ASM Sc. J., 14, 2021

https://doi.org/10.32802/asmscj.2020.629

Synthesis of 1-acetyl-3,5-diphenyl-1*H*-pyrazole from Chalcone

Noor Hidayah Pungot[1*], Najwa Amira Mohamad Latif[2] and Nur Ain Nabilah Ash'ari[3]

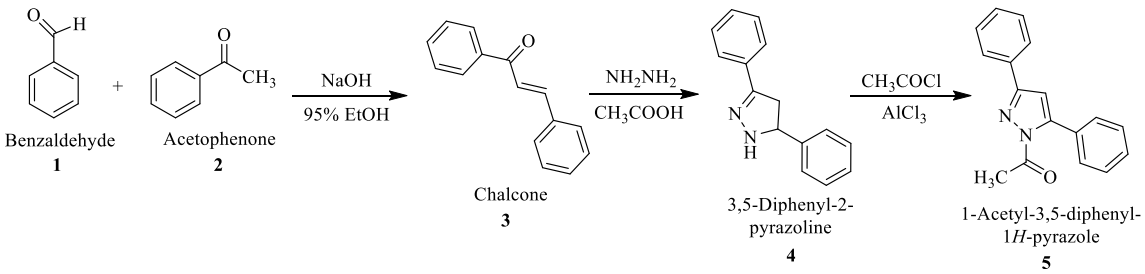
[1, 3]*Organic Synthesis Laboratory, Institute of Science, Universiti Tekonologi MARA, Puncak Alam Campus, 43200 Bandar Puncak Alam, Selangor, Malaysia*

[2]*School of Chemistry & Environment, Faculty of Applied Sciences, Universiti Tekonologi MARA, Kuala Pilah Campus, 72000 Kuala Pilah, Negeri Sembilan, Malaysia*

The synthesis of chalcone has drawn tremendous interest over the past years due to its wide applications in the pharmaceutical and biological sectors. Indeed, this compound is reported to possess a broad spectrum of promising bioactivities, including anti-inflammatory, anti-invasive, antioxidant, antitumor and antibacterial properties. In this work, chalcone **3** was synthesised via Claisen-Schmidt condensation by using a common starting material of benzaldehyde **1** and acetophenone **2** in the presence of alcoholic alkaline base. Subsequently, 3,5-diphenyl-2-pyrazoline **4** intermediate was successfully synthesised by reductive amination reaction of **3** with hydrazine hydrate. Thereafter, insertion of acyl subunit at N-1 position of the corresponding amine via ^{1}N-acylation reaction afforded the targeted 1-acetyl-3,5-diphenyl-1*H*-pyrazole **5** derivative. The structures of all the synthesised compounds were confirmed by elemental analyses, IR, GC-MS and NMR spectra.

Keywords: chalcone; Claisen-Schmidt condensation; reductive amination

Graphical Abstract



I. INTRODUCTION

Chalcone **3** or 1,3-diphenyl-2-propene-1-one, belongs to the family of flavonoids. Generally, flavonoids are a group of naturally occurring oxygen heterocyclic compounds that are abundant, especially in plants. They can be found in seeds, tea, citrus fruits, olive oil and red wine (Mughal *et al.*, 2006). According to Kshatriya *et al.* (2018), the name flavonoid originated from the Greek word, "flavus" which means "yellow". They are derived from a secondary metabolite in plants and fungus, and thus has become the essential plant pigments which are responsible for the colouration of flowers. Flavonoids are commonly consumed in the human diet ever since they were reported to possess many useful properties, such as antioxidant, anti-inflammatory, antiallergic and antitumoral actions (Yoshida *et al.*, 2011). Furthermore, flavonoids act as protective agents against many infectious bacterial, viral and degenerative diseases such as cardiovascular diseases, cancers and other age-related diseases (Cushnie & Lamb,

*Corresponding author's e-mail: noorhidayah977@uitm.edu.my

2005). The chemical nature of flavonoids depends on their structural class, degree of hydroxylation, substitutions, conjugations and degree of polymerisation (Murti *et al*., 2013). It can be classified into different subgroups, depending on the carbon of the C-ring on which the B-ring is attached as well as the degree of unsaturation and oxidation of the C-ring. These subgroups are chalcones, flavones, flavonols and flavanones (Figure 1) (Panche *et al*., 2016).

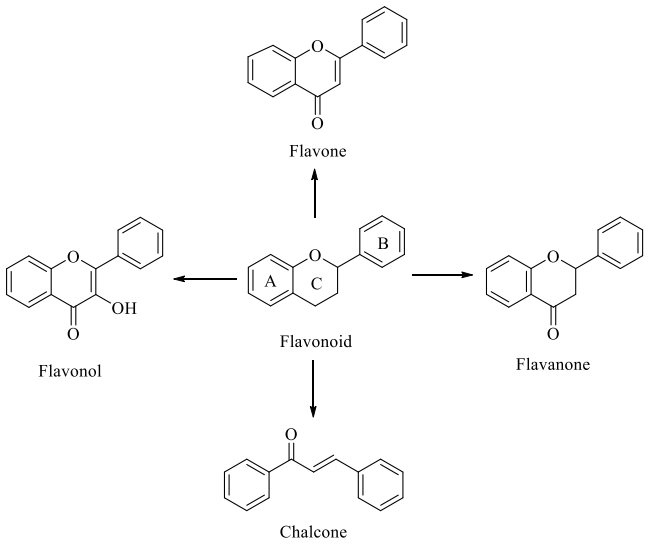


Figure 1. Basic skeleton structure of flavonoid and their subgroups

In their families, chalcone **3** was proven to exhibit similar potentials. Chalcone, which comprises of an α,β-unsaturated carbonyl system (Patil *et al*., 2009), serves as the precursor for the synthesis of most flavonoids and isoflavonoids. It can be found naturally in plants such as fruits, vegetables, soy and tea (Taruscio *et al*., 2004). For instance, okanin and marein are bioactive chalcone derivatives contained in *Coreopsis tinctoria*, an annual forb that is common to Canada and the United States (Cai *et al*., 2010). In addition, Ibrahimawad *et al*. (2018) had successfully isolated two chalcone derivatives; pinostrobinchalcone and cardamone from *Boesenbergia rotunda* belonging to the family of Zingiberaceae. The largest number of natural chalcones has been isolated from species of the Leguminosae, Asteraceae and Moraceae families (Banoth & Thatikonda, 2020).

For centuries, chalcones obtained from plants were used by physicians and lay healers for the treatment of human diseases because of their remarkable bioactivities, which include antioxidant, anticancer, antitumor and antibacterial properties. To date, the use of herbal medicines continues to expand rapidly across the world (Banoth & Thatikonda, 2020). For these reasons, chalcone is required in larger amounts, which can be achieved by chemical synthesis.

Claisen-Schmidt condensation, developed in 1962, is the prominent synthetic methodology that was first applied for chalcone synthesis (Kshatriya *et al*., 2018). This reaction is also considered as the standard method to synthesise chalcone, which involves condensation reaction between benzaldehyde **1** and acetophenone **2** derivatives. Due to its affordable and uncomplicated procedure, Claisen-Schmidt condensation is widely used in many research studies (Rafiee & Rahimi, 2013).

In general, Ahmad *et al.,* (2016) reviewed that Claisen–Schmidt condensation involves cross aldol condensation of appropriate aldehydes and ketones by acid or base catalysed reactions, followed by dehydration. According to Mahapatra *et al.* (2015), Claisen-Schmidt condensation is a method to yield chalcone which involves condensation of an equimolar quantity of benzaldehyde **1** and acetophenone **2** in the presence of alcoholic alkaline solution. Such reaction is usually catalysed by acids or bases under homogeneous conditions, which causes several disadvantages such as catalyst recovery and waste disposal. By contrast, Winter and co-workers (2016) conducted this method by using heterogeneous catalysts as an alternative as they are more environmental-friendly and can be easily recovered by filtration.

On the other hand, pyrazole (Figure 2) is a chemical compound that comprises of five-membered heterocyclic with two nitrogen atoms and three head-to-head carbons. It is broadly found as the main structure in abundance of compounds and because of that, pyrzole has played an important portion in the development of theory in heterocyclic chemistry. Compounds containing pyrazole moiety are proven to exhibit essential pharmaceutical and agrochemical activities in addition to biological activity such as antifungal, antiphrastic, antitumor, antiviral, antibacterial and anti-tubercular. This compound also plays a significant role in some drugs construction. Owing to this diversity in the biological field, this compound has attracted

the attention of many researchers to study its skeleton chemically and biologically (Majid, 2018).

Figure 2. Structure of pyrazole

Literature survey revealed that only few studies were done on the chemical synthesis of 3,5-diaryl pyrazole from α, β-unsaturated ketones, with carbonyl chromophore on the N-1 position. Therefore, this study aims to develop 3,5-diaryl pyrazole derivative from the precursor chalcone. It is hoped that this work may provide beneficial information in the discovery of lead compounds for medical application.

II. MATERIALS AND METHODS

General procedures: ^{1}H-NMR and ^{13}C-NMR spectra were recorded in deuterated solvents with tetramethylsilane as an internal standard that was measured with JEOL NMR instrument at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) were expressed in parts per million (ppm). IR spectra (4000 cm^{-1} – 400 cm^{-1}) were recorded on Varian Excalibur 3100 FT-IR spectrometer. The mass spectra were recorded on GC-MS Agilent Technologies 7890 A (GC System). All chemicals used were purchased from Sigma-Aldrich Co., USA.

Chalcone (3). Benzaldehyde (4.71 mmol) was added to a solution of acetophenone (0.5 mL, 4.71 mmol) in 95% ethanol (4 mL). The mixture was stirred until the entire solid dissolved. NaOH solution (0.5 mL) was added and the stirring resumed. Then, ice water (10 mL) was added and scratching was performed. The reaction mixture was then transferred into a beaker that contained 15 mL of ice water and then filtered. The solid collected was left to dry in an oven at 80°C for 30 min, followed by recrystallisation in hot methanol solution (43 mL) and dried again overnight in the oven at 85°C to give a pale-yellow solid in 1.597g (72%). ^{1}H NMR (400 MHz, CDCl3): δ 7.39–7.45 (3H, m, 3xCH), 7.50 (2H, t, 2xCH), 7.54 (1H, d, CH), 7.59 (1H, tt, CH), 7.61–7.67 (2H, m, 2xCH), 7.82 (1H, d, CH), 8.03 (2H, d, 2xCH). 13C NMR (100 MHz, CDCl3): δ 122.0 (CH), 128.4 (Ar 2C), 128.5 (Ar 2C), 128.6 (Ar 2C), 128.9 (Ar 2C), 130.5 (Ar C), 132.7 (Ar C), 134.8 (Ar C), 138.2 (Ar C), 144.8 (CH), 190.5 (C=O). IR υ cm^{-1}: 1662, 1603, 1335, 1213, 1015, 977. MS (ESI) m/z: calculated for $C_{15}H_{12}O$, (M^+ 208.09) found (M^+ 208.01).

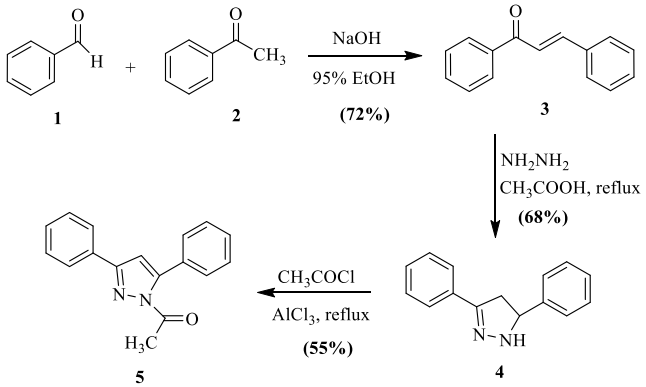
3,5-Diphenyl-2-pyrazoline (4). A mixture of dry chalcone **3** (5.0 mmol), hydrazine hydrate (25.0 mmol) and acetic acid (30 mL) were added into a conical flask. The reaction mixture was refluxed for 4 h. Subsequently, the reaction mixture was poured onto crushed ice. The precipitate was then separated by filtration, washed with water, and crystallised from methanol to yield yellowish crystalline solid in 0.9731 g (68%). ^{1}H NMR (DMSO-d6, 400 MHz): δ 3.89 (1H, t, CH), 3.94 & 3.67 (2H, d, CH_2), 7.45 (5H, m, Ar H), 7.84 (5H, m, Ar H), 10.40 (1H, brs, NH). ^{13}C NMR (DMSO-d6, 100 MHz,): δ 45.6 (CH_2), 67.4 (CH), 99.8 (Ar C), 125.2 (Ar C), 128.0 (Ar C), 128.9 (quat. C), 131.3 (quat. C), 147.4 (C=N). IR υ cm^{-1}: 3241, 2834, 1462, 1274, 1182, 1075, 978, 750, 688. MS (ESI) m/z: calculated for $C_{15}H_{14}N_2$, (M^+ 222.12) found (M^+ 222.10).

1-Acetyl-3,5-diphenyl-1*H*-pyrazole (5). 3,5-Diphenyl-2-pyrazoline **4** was added into a flask which contained anhydrous $AlCl_3$ (1.564 mmol), followed by the addition of acetyl chloride (100 mL). The reaction mixture was refluxed at 65°C in a sealed tube for 3 h. The reaction was stirred until all solids were dissolved and then purified by using dichloromethane in the fractional crystallisation method. Then, petroleum ether was added and filtered under vacuum pressure. The crude product was oven dried at 40°C to give a brownish solid in 0.4562 g (55%). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.24 (3H, s, CH_3), 7.34 (1H, s CH), 7.49–7.58 (6H, m, Ar H), 7.86 (2H, dd, Ar 2H), 8.12 (2H, dd, Ar 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 21.7 (CH_3), 106.5 (CH), 127.7 (Ar C), 128.9 (Ar C), 129.1 (Ar C), 135.22 (quat. C), 142.4 (quat. C), 147.3 (quat. C), 172.4 (C=O). IR υ cm^{-1}: 3384, 1684, 1662, 1528. MS (ESI) m/z: calculated for $C_{17}H_{14}N_2O$, (M^+ 262.11) found (M^+ 262.08).

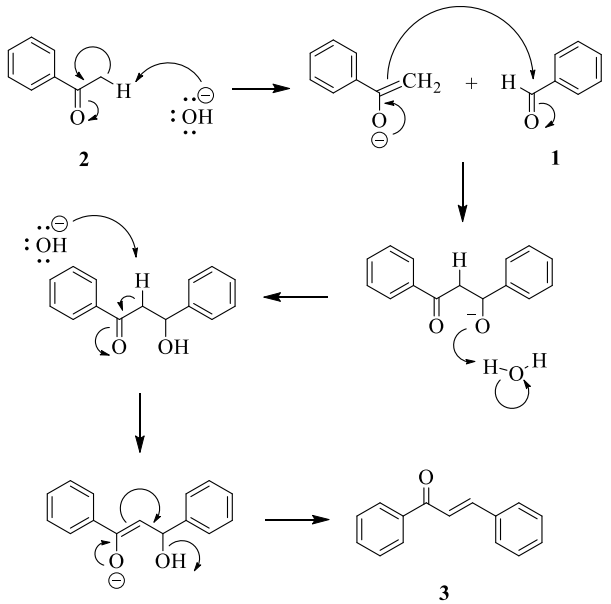
III. RESULT AND DISCUSSION

The synthetic route (Scheme 1) begin with readily available starting material benzaldehyde **1** and acetophenone **2** by using sodium hydroxide as the catalyst in 95% ethanol to obtain the expected precursor, chalcone **3** in 72% yield. In the first step, acetophenone lost an alpha-hydrogen, forming an enol or enolate ion, which subsequently reacted with the

carbonyl of benzaldehyde to form β-hydroxyketone, followed by dehydration to give the desired product **3**, as illustrated in Scheme 2. Alpha-hydrogen is required for this reaction to happen, in which it is removed in the Claisen-Schmidt condensation reaction. Due to this reason, the lack of alpha-hydrogen in benzaldehyde has hindered it from reacting with itself. Likewise, acetophenone also does not react easily with itself in an aqueous base (NaOH). That is why the reaction occurs between acetophenone having the alpha-hydrogen needed with benzaldehyde, yielded the chalcone.



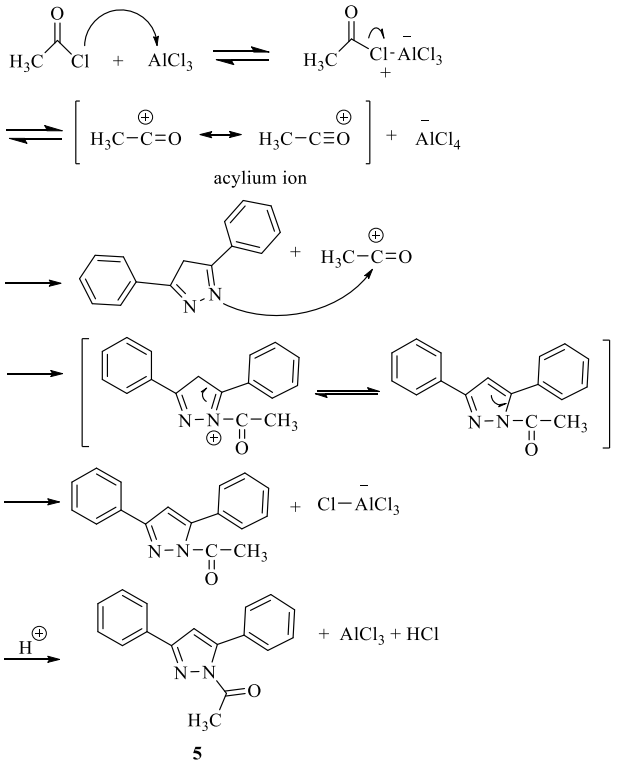
Scheme 1. Overall synthetic route to compound **5**



Scheme 2. Claisen-Schmidt condensation of chalcone **3**

Having successfully synthesised **3**, the next attempt is to convert **3** into **4**. Employing the previously reported method (Lévai & Jekő, 2005), the strategy is achieved by reacting **3** with hydrazine hydrate, in which reductive elimination reaction took place. The amine compound, **4** is obtained as a yellowish crystalline solid in moderate yield (68%). In previous study by Mohammadizadeh (2006), hydrazines and the α,β-unsaturated ketones are allowed to react in hot alcohol solution or in boiling mixture of benzene with ethanol, which afforded a better yield (91–96%). However, in his work, the 2-pyrazoline compounds are made by one-pot procedure without purification of the intermediate chalcones. Hence, the higher yield as compared to the yield reported in this study (68%) due to the recrystallisation step conducted to get product **4** in high purity.

The final step involves the insertion of acyl subunit by using acetyl chloride at N-1 position of the corresponding amine via [1]*N*-acylation reaction to give a brownish solid of amide compound, **5** in 55% yield. Having coordination to halogen, the Lewis acid catalyst, $AlCl_3$ was used in the reaction to facilitate the bond breaking. In doing so, the electrophilicity of its binding partner increased as acylium ion was formed due to the loss of halide to the Lewis acid, making it much more reactive, followed by the attack of the nucleophilic amine group to the resulting strong electrophile. Subsequently, the removal of a proton reformed the C=C, generating HCl and regenerating the active catalyst which produced **5** (Kumar *et al.*, 2010). The mechanism of reaction is illustrated in scheme 3 below.



Scheme 3. N-acylation reaction of compound **5**

IV. CONCLUSION

A short synthesis of 1-acetyl-3,5-diphenyl-1*H*-pyrazole **5** derivatived from chalcone was accomplished *via* three-sequential synthetic steps with an overall yield of 11.55%.

V. ACKNOWLEDGEMENT

The authors acknowledge the generous support of Faculty of Applied Sciences, Universiti Tekonologi MARA, Kuala Pilah Campus, Negeri Sembilan and Organic Synthesis Laboratory, Institute of Science, Universiti Tekonologi MARA, Puncak Alam Campus, Selangor in providing all the required chemicals and instruments throughout the completion of this study.

VI. REFERENCES

Ahmad, MR, Sastry, VG, Bano, N & Anwar, S 2016, 'Synthesis of novel chalcone derivatives by conventional and microwave irradiation methods and their pharmacological activities', Arabian Journal of Chemistry, vol.9, pp. S931-S935.

Banoth, RK & Thatikonda, A 2020, 'A review on natural chalcones an update', International Journal of Pharmaceutical Sciences & Research 2020, vol. 11, no. 3, pp. 546-55.

Cai, Y, Liu, X, Hui, Y, Jiang, J, Wang, W, Chen, W & Feng, X 2010, 'Catalytic asymmetric bromoamination of chalcones: highly efficient synthesis of chiral α - bromo - β - amino ketone derivatives', Angewandte Chemie International Edition, vol. 49, no. 35, pp. 6160-6164.

Cushnie & Lamb, AJ 2005, 'Antimicrobial activity of flavonoids', International Journal of Antimicrobial Agents, vol. 26, no. 5, pp. 343-356.

Harborne, JB & Williams, CA 2000, 'Advances in flavonoid research since 1992', Phytochemistry, vol. 55, no. 6, pp. 481-504.

Ibrahimawad, M, Abdullah, HD, Nadeem, AM & Hamid, H 2018, 'Characterization of two chalcone derivatives isolated from Finger root with nutraceutical potentials', International Journal of Advanced Research, vol. 6, no. 11, pp. 1089-1094.

Kshatriya, R, Jejurkar, VP & Saha, S 2018, 'In memory of Prof. Venkataraman: recent advances in the synthetic methodologies of flavones', Tetrahedron, vol. 74, pp. 811-833.

Kumar, D, Kumar, NM, Akamatsu, K, Kusaka, E, Harada, H & Ito, T 2010, 'Synthesis and biological evaluation of indolyl chalcones as antitumor agents', Bioorganic & Medicinal Chemistry Letters, vol. 20, no. 13, pp. 3916-3919.

Lévai, A & Jekőb, J 2005, 'Synthesis of hydroxylated 3, 5-diaryl-2-pyrazolines by the reaction of hydroxychalcones with hydrazines', Arkivoc, vol. 10, pp. 199-205.

Mahapatra, DK, Bharti, SK & Asati, V 2015, 'Chalcone scaffolds as anti-infective agents: structural and molecular target perspectives', European Journal of Medicinal Chemistry, vol. 101, pp. 496-524.

Majeed, N 2018, 'A literature review on the synthesis of pyrazole heterocycles', Journal of Advance Research in Dynamical & Control Systems, vol. 10, no. 10.

Mohammadizadeh, MR 2006, 'One-pot rapid and efficient synthesis of new spiro derivatives of 11H-indeno [1, 2-b] quinoxalin-11-one, 6H-indeno [1, 2-b] pyrido [3, 2-e] pyrazin-6-one and isatin-based 2-pyrazolines', Arkivoc, no. 11, pp. 47-58.

Mughal, EU, Ayaz, M, Hussain, Z, Hasan, A, Sadiq, A, Riaz, M, & Choudhary, MI 2006, 'Synthesis and antibacterial activity of substituted flavones, 4-thioflavones and 4-iminoflavones', Bioorganic & Medicinal Chemistry, vol. 14, no. 14, pp. 4704-4711.

Murti, Y, Goswam, A & Mishra, P 2013, 'Synthesis and antioxidant activity of some chalcones and flavanoids', International Journal of PharmTech Research, no. 5, pp. 811-818.

Panche, AN, Diwan, AD & Chandra, SR 2016, 'Flavonoids: an overview', Journal of Nutritional Science, vol. 5, e47.

Patil, CB, Mahajan, SK & Katti, SA 2009, 'Chalcone: a versatile molecule', Journal of Pharmaceutical Sciences and Research, vol. 1, no. 3, pp. 11.

Rafiee, E & Rahimi, F 2013, 'Synthesis of biologically active chalcone analogues *via* Claisen-Schmidt condensation in

solvent-free conditions: supported mixed addenda heteropoly acid as a heterogeneous catalyst', Journal of the Chilean Chemical Society, vol. 58, no. 3, pp. 1926-1929.

Raiford, LC & Gundy, GV 1938, 'α, β-unsaturated ketones obtained from acetophenone, and their reaction with phenylhydrazine', The Journal of Organic Chemistry, vol. 3, no. 3, pp. 265-272.

Tajammal, A, Batool, M, Ramzan, A, Samra, MM, Mahnoor, I, Verpoort, F & Basra, MAR 2017, 'Synthesis, antihyperglycemic activity and computational studies of antioxidant chalcones and flavanones derived from 2, 5 dihydroxyacetophenone', Journal of Molecular Structure, no. 1148, pp. 512-520.

Taruscio, TG, Barney, DL & Exon, J 2004, 'Content and profile of flavanoid and phenolic acid compounds in conjunction with the antioxidant capacity for a variety of northwest Vaccinium berries', Journal of Agricultural and Food Chemistry, vol. 52, no. 10, pp. 3169-3176.

Winter, C, Caetano, JN, Araújo, ABC, Chaves, AR, Ostroski, IC, Vaz, BG & Alonso, CG 2016, 'Activated carbons for chalcone production: Claisen-Schmidt condensation reaction', Chemical Engineering Journal, no. 303, pp. 604-610.

Yoshida, M, Fujino, Y, Saito, K & Doi, T 2011, 'Regioselective synthesis of flavone derivatives via DMAP-catalyzed cyclization of o-alkynoylphenols', Tetrahedron, vol. 67, no. 51, pp. 9993-9997.