm 0.19 \mu M$, which proves that the sulfonamide chalcone has enormous potential as an α -glucosidase inhibitor. Further research is needed to utilize this compound as a medicinal ingredient. Besides, this research opens up opportunities to find new compounds that have better activity.

6. Acknowledgements

The author would like to express his sincere gratitude to all ASEAN and NON-ASEAN scholarship sponsors who have supported the author's tuition and living expenses while studying for his Master's at Chulalongkorn University. In addition, the authors would like to thank all members of the Warinthorn Chavasiri lab.

7. References

- Bahekar, S. P., Hande, S. V., Agrawal, N. R., Chandak, H. S., Bhoj, P. S., Goswami, K., & Reddy, M. V. R. (2016). Sulfonamide chalcones: Synthesis and in vitro exploration for therapeutic potential against *Brugia malayi*. *Eur. J. Med. Chem.*, *124*, 262-269.
- Bahekar, S. P., Agrawal, N. R., Sarode, P. B., Agrawal, A. R., & Chandak, H. S. (2017). L- Proline nitrate: an amino acid ionic liquid for green and efficient conjugate addition of thiols to sulfonamide chalcones. *ChemistrySelect*, *2*, 9326–9329.



- Bharatham, K., Bharatham, N., Park, K. H., & Lee, K. W. (2008). Binding mode analyses and pharmacophore model development for sulfonamide chalcone derivatives, a new class of α -glucosidase inhibitors. *J. Mol. Graph. Model.*, *26*, 1202–1212.
- Cai, C.-Y., Rao, L., Rao, Y., Guo, J.-X., Xiao, Z.-Z., Cao, J.-Y., Huang, Z.-S., & Wang, B. (2017). Analogues of xanthenes-chalcones and bis-chalcones as α -glucosidase inhibitors and anti-diabetes candidates. *Eur. J. Med.*, *130*, 51-59.
- Chaudhury, A., Duvoor, C., Dendi, V. S. R., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham, C. K., Lohani, G. P., & Mirza, W. (2017). Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. *Front. Endocrinol.*, *8*, 1–12.
- DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., Hu, F. B., Kahn, C. R., Raz, I., Shulman, G. I., Simonson, D. C., Testa, M. A., & Weiss, R. (2015). Type 2 diabetes mellitus. *Nat. Rev. Dis. Primers*, *1*, 1–22.
- Ghorab, M. M., Ragab, F. A., Heiba, H. I., El-Gazzar, M. G., & Zahran, S. S. (2015). Synthesis, anticancer and radiosensitizing evaluation of some novel sulfonamide derivatives. *Eur. J. Med. Chem.*, *92*, 682–692.
- Hisieh, C.-T., Hisieh, T.-J., Ei-Shazly, M., Chuang, D.-W., Tsai, Y.-H., Yen, C.-T., Wu, S.-F., Wu, Y.-C., & Chang, F.-R. (2012). Synthesis of chalcone derivatives as potential anti-diabetic agents. *Bioorg. Med. Chem. Lett.*, *22*, 3912–3915.
- Kim, E.-J., Ryu, H. W., Curtis-Long, M. J., Han, J., Kim, J. Y., Cho, J. K., & Park, K. H. (2010). Chemoselective regulation of TREK2 channel: Activation by sulfonate chalcones and inhibition by sulfonamide chalcones. *Bioorg. Med. Chem. Lett.*, *20*, 4237–4239.
- Mehta, K. J., & Parikh, A. R. (1979). Preparation and antimicrobial activity of chalcones derived from 4-(*p*-toluene- or -*p*-chlorobenzenesulfonamido)acetophenone. *J. Institution Chemists (India)*, *51*, 60-61.
- Ramadhan, R., & Phuwapraisirisan, P. (2015). New arylalkanones from *Horsfieldia macrobotrys*, effective antidiabetic agents concomitantly inhibiting α -glucosidase and free radicals. *Bioorg. Med. Chem. Lett.*, *25*, 4529-4533.
- Rocha, S., Sousa, A., Ribeiro, D., Correia, C. M., Silva, V. L. M., Santos, C. M. M., Silva, A. M. S., Araújo, A.N., Fernandes, E., & Freitas, M. (2019). A study towards drug discovery for the management of type 2 diabetes mellitus through inhibition of the carbohydrate-hydrolyzing enzymes α -amylase and α -glucosidase by chalcone derivatives, *Food Funct.*, *10*, 5510-5520.
- Seo, W.D., Kim, J. H., Kang, J. E., Ryu, H. W., Curtis-Long, M. J., Lee, H. S., Yang, M. S., & Park, K. H. (2005). Sulfonamide chalcone as a new class of α -glucosidase inhibitors. *Bioorg. Med. Chem. Lett.*, *15*, 5514–5516.
- Srinivasan, B., Johnson, T. E., Lad, R., & Xing, C. (2009). Structure–activity relationship studies of chalcone leading to 3-hydroxy-4,3',4',5'-tetramethoxychalcone and its analogues as potent nuclear factor κ B inhibitors and their anticancer activities. *J. Med. Chem.*, *52*, 7228-7235.
- Wu, J., Li, J., Cai, Y., Pan, Y., Ye, F., Zhang, Y., Zhao, Y., Yang, S., Li, X., Liang, G. (2011). Evaluation and discovery of novel synthetic chalcone derivatives as anti-inflammatory agents. *J. Med. Chem.*, *54*, 8110-8123.