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Synthesis of Isatin-based Chalcone Derivatives and Their Antioxidant Activity Evaluation

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Abstract

Human body needs antioxidants to combat free radicals and guard healthy cells from their damaging effects that might result in degenerative diseases. Currently, several degenerative diseases include hypertension, heart attack, diabetes, stroke, and cancer. To allow human body deals with free radical attacks caused by radiation, stress, cigarette smoke, and environmental pollution, external antioxidants are required. Chalcones are compounds that have an α,β-unsaturated carbonyl system, which makes them exhibit important biological activities. In fats, they may be used in medication procedure as antioxidants, antifungals, antibacterial agents, anticancer agents, and for other biological activities. This study aims to synthesize a chalcone derivative, namely 3-(2-oxo-2-phenylethylidene)indolin-2-one and 5-chloro-3-(2-oxo-2-phenylethylidene)indolin-2-one containing a chloro substituent, as well as test the potential of these compounds as antioxidants. The reflux method of claisen-schmidt condensation of isatin and acetophenone was used to form chalcone derivatives. Spectroscopy-based analysis (UV-VIS, IR, and LCMS) were used to characterize the resulted products. Meanwhile, DPPH method was used to evaluate their antioxidant activity. This study showed that the antioxidant activity of 3-(2-oxo-2-phenylethylidene)indolin-2-one and 5-chloro-3-(2-oxo-2-phenylethylidene)indolin-2-one compounds is very weak at low concentrations.

Keywords: *Antioxidant; Chalcone Derivatives; Claisen-Schmidt Condensation; DPPH Method; Isatin*

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INTRODUCTION

Atoms, molecules, or ions with an unpaired electron in orbit are known as free radicals. They are continuously produced by the body and can become harmful when they are in large concentrations or when the naturally occurring body antioxidant defenses do not functioni properly. Free radicals can oxidize lipids, proteins, and DNA in cells and tissues when their concentration is sufficiently high. Although human body does have vital defense mechanisms against free radicals in the form of enzymes such glutathione peroxidase, catalase, and superoxide dismutase, oxidative stress is also developing as a result of imbalances between the generation and detoxification of free radical species. Serious degenerative diseases include cancer, atherosclerosis, aging,

immunosuppression, inflammation, ischemic heart disease, diabetes, and neurological disorders emerge as a result of this phenomenon (Martemucci *et al.*, 2022). Antioxidants are substances that interact safely with free radicals, stop the reaction, and change them into a harmless molecule by providing an electron. Antioxidants thus protect cells from oxidative damage by reducing oxidative stress (Hoang, Moon and Lee, 2021).

Chalcone is a natural product that is widely distributed in plants (Batovska and Todorova, 2010) (**Figure 1a**). Chalcones that are originated in nature can be found in a variety of plants heartwood, leaves, bark, fruits, and roots, where they are primarily found as petal hues (Salehi *et al.*, 2021). Many angiosperm families, including *leguminosae*, *asteraceae*, and *moraceae*, are the common sources of natural chalcone. Citrus, apple, tomato, beans, potatoes, licorice, and other fruits and vegetables are also the main sources of chalcone (Kuber Banoth and Thatikonda, 2020). Both cis and trans isomers of chalcones can exist, however, the trans isomer is more thermodynamically stable (Sahu *et al.*, 2012). Chalcone is a group of open chain flavonoids with two aromatic rings joined by three carbons in the α,β-unsaturated carbonyl system. Conventionally, chalcone is synthsized using a process called claisen-schmidt condensation, which entails the cross-aldol condensation of aldehydes and ketones with an acid or base catalyst, followed by a dehydration reaction (Septianingtyas *et al*., 2021). According to previous reports, chalcone possesses a variety of biological properties, including anti-inflammatory (Cheng *et al.*, 2008) and antifungal effects (Sortino *et al.*, 2007; Zheng *et al.*, 2015), and antitumor (Sharma *et al.*, 2015; Li *et al.*, 2020; Moreira *et al.*, 2021). It was discovered that the chalcone's double bond in the enone system was responsible to its anticancer activity (Ouyang *et al.*, 2021). Halogen substituted chalcones can be a potential candidate for promising antioxidants of future. In fact, the bromo substituted chalcones have the highest percentage inhibition activity both at 10 g/mL and 100 g/mL, whereas the chloro substituted ones have a poorer percentage inhibition both at 10 g/mL and 100 g/mL concentrations (Isaac *et al.*, 2012).

Isatin is also known as indole quinone and indenediode (1H-indole-2,3-dione), which in its heterocyclic part is biologically active (**Figure 1b**). Isatin is composed of a nitrogen atom, two carbonyl groups, a six-membered aromatic cyclic ring, and a five-membered cyclic ring, which has anti-aromatic characteristics (Varun *et al.*, 2019). The study found that isatin and its derivatives have a variety of biological properties, including antimicrobial (Meeran and Hussain, 2017), antibacterial, antifungal (Jarrahpour *et al.*, 2007), antiviral (Zhang *et al.*, 2014), anticancer (Prasad *et al.*, 2009; Teng *et al.*, 2016), and antioxidant activity (Prakash *et al.*, 2011).

Among antioxidant tests, the DPPH assay is one of the most preferred and regularly used techniques. The process is easy, effective, reasonably priced, and fast. It does, however, require a UV-Vis spectrophotometer, just like the majority of antioxidant assays. This technique uses a stable free radical called α,α-diphenyl-β-picrylhydrazyl to measure the antioxidant activity, by adding a proton from the antioxidant to the matching hydrazine, the odd nitrogen atom electron in DPPH is decreased. (Kedare and Singh, 2011).

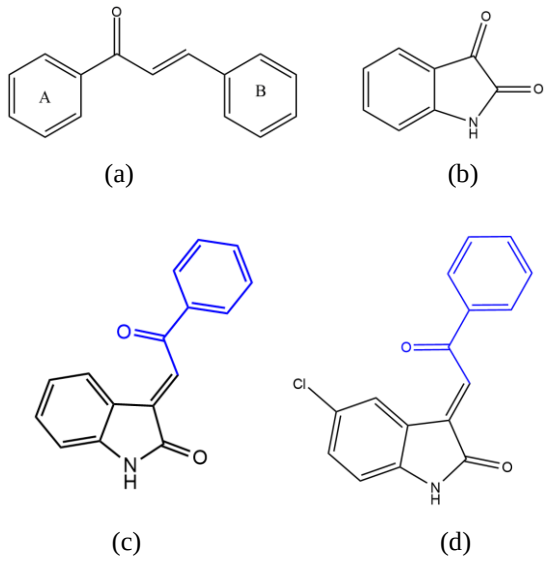


Figure 1. Molecule structure of (a) Chalcone, (b) Isatin, (c) 3-(2-oxo-2-phenylethylidene)indolin-2-one, (d) 5-chloro-3-(2-oxo-2-phenylethylidene)indolin-2-one.

The free radical DPPH produces a maximum absorption at 517 nm when it has an odd electron (purple color). When antioxidants and DPPH interact, DPPH is converted to DPPHH, which lowers its absorbance. The quantity of electrons collected determines how much yellow hue is decolorized when radicals are formed from DPPH-H. (Anju, 2014).

In 2010, Andreani *et al.* synthesized isatin with 2,5-dimethoxyaniline and analyzed the antioxidant activity at various concentrations ranging from 1.48 to 3.71 µM. The compound formed shows good chemical antioxidant activity in accordance with the molecular design, which includes the -OCH_3 group in its structure. Prakash *et al.* in 2011, synthesized imesatin by reacting isatin with p-phenylenediamine. The compound formed as 3-(4-(4-dimethyl amino benzylidene amino) phenylimino) indoline-2-one shows the highest antioxidant activity due to the presence of electron donating groups. Furthermore, in 2020, Shaik *et al.* did research about analysis of antioxidant activity for isoxazole-based chalcone products with various concentration range (5 – 100 µg/mL) . The test results using the DPPH method showed that isoxazole-based chalcone showed significant antioxidant activity, and the substitution of electron donating groups (-OCH3) could increase antioxidant activity.

This study aims to synthesize isatin-based chalcone derivatives as well as to evaluate their antioxidant activities. 3-(2-oxo-2-

phenylethylidene)indolin-2-one (**Figure 1c**) and 5-chloro-3-(2-oxo-2 phenylethylidene)indolin-2-one (**Figure 1d**) compounds were synthesized which are derivatives of chalcone with side chain modification in ring B. This compound was synthesized through the claisen-schmidt aldol condensation reaction of isatin and acetophenone compounds, where thin layer chromatography was used to determine whether the reaction was complete (TLC). The results of the synthesis were then evaluated using UV-VIS and FT-IR. The DPPH technique was then used to determine the compounds antioxidant activity.

EXPERIMENTAL

Materials

Materials utilized in this study include isatin, acetophenone, HCl, ethanol, aquadest, diethylamine, glacial acetic acid, n-hexane, DPPH (2,2-Diphenyl-1-picrylhydrazyl), methanol, ethyl acetate. All chemicals and reagents were obtained from Merck and Sigma-Aldrich analytical grade and used without additional purification. The equipment employed in this study were pipettes, glassware, an analytical balance, a hot plate stirrer, and a set of reflux tools. Thin layer chromatography (TLC) silica gel 60 F254 Merck, fourier transform infrared (FT-IR) Shimadzu IR Prestige 21, UV-Vis spectrophotometer UV-2450 Shimadzu, and liquid chromatography mass spectrometry (LCMS) Shimadzu Prominance 20-Abesciex are the analytical tools used to selectively identify constituent components. Chemdraw ultra version 12.0.2 by Cambridge soft corporation is used to name compounds.

Method

General Process for the Synthesis of Chalcone Derivatives

Isatin derivative (isatin and 5-chloroisatin) 2 milimoles, acetophenone 2 milimoles, 2 drops of diethylamine, glacial acetic acid in 2 milliliters, and 2 drops of HCl were combined, and then ethanol was added. After that, the mixture was refluxed for three hours at 80°C. Following separation and washing with distilled water (2 ×5 mL), the final chalcone was recrystallized. Compounds were characterized by IR, UV-Vis, and LCMS spectroscopy. The resulting compound was purified using column chromatography with the isocratic method using n-hexane : ethyl acetate (2:1) as eluent.

DPPH Inhibition Activity

The compounds produced are continued with activity tests as antioxidants. This test uses the DPPH method (2,2-diphenyl-1-picrylhydrazyl). In order to make the mother liquor, ethanol and DPPH were mixed together (0,1 mM). Different concentrations of sample solutions (10 ppm, 15 ppm, 20 ppm, 25 ppm, 30 ppm, 50 ppm, 100 ppm, and 1000 ppm) in ethanol were created. The sample to be analyzed was taken as much as 2 mL and added 2 mL of 0.1 mM DPPH, while 2 mL of ethanol p.a and 2 mL of 0.1 mM DPPH were used as a negative control. After 30 minutes of incubation, the radical scavenging activity was determined using UV-Vis spectroscopy at a wavelength of 517 nm as a decrease in DPPH absorbance. The following formula was used to calculate the percentage of DPPH antioxidant activity:

Antioxidant Activity (%) =

$$\frac{(Absorbance\ of\ control - Absorbance\ of\ test\ sample}{Absorbance\ of\ control} \times 100\% \quad (1)$$

(Venkatesh and Bodke, 2016)

where: a control solution is the absorbance of a DPPH solution without an unknown sample. The test is the absorbance of the test compound with DPPH. The degree of discoloration indicates the free radical scavenging efficiency of the compound.

RESULT AND DISCUSSION

Synthesis of isatin-based chalcone derivatives

The claisen-schmidt aldol condensation reaction was used to synthesize isatin-based chalcone compounds, specifically compounds 1c and 1d (**Figure 1**), as illustrated in **Figure 2**. The starting material used is isatin which functions as an electrophile and acetophenone as a nucleophile. Acetophenone has a Hα atom in the carbonyl group so that under basic conditions it can form a carbanion. This carbanion is relatively stable because it can conjugate to produce enolate ions. The carbanion of acetophenone attacks the carbon of the isatin carbonyl group. The result of this nucleophilic addition reaction will produce β-hydroxy ketone. This β–hydroxy ketone compound has Hα in the carbonyl group so that when acid is added, a dehydration process will occur and produce derivatives of chalcone compounds. In order to ascertain the role of chloro substituents in the production of chalcone, isatin was converted into 5-chloroisatin in a variety of ways.**)**

The synthesis was carried out under acidic conditions and ethanol, the reaction was carried out using reflux at 80°C for 3 hours.

The synthesis of isatin-based chalcone derivatives showed good prospects with the successful formation of chalcones and obtained are quite high yields, as demonstrated in the FTIR, UV-Vis, and LCMS characterization results in **Table 1**. The antioxidant activity test of the products was carried out by DPPH radical scavenging. The results demonstrated that the isatin-based chalcone derivative has very weak percent inhibition with increasing concentration **(see figure 7)**

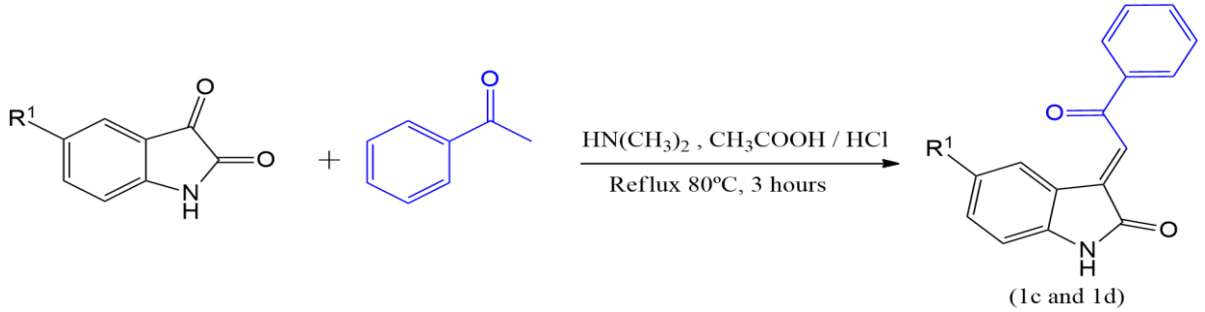
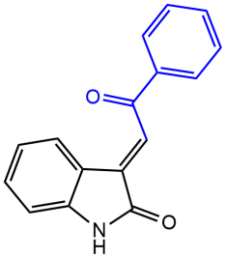
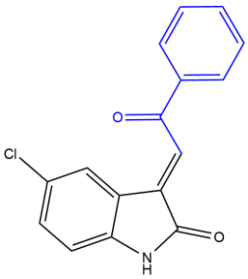


Figure 2. The formation of isatin-based chalcone derivatives. R^1 = H or Cl

Table 1. Chemical analysis of the synthesized compounds

Compound	Molecular structure	Characterization result	Yield (%)
Chalcone (3-(2-oxo-2-phenylethylidene)indolin -2-one)		Orange crystalline, solid. $C_{16}H_{11}NO_2$, mp: 184 - 186°C. IR: 3159 cm^{-1} (N – H stretching vibration), 3004 cm^{-1} (C – H stretching vibration), 1710 cm^{-1} (C = O ketone), 1659 cm^{-1} (C = O lactam), 1605 cm^{-1} (secondary N – H stretching vibration), 1455 cm^{-1} (aromatic C = C), 1225 cm^{-1} and 756 cm^{-1} (aromatic C – H bending). UV-Vis (nm): 207, 260, 336, and 437.	**61.14**
Chalcone 5-chloroisatin (5-chloro-3-(2-oxo-2-phenylethylidene)indolin -2-one)		Brownish-yellow, solid. $C_{16}H_{10}ClNO_2$, mp: 201 - 204°C. IR: 3024 cm^{-1} (aromatic C – H stretching), 1720 cm^{-1} (C = O ketone), 1619 cm^{-1} (secondary N – H amide stretching), 1470 cm^{-1} (aromatic C = C), 1048 cm^{-1} (aromatic C – H bending), 777 cm^{-1} (C – Cl). UV-Vis (nm): 212, 255, 335, and 438	**53.99**

Synthesis and characterization of the isatin-based chalcone derivatives

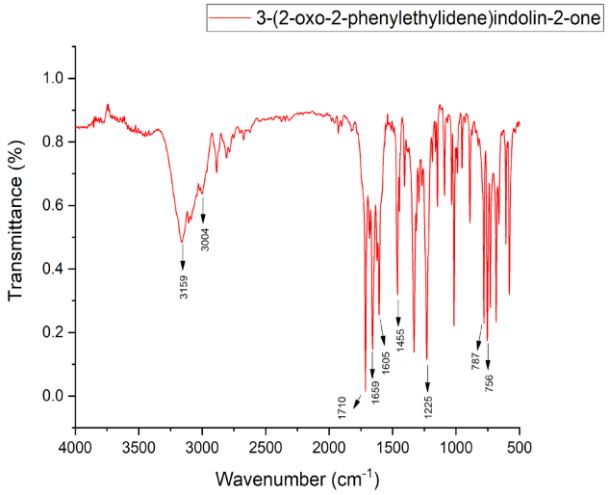
3-(2-oxo-2-phenylethylidene)indolin-2-one (1c)

The isatin-based chalcone was synthesized by the claisen-schmidt condensation reaction between isatin and acetophenone. The product obtained was 3-(2-oxo-2-phenylethylidene)indolin-2-one, confirmed by the FTIR, UV-Vis, and LCMS characterization. **Figure 3a** shows the infrared (IR) spectrum band of the synthesized compounds, while its analysis results are presented in Table 1. UV-Vis spectrum of this compound shows bathochromic shift towards isatin as the precursor, which is a shift in the absorbance to a longer wavelength. This phenomenon is most likely due to the extended π-conjugation. In addition, the wavelength of 437 nm

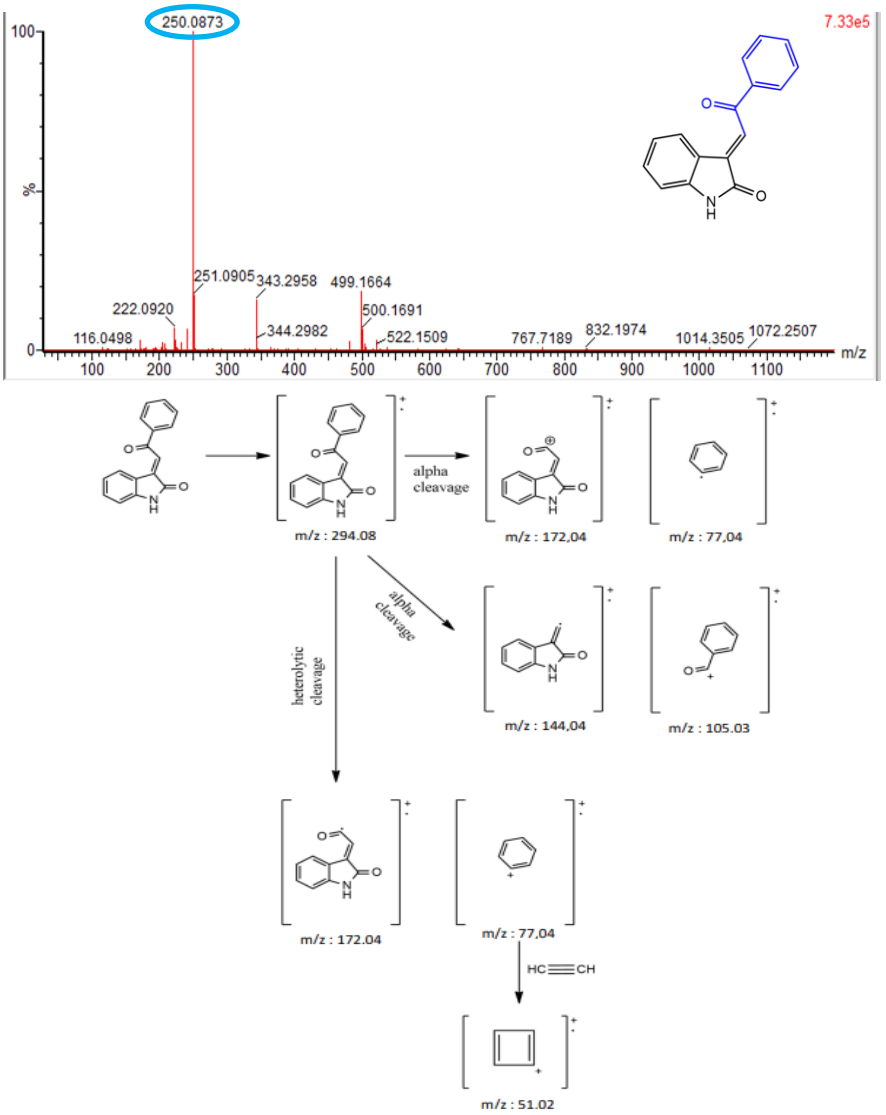
was identified as the formation of the product because it has a different wavelength from the precursor. The mass spectrum in **Figure 3b** shows for $[M + H]^+$ $C_{16}H_{11}NO_2$ requires m/z = 250.0868, and found: 250.0873 at retention time 9.957 minutes.

5-chloro-3-(2-oxo-2-phenylethylidene)indolin-2-one (1d).

The 5-chloroisatin was reacted with acetophenone to form 5-chloro-3-(2-oxo-2-phenylethylidene)indolin-2-one. The formation of the product was identified by TLC after the completion of the reaction, as shown in **Figure 2**. The synthesized compound was characterized by FTIR, UV-Vis spectrophotometry, and LCMS. The IR absorption peak confirmed the formation of 1d compound, as shown in **Figure 4a**, while the analysis results of the synthesized compound are presented in **Table 1**. UV-vis spectrum shows that the presence of new wavelength at 335 nm that is different from the wavelength of the precursor can be identified as the formation of a product by the presence of a bathochromic shift towards 5-chloroisatin. The bathochromic effect can be identified by a shift in the wavelength absorption to a longer wavelength, and it is due to the extended π-conjugation. The mass spectrum of the compound 1d in **Figure 4b** shows for $[M + H]^+$ $C_{16}H_{10}ClNO_2$ requires m/z = 284.0478, found: 284.0464 at retention time 11.124 minutes

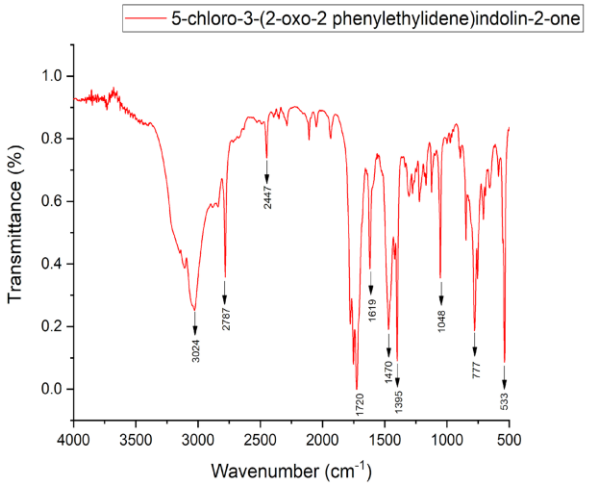


(a)

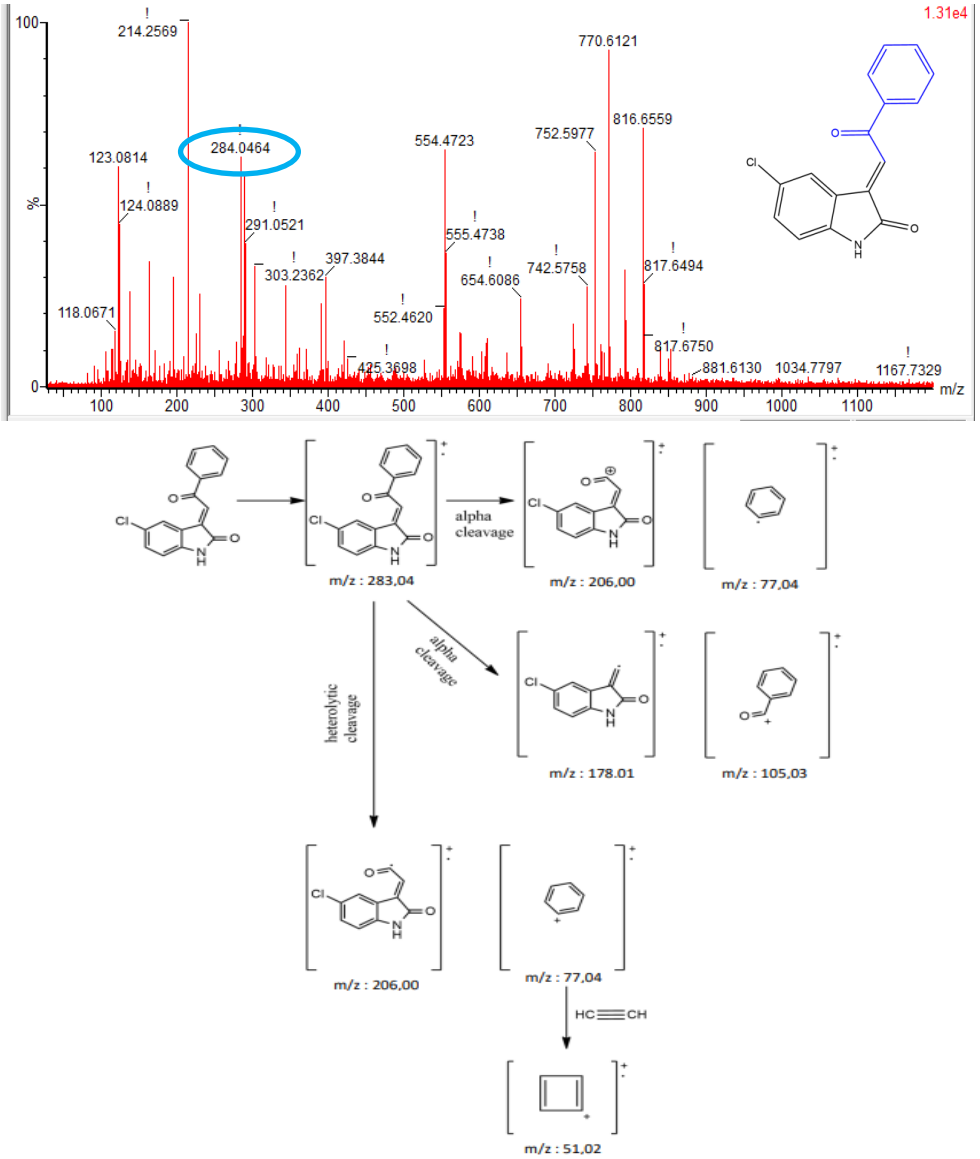


(b)

Figure 3. The spectrum of 3-(2-oxo-2-phenylethylidene)indolin-2-one (a) FTIR spectrum (b) LCMS spectrum and propose fragmentation



(a)



(b)

Figure 4. The spectrum of 5-chloro-3-(2-oxo-2-phenylethylidene) indolin-2-one (a) FTIR spectrum (b) LCMS spectrum and propose fragmentation

DPPH Inhibition Activity

In this study, antioxidant capacity of the samples were also examined to ascertain their response to the standard free radical compound DPPH (2,2-diphenyl-1-picrylhydrazyl). This approach is selected because it is straightforward, effective, reasonably priced, and quick. Free radical DPPH can take electrons or hydrogen radicals to transform into a stable diamagnetic molecule, which is stable at ambient temperature. Antioxidants absorb DPPH radicals through proton donation to form a reduced DPPH. When DPPH reacts with antioxidant compounds, its free radical properties are lost and resulting in a clear color change from purple to yellow (**Figure 5**) (Alam et al., 2013).

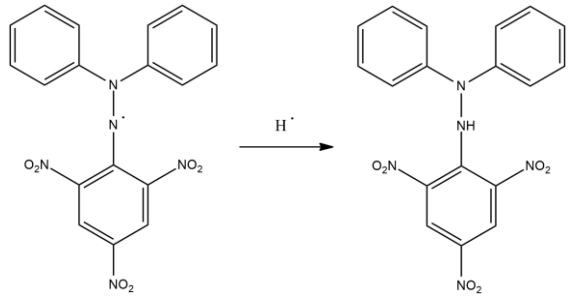


Figure 5. Radical form (deep purple) and non-radical form after taking the hydrogen (pale yellow) of DPPH

Based on the IR characterization results for compound 1c, it can be seen that compound 1c was successfully formed with the appearance of a wavelength of 1659 cm^{-1} as an indication of a keto-lactam ring and the presence of N-H groups at wavelengths of 3159 cm^{-1} and 1605 cm^{-1}, which play a role in antioxidant activity. Further confirmation regarding the success of the product was characterized using LCMS, which showed that the product compound 1c was indeed confirmed to have formed in the presence of peak m/z, which was in accordance with the theory, so that the antioxidant activity test showed that compound 1c played a role in inhibition against free radicals. The results of the IR characterization of compound 1d, it can be seen that an N-H group is formed at a wavelength of 1619 cm^{-1}, a C-Cl bond at a wavelength of 777 cm^{-1}, and a ketone group at 1720 cm^{-1}. Furthermore, further confirmation was carried out regarding the successful synthesis of the product using LCMS. The results exhibited that compound 1d was indeed confirmed to have formed as seen from the appearance of peak m/z, which was in accordance with the theory, and then the antioxidant activity test showed that compound 1d played a role in the inhibition of free radicals. However, the presence of Cl in compound 1d caused a lower antioxidant activity effect than compound 1c, which was without Cl substituents. It is because Cl is an electron withdrawing group. (Shaik *et al.*, 2020). Furthermore, the test results showed that compounds 1c and 1d had very weak percent inhibition. As seen in **Figure 6**, compound 1c showed inhibition of 2.66% at a concentration of 10 ppm and then decreased to 2.35% at a concentration of 15 ppm. However, it did not exhibit any antioxidant activity at higher concentrations. Meanwhile, compound 1d gave 0.7% inhibition at a concentration of 15 ppm and increased to 20% inhibition at a concentration of 20 ppm. Therefore, it is confirmed that an increase in the concentration of the sample leads to reduce its antioxidant activity. The existence of heterocyclics with an oxindole core which in low concentrations have moderate to good antioxidant activity is likely the cause of this. This makes it possible for a keto-lactam ring to exist, and its N – H and C = O groups are what cause free activity to begin (Gupta, Kalpana and Malik, 2012).

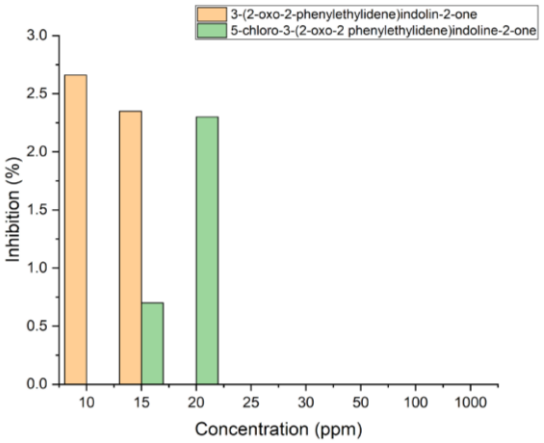


Figure 7. Percent inhibition of antioxidant activity

CONCLUSION

This research has demonstrated as successful effort to synthesize isatin-based chalcone derivatives, namely 3-(2-oxo-2-phenylethylidene) indolin-2-one, and 5-chloro-3-(2-oxo-2 phenylethylidene) indolin-2-one. The antioxidant activity of these two compounds as represented by their percent inhibition reduced with increasing their concentration. The existence of heterocyclics with oxindole cores, which exhibit moderate to high antioxidant activity present at low concentrations, is likely to be the cause of this finding. The presence of chloro substitution in isatin provided a lower antioxidant activity than isatin sample without substitution.

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