Short Communication:

Iodine-catalyzed Synthesis, Antibacterial, and Antioxidant Activity of Isatin Derivatives

Antonius Herry Cahyana[1*], Agus Rimus Liandi[2], and Yosua Ongkowidjawa[1]**

[1]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Indonesia, Depok 16424, Indonesia*

[2]*Department of Chemistry, Faculty of Science and Technology, Syarif Hidayatullah State Islamic University Jakarta, Tangerang Selatan 15412, Indonesia*

**** Corresponding author:***

email: herrykim@sci.ui.ac.id; agusrimus@uinjkt.ac.id***

Received: April 29, 2023
Accepted: January 30, 2024

DOI: 10.22146/ijc.84113

Abstract: *Isatin is a unique compound with many bioactivities such as antiviral, anti-HIV, antitumor, anti-inflammatory, anticonvulsant, and antifungal. In this study, isatin derivatives were synthesized with an iodine catalyst and tested for antibacterial and antioxidant activities. Isatin derivatives were conducted through a Knoevenagel condensation reaction between isatin and malononitrile. The products were confirmed by thin-layer chromatography, melting point apparatus, FTIR, UV-vis spectroscopy, and LC-MS. The optimum reaction conditions were obtained at 10% mol of catalyst, at boiling point ethanol solvent for 30 min. The yield of the isatin derivative products was 71% (**3a**), 61% (**3b**), and 67% (**3c**). The antibacterial activities of the synthesized compounds were weak activity against* S. aureus *and* E. coli. *The antioxidant activity test resulted in* IC_{50} *values of 266.47, 220.43, and 654.85 ppm for compounds **3a**, **3b**, and **3c**, respectively. The synthesis method using an iodine catalyst in this reaction offers a higher product yield compared to a catalyst-free reaction.*

Keywords: *isatin; Knoevenagel condensation reaction; iodine catalyst; antibacterial; antioxidant*

■ INTRODUCTION

Heterocyclic compounds have recently been widely researched and developed in the medical field because these compounds are the core structure of many drugs used in medicine [1-2]. In addition to the widely available heterocyclic compounds, they also have significant chemical, biological, and technical applications [3]. Heterocyclics can be found in natural materials, such as vitamins, hormones, antibiotics, and alkaloids, as well as drugs, herbicides, dyes, and other products, such as corrosion inhibitors and stabilizer agents [4-6]. One of the heterocyclic compounds with broad bioactivities is isatin and its derivatives [7-8].

Isatin is a heterocyclic compound that is versatile and important in its application in organic chemical synthesis [9-10]. Isatin is considered a versatile building block for synthesizing various pharmacologically active compounds [11]. Isatin and its derivatives exhibit broad biological and pharmacological activities, such as antibacterial, antifungal, anti-HIV, antiviral, antidiabetic, antitumor, anticonvulsant, anticancer, antioxidant, neuroprotective, antidepressant, anticonvulsant, and anti-inflammatory [12-15].

Synthesis of isatin derivatives compounds has been carried out in various ways, including using catalysts. Some catalysts that have been used in the synthesis of isatin derivatives are palladium [16], Ru(II)-Pheo [17], dirhodium(II) [18], and boron trifluoride [19]. Using a catalyst in the organic synthesis reaction gives significantly higher product yields and a shorter time than without a catalyst [20]. In previous studies, the reaction in the synthesis of isatin derivatives was carried out without a solvent [21-23]. Therefore, the synthesis of isatin and its derivatives in this study was carried out with the assistance of an iodine catalyst. The reaction occurs

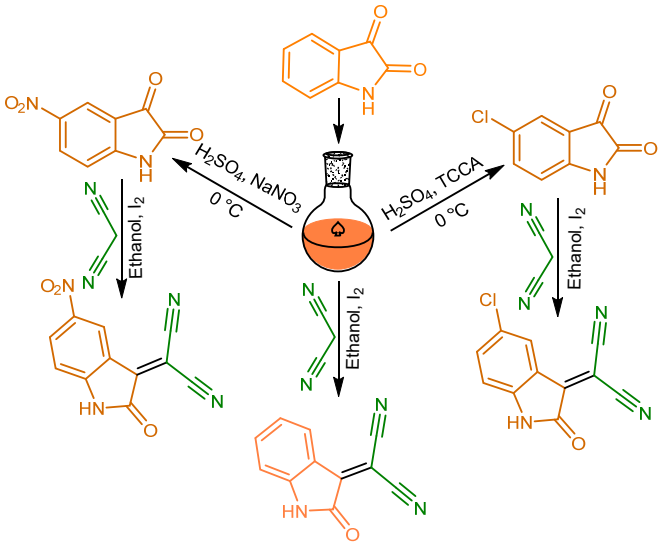


Fig 1. Illustration of a general reaction for the synthesis of isatin derivatives

through Knoevenagel condensation by reacting between isatin and malononitrile and testing their bioactivity as antibacterial and antioxidant. The general schematic of this research is illustrated in Fig. 1.

■ EXPERIMENTAL SECTION

Materials

Chemicals were obtained from Sigma-Aldrich and used without further purification, such as isatin ($C_8H_5NO_2$; CAS 91-56-5), malononitrile ($CH_2(CN)_2$; CAS 109-77-3), iodine (I_2; CAS 7553-56-2), acetonitrile (CH_3CN; CAS 75-05-8), trichloroisocyanuric acid/TCCA ($C_3Cl_3N_3O_3$; CAS 87-90-1), sulfuric acid (H_2SO_4; CAS 7664-93-9), *n*-hexane (C_6H_{14}; CAS 110-54-3), ethanol (C_2H_5OH; CAS 64-17-5), methanol (CH_3OH; CAS 67-56-1), sodium nitrate ($NaNO_3$; CAS 7631-99-4), nutrient agar, 2,2-diphenyl-1-picrylhydrazyl/DPPH ($C_{18}H_{12}N_5O$; CAS 1898-66-4), dimethyl sulfoxide/DMSO ($(CH_3)_2SO$; CAS 67-68-5), amoxicillin ($C_{16}H_{25}N_3O_8S$; CAS 26787-78-0), and ascorbic acid ($C_6H_8O_6$; CAS Number: 50-81-7).

Instrumentation

The instruments used in this study were melting point apparatus, Fourier transform infrared spectroscopy (FTIR, IR Prestige-21 Shimadzu spectrometer), UV–vis spectrophotometer (Shimadzu 2450), and liquid chromatography-mass spectrometry (LC-MS, Thermo HPLC-DIONEX ULTIMATE -TSQ Quantum Access MAX Triple Quadrupole Mass Spectrometer).

Procedure

Synthesis of 5-chloroisatin

Isatin (10 mmol; 1.47 g) and trichloroisocyanuric acid (10 mmol; 2.32 g) were mixed in a flask. Then 12 mL of sulfuric acid was added slowly. The flask was placed in an ice bath and stirred for 15 min. After completion, cold water was poured into the reaction mixture to obtain the product. The product **2a** was purified by recrystallization using hot ethanol, and the product was obtained in the form of orange powder.

Synthesis of 5-nitroisatin

Isatin (10 mmol; 1.47 g) and $NaNO_3$ (10 mmol; 0.85 g) were mixed in a flask. Then 12 mL of sulfuric acid was added slowly. The flask was placed in an ice bath and stirred for 15 min. After completion, cold water was poured into the reaction mixture to obtain the product. The product **2b** was purified by recrystallization using hot ethanol, and the product was obtained in the form of yellow powder.

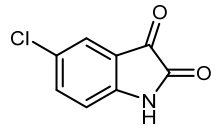
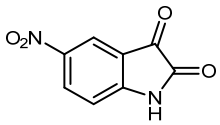
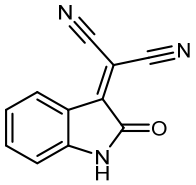
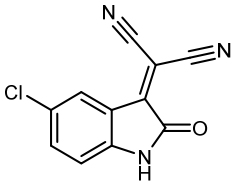
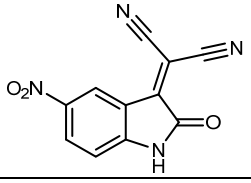
Synthesis of malononitrile isatins

To obtain the optimum condition for the reaction, isatin (1 mmol; 0.147), malononitrile (1 mmol; 0.066), and iodine were mixed at various conditions in 10 mL solvent to obtain compound **3a**. The reaction was monitored by thin-layer chromatography (TLC). After completion, the product was recrystallized using hot ethanol. Optimization of reaction conditions was carried out by varying catalyst concentration, temperature, and solvent type. Compound **3b** (1 mmol compound **2a**; 0.1815 g and 1 mmol malononitrile; 0.066 g) and compound **3c** (1 mmol compound **2b**; 0.192 g and 1 mmol malononitrile; 0.066 g) were synthesized under optimum conditions. All synthesis products were characterized by melting point apparatus, UV-vis spectroscopy, FTIR, and LC-MS (Table 1).

Antibacterial activity test

The antibacterial activity test was carried out using the disk diffusion method against Gram-positive bacteria *Staphylococcus aureus* (ATCC 6538P) and Gram-negative bacteria *Escherichia coli* (ATCC 8739) [24-25].

Table 1. Characterization data and yield of synthesized compounds

Compound	Structure	Characterization	Yield (%)
2a		Orange powder-like solid. m.p.: 250.8–251.3 °C. UV-vis (nm): 252 and 297. IR (cm^{-1}): 3180 (N–H), 3062 (C–H sp^2), 1750 and 1715 (C=O), 1620 (C=C), 1451 (C–N), 848 (C-Cl).	45
2b		Yellow powder. m.p.: 251.3–252.7 °C. UV-vis (nm): 324. IR (cm^{-1}): 3330 (N–H), 3092 (C–H sp^2), 1780 and 1732 (C=O), 1620 (C=C), 1455 (C–N), 1531 and 1338 (N–O).	58
3a		Red powder-like solid. m.p.: 199.2–200.4 °C. UV-vis (nm): 260 and 347. FTIR (cm^{-1}): 3266 (N–H), 3107 (C–H sp^2), 1718 (C=O), 1566 (C=C), 2232 (C≡N), 1461 (C–N). MS (*m/z*): 195.	71
3b		Red powder-like solid. m.p.: 228.3–229.5 °C. UV-vis (nm): 264 and 337. FTIR (cm^{-1}): 3249 (N–H), 3109 (C–H sp^2), 1731 (C=O), 1595 (C=C), 2230 (C≡N), 1452 (C–N), 850 (C–Cl). MS (*m/z*): 229.	61
3c		Red crystal. m.p.: 262.3–263.1 °C. UV-vis (nm): 310. FTIR (cm^{-1}): 3237 (N–H), 3109 (C–H sp^2), 1743 (C=O), 1610 (C=C), 2246 (C≡N), 1454 (C–N), 1520 and 1341 (N–O). MS (*m/z*): 240.	67

Each synthesized compound was dissolved in DMSO with a concentration variation of 62.5, 125, 250, 500, and 1000 ppm. Paper discs were dipped into each solution and placed on agar media that had been inoculated with bacteria. Amoxicillin in DMSO was used as a positive control, and DMSO was used as a negative control. All treatments were incubated for 24 h at 37 °C. The inhibition zone of each synthesized compound was measured from the diameter of the clear zone around the disc and expressed in mm.

Antioxidant activity test

The antioxidant activity test was carried out by free radical scavenging activity with the DPPH method [26-27]. An amount of 1 mM DPPH was diluted in ethanol to obtain 0.1 mM DPPH solution. Each synthesized compound was dissolved in ethanol and made a series of 100–1000 ppm concentrations. Antioxidant activity was carried out by mixing 0.5 mL of sample solution with 0.5 mL of 0.1 mM DPPH solution and incubating in the dark room for 30 min. The absorption of the sample was measured by UV-vis spectrophotometer at a wavelength of 517 nm. The ability of the synthesized compound as an antioxidant is expressed in %inhibition, calculated by Eq. (1).

$$\%\text{inhibition} = \frac{\text{Abs.}_{\text{control}} - \text{Abs.}_{\text{sample}}}{\text{Abs.}_{\text{control}}} \times 100 \quad (1)$$

■ RESULTS AND DISCUSSION

The synthesis of isatin derivatives has been conducted through the Knoevenagel condensation reaction between isatin and malononitrile. In order to enrich the isatin derivatives, isatin was chlorinated with trichloroisocyanuric acid to form 5-chloroisatin (**2a**). In a separate flask, isatin was also titrated with sodium nitrate to form the 5-nitroisatin (**2b**). For the formation of isatin derivatives, the three compounds (isatin, **2a**, and **2b**) were reacted with malononitrile in a separate flask by reflux method catalyzed by iodine. The presence

of iodine as a catalyst will increase the electrophilic properties of the carbonyl ketone group in isatin. The more positive carbon atoms will facilitate the nucleophilic attack of malononitrile to form isatin derivative compounds. The proposed mechanism is depicted in Fig. 2.

Evaluation and determination of the optimum reaction conditions were carried out by varying the reaction conditions, namely variations in temperature, solvent, and catalyst concentration. All substrates were reacted in a 1:1:1 mol ratio. The yield of the product obtained from the variation of these conditions can be seen in Table 2. Table 2 shows that the use of ethanol as a solvent gave the highest yield (71%) with a reaction time of 30 min, at a temperature of 75 °C, with the use of 10% mol of catalyst. The role of the catalyst in the reaction is clearly illustrated in this experiment. Under the same conditions (75 °C, 30 min), the reaction without a catalyst was only able to produce a product yield of 17%. The carbonyl group in isatin was activated by I_2 which makes it easier for the nucleophilic carbon in malononitrile to attack this system. Previous studies have synthesized the same compound (under piperidine acetate, CH_3CN, reflux) with a time of 120 min to produce a yield of 85% [28]. In another literature, the use of ZIF-8 and ZIF-67 catalysts resulted in a product yield of 75–93% with a time of 10 min at a temperature of 60 °C [29]. So, the use of I_2 as a catalyst demonstrated a better performance.

Under the optimum conditions, three isatin derivatives were synthesized, namely 2-(2-oxo-1,2-dihydro-indol-3-ylidene)-malononitrile (**3a**; 71%), 2-(5-chloro-2-oxo-1,2-dihydro-indol-3-ylidene)-malononitri le (**3b**; 61%), and 2-(5-nitro-2-oxo-1,2-dihydro-indol-3-ylidene)-malononitrile (**3c**; 67%). The decrease in product yields in compounds **3b** and **3c** compared to compound **3a** may be due to the presence of chloro- and nitro- substituents which are electron-withdrawing groups. This substituent makes the position of *m*-benzene negative (-) which will reduce the positive charge on the C carbonyl.

The structure analysis of products was conducted by determination of melting point, functional group vibration, maximum wavelength, and molecular weight. Fig. 3(a) shows the FTIR spectrum of **3a**, which has several

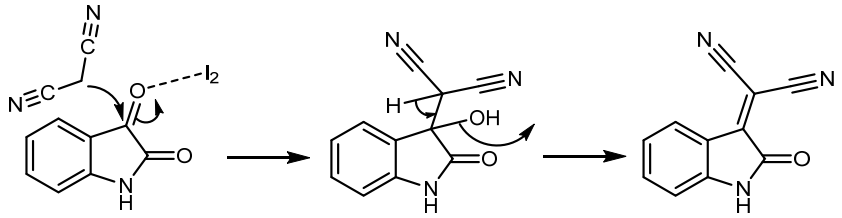


Fig 2. Proposed reaction mechanism for the formation of malononitrile isatins

Table 2. Optimization of reaction condition for **3a**

Entry	Temperature (°C)	Reaction time (h)	Solvent	I_2 (%mol)	Yield (%)
1	60	0.5	EtOH	0	19
2	60	0.5	EtOH	5	41
3	60	0.5	EtOH	10	61
4	60	0.5	EtOH	15	47
5	75	0.5	EtOH	0	49
6	**75**	**0.5**	**EtOH**	**10**	**71**
7	25	0.5	EtOH	0	17
8	25	0.5	EtOH	10	46
9	75	0.5	CH_3CN	0	23
10	75	0.5	CH_3CN	10	39
11	75	0.5	Solvent-free	0	40
12	75	0.5	Solvent-free	10	46

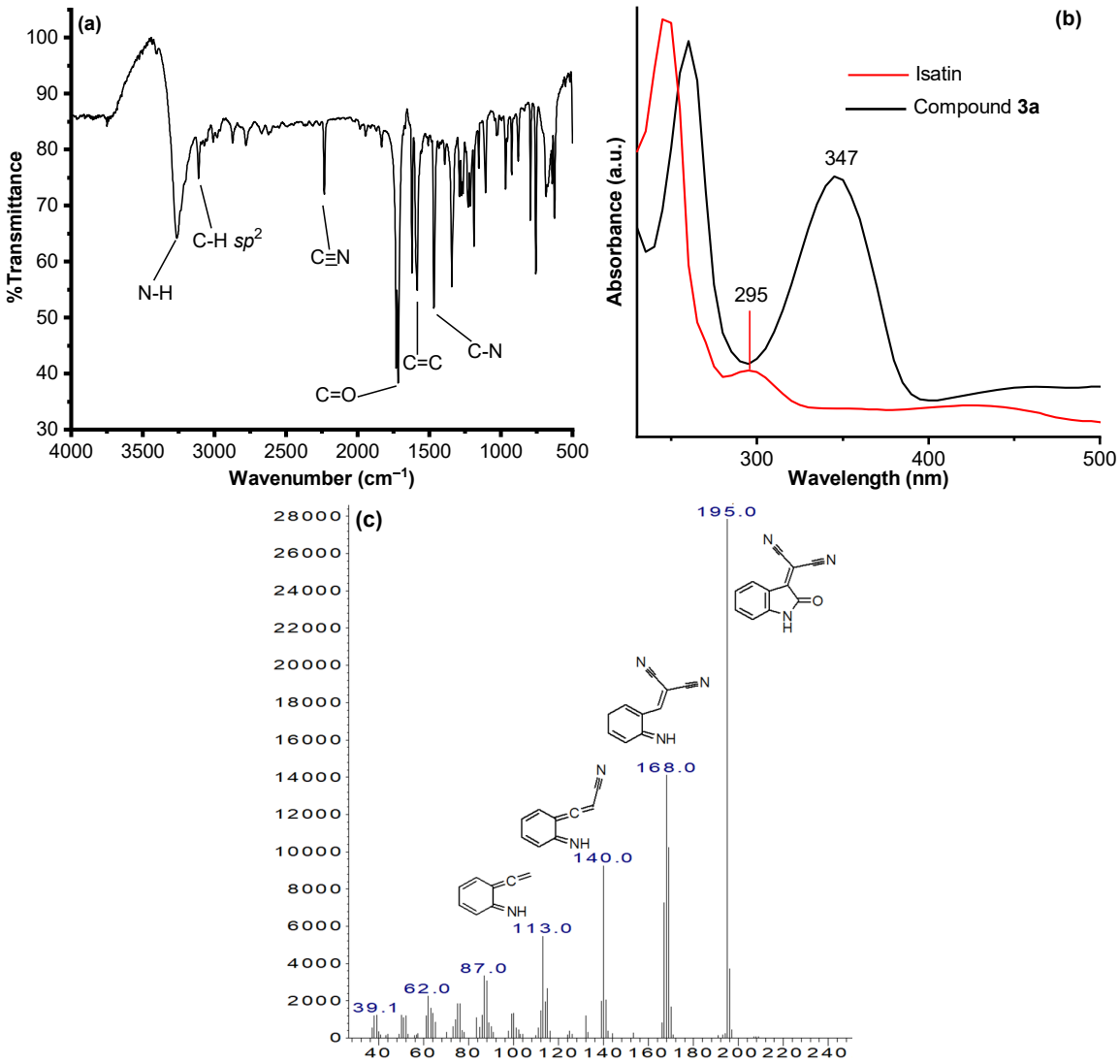


Fig 3. The (a) FTIR, (b) UV-vis, and (c) mass spectrum of compound **3a**

absorption peaks. The peak at 3266 cm^{-1} is stretching vibrations of secondary amines (N–H). In addition, there was also a stretching vibration of C–N at 1461 cm^{-1} with strong intensity. The area of 3107 and 1566 cm^{-1} are stretching vibrations of C–H (sp^2) and C=C aromatic, respectively that are found on the benzene ring. The peak that contributed as a sign that resorcinol had reacted with isatin was the absorption in the area of 2232 cm^{-1}. This peak is a stretching vibration of the C≡N group which indicates that the target product has been formed. The maximum wavelength of **3a** is 347 nm (Fig. 3(b)). The wavelength of **3a** seems to have shifted to the right (bathochromic shift) when compared to the maximum wavelength of isatin (295 nm). This shift occurs due to the presence of additional substituents that experience resonance in the product structure at the C=C and C≡N bonds (n→π*) as the contribution of resorcinol in the product structure framework. Fig. 3(c) shows the mass spectrum of **3a** which indicates the molecular ion mass at *m/z* 195. This shows that the reaction between isatin and resorcinol through the Knoevenagel reaction produced the desired compound with a molecular mass of 195 g/mol with the molecular formula $C_{11}H_5N_3O$. The base peak of this compound fragment is also at m/z 195 and other fragments were found at *m/z* 168, 140, and 113.

The antimicrobial activity of the synthesized compounds was tested using the disc diffusion method against two types of bacteria, namely *S. aureus* as Gram-positive bacteria and *E. coli* as Gram-negative bacteria. The inhibition zone of synthesized compounds is shown in Table 3. It was found that compounds **3a**, **3b**, and **3c** gave quite weak antimicrobial activity. The addition of electron-withdrawing groups such as chlorine and NO_2 to the aromatic ring of isatin was able to increase the antimicrobial activity, although not significantly and only occurred in the test on the growth of *S. aureus*. The presence of an electron-withdrawing group provides a more significant potential for antimicrobial activity than the presence of an electro-donating group [30].

The antioxidant activity test of the synthesized compounds was carried out using the free radical scavenging method using DPPH. The antioxidant activity of the test compound (Table 4) was determined as IC_{50}, which is the concentration of the compound capable of inhibiting the action of free radicals by 50%. The IC_{50} of **3a** was 266.47 ppm classified as a weak antioxidant; **3b** was 220.43 ppm as a moderate antioxidant, and **3c** was 654.85 ppm classified as an inactive antioxidant (strong antioxidant < 50 ppm, active 50–100 ppm, moderate 101–250 ppm, weak 251–500 ppm, and inactive > 500) [31]. As a comparison, the antioxidant activity of ascorbic acid was measured under the same conditions. Ascorbic acid has an IC_{50} value of 10.75 ppm and is classified as a very active antioxidant compound because it has a hydroxyl group that can easily release protons.

Table 4. Antioxidant activity of the synthesized compounds

Compound	IC_{50} (ppm)	Category
3a	266.47	Weak
3b	220.43	Moderate
3c	654.85	Inactive
Ascorbic acid (control)	10.75	Strong

Table 3. Inhibition zones of the synthesized compounds

Compound	Concentration (ppm)	Inhibition zone *S. aureus* (mm)	Inhibition zone *E. coli* (mm)
3a	62.5	-	-
	125.0	-	-
	250.0	-	-
	500.0	-	7.0 ± 0.0
	1000.0	7.0 ± 0.0	8.0 ± 0.0
3b	62.5	-	-
	125.0	-	-
	250.0	-	-
	500.0	8.5 ± 0.5	6.5 ± 0.5
	1000.0	10 ± 1.0	8.5±0.5
3c	62.5	-	-
	125.0	-	-
	250.0	-	-
	500.0	8.5 ± 0.5	6.5 ± 0.5
	1000.0	9.5 ± 0.5	8.0 ± 1.0
Amoxicillin (positive control)	62.5	-	1.5
	125.0	3.7	1.8
	250.0	4.2	2.0
	500.0	4.6	2.2
	1000.0	4.9	2.5
DMSO (negative control)	-	-	-

■ CONCLUSION

In summary, isatin derivative compounds have been successfully synthesized using variations of isatin and resorcinol through the Knoevenagel reaction using an iodine catalyst and produced three products. The approach of using an iodine catalyst in this reaction gave a significantly higher yield than the uncatalyzed reaction. The optimum reaction conditions were obtained with 10% mol of catalyst at a temperature of 75 °C using ethanol as a solvent. The three isatin derivatives have weak antimicrobial activity, and the best antioxidant is compound **3a** with IC_{50} of 220.43 ppm.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from Universitas Indonesia through the grant of PUTI Q1 Contract number: NKB-460/UN2.RST/HKP.05.00/2023.

■ CONFLICT OF INTEREST

The authors declared no conflict of interest.

■ AUTHOR CONTRIBUTIONS

Concept – Antonius Herry Cahyana, Agus Rimus Liandi; Design – Antonius Herry Cahyana; Supervision – Antonius Herry Cahyana; Resources – Antonius Herry Cahyana; Materials – Antonius Herry Cahyana; Data Collection and/or Processing – Yosua Ongkowidjawa, Agus Rimus Liandi; Analysis and/or Interpretation – Antonius Herry Cahyana, Agus Rimus Liandi, Yosua Ongkowidjawa; Literature Search – Antonius Herry Cahyana, Agus Rimus Liandi, Yosua Ongkowidjawa.; Writing – Antonius Herry Cahyana, Agus Rimus Liandi; Critical Reviews – Antonius Herry Cahyana, Agus Rimus Liandi.

■ REFERENCES

[1] Gomtsyan, A., 2012, Heterocycles in drugs and drug discovery, *Chem. Heterocycl. Compd.*, 48 (1), 7–10.

[2] Martins, P., Jesus, J., Santos, S., Raposo, L.R., Roma-Rodrigues, C., Baptista, P.V., and Fernandes, A.R., 2015, Heterocyclic anticancer compounds: Recent advances and the paradigm shift towards the use of nanomedicine's tool box, *Molecules*, 20 (9), 16852–16891.

[3] Mishra, P., Mishra, A., Bahe, A.K., Roy, A., and Das, R., 2021, Synthesis of isatin and its derivatives containing heterocyclic compounds, *J. Turk. Chem. Soc., Sect. A*, 8 (4), 1089–1098.

[4] Borissov, A., Maurya, Y.K., Moshniaha, L., Wong, W.S., Żyła-Karwowska, M., and Stępień, M., 2022, Recent advances in heterocyclic nanographenes and other polycyclic heteroaromatic compounds, *Chem. Rev.*, 122 (1), 565–788.

[5] Purbaningtias, T.E., Prasetyoko, D., Bahruji, H., Zein, Y.M., Triwahyono, S., Fadlan, A., and Qoniah, I., 2015, Condensation of indole with isatin over $AlCl_3$/mesoporous aluminosilicate, *Indones. J. Chem.*, 15 (1), 56–63.

[6] Kumar, V., Kaur, K., Gupta, G.K., and Sharma, A.K., 2013, Pyrazole containing natural products: Synthetic preview and biological significance, *Eur. J. Med. Chem.*, 69, 735–753.

[7] Liandi, A.R., Cahyana, A.H., Alfariza, D.N., Nuraini, R., Sari, R.W., and Wendari, T.P., 2024, Spirooxindoles: Recent report of green synthesis approach, *Green Synth. Catal.*, 5 (1), 1–13.

[8] Navaneethgowda, P.V., Bodke, Y.D., Manjunatha, B., and Mussuvir Pasha, K.M, 2022, Benzothiazole-isatin hybrids: Synthesis, characterization, computational and cytotoxic activity studies, *J. Mol. Struct.*, 1266, 133517.

[9] El Malah, T.E., Farag, H., Hemdan, B.A., Abdel Mageid, R.E., Abdelrahman, M.T., El-Manawaty, M.A., and Nour, H.F., 2022, Synthesis, *in vitro* antimicrobial evaluation, and molecular docking studies of new isatin-1,2,3-triazole hybrids, *J. Mol. Struct.*, 1250, 131855.

[10] Mathur, G., and Nain, S., 2014, Recent advancement in synthesis of ısatin as anticonvulsant agents: A review, *Med. Chem.*, 4 (4), 417–427.

[11] Silva, B.V., Esteves, P.M., and Pinto, A.C., 2011, Chlorination of isatins with trichloroisocyanuric acid, *J. Braz. Chem. Soc.*, 22 (2), 257–263.

[12] Adam, M.S.S., Makhlouf, M.M., Alharbi, A., and El-Metwaly, N.M., 2022, Novel isatin-based complexes of Mn(II) and Cu(II) ions: Characterization, homogeneous catalysts for sulfides oxidation,

bioactivity screening and theoretical implementations *via* DFT and pharmacokinetic studies, *J. Mol. Liq*., 351, 118620.

[13] Brandão, P., Marques, C., Burke, A.J., and Pineiro, M., 2021, The application of isatin-based multicomponent-reactions in the quest for new bioactive and druglike molecules, *Eur. J. Med. Chem*., 211, 113102.

[14] Periyasami, G., Karuppiah, P., Stalin, A., Prasad, S., Rahaman, M., Alrehaili, A.A., Al-Dhabi, N.A., and Aldalbahi, A., 2021, Synthesis, absorption, emission and solvatochromic investigation of bioactive isatin tethered acridinedione conjugates, *Mater. Today Commun.*, 26, 102109.

[15] Yagnam, S., Trivedi, R., Krishna, S., Giribabu, L., Praveena, G., and Prakasham, R.S., 2021, Bioactive isatin (oxime)-triazole-thiazolidinedione ferrocene molecular conjugates: Design, synthesis and antimicrobial activities, *J. Organomet. Chem.*, 937, 121716.

[16] Salameh, N., Anastasiou, I., Ferlin, F., Minio, F., Chen, S., Santoro, S., Liu, P., Gu, Y., and Vaccaro, L., 2022, Heterogeneous palladium-catalysed intramolecular C(sp^3)[sbnd]H α-arylation for the green synthesis of oxindoles, *Mol. Catal.*, 522, 112211.

[17] Phan Thi Thanh, N., Dang Thi Thu, H., Tone, M., Inoue, H., and Iwasa, S., 2020, Synthesis of oxindole derivatives *via* intramolecular C–H insertion of diazoamides using Ru(II)-Pheox catalyst, *Tetrahedron*, 76 (43), 131481.

[18] Gao, K., Kou, L., Fu, R., and Bao, X., 2020, Synthesis of 2-(3-arylallylidene)-3-oxindoles via dirhodium(II)-catalyzed reaction of 3-diazoindolin-2-imines with 1-aryl-substituted allylic alcohols and computational insights, *Adv. Synth. Catal.*, 362 (6), 1292–1297.

[19] Muthusamy, S., Balasubramani, A., and Suresh, E., 2019, Boron trifluoride catalyzed divergent synthesis of 3-alkenyl-3-amino-2-oxindoles and spiro-indeneindolones from propargylic alcohols, *Adv. Synth. Catal*., 361 (4), 702–707.

[20] Oktavia, S.H., Cahyana, A.H., Hapsari, M., Yunarti, R.T., and Liandi, A.R. 2021, Synthesis and antimicrobial activity of spiro-oxindole-chromene derivative compounds based curcuminoid and chalcone, *Rasayan J. Chem.*, 14 (3), 1990–1997.

[21] Mohamadpour, F., Maghsoodlou, M.T., Lashkari, M., Heydari, R., and Hazeri, N., 2019, Synthesis of quinolines, spiro[4*H*-pyran-oxindoles] and xanthenes under solvent-free conditions, *Org. Prep. Proced. Int.*, 51 (5), 456–476.

[22] Muthusamy, S., and Ramkumar, R., 2014, Solvent and transition metal-free synthesis of spiro[cyclopropane-1,3-oxindoles] from cyclic diazoamides, *Tetrahedron Lett.*, 55 (47), 6389–6393.

[23] Yaragorla, S., Pareek, A., and Dada, R., 2017, Cycloisomerization of oxindole-derived 1,5-enynes: A calcium(II)-catalyzed one-pot, solvent-free synthesis of phenanthridinones, 3-(cyclopentenylidene)indolin-2-ones and 3-spirocyclic indolin-2-ones, *Adv. Synth. Catal.*, 359 (17), 3068–3075.

[24] Alsaud, N., Shahbaz, K., and Farid, M., 2021, Antioxidant and antibacterial evaluation of Manuka leaves (*Leptospermum scoparium*) extracted by hydrophobic deep eutectic solvent, *Chem. Eng. Res. Des.*, 174, 96–106.

[25] Ilić, D.P., Troter, D.Z., Stanojević, L.P., Zvezdanović, J.B., Vukotić, D.D., and Nikolić, V.D., 2021, Cranberry (*Vaccinium macrocarpon* L.) fruit juice from Serbia: UHPLC-DAD-MS/MS characterization, antibacterial and antioxidant activities, *LWT*, 146, 111399.

[26] Hapsari, M., Cahyana, A.H., Oktavia, S.H., and Liandi, A.R. 2020, Synthesis of spirooxindole-pyrrolizidine compounds using Fe_3O_4-go catalyst and their bioactivity assays, *Rasayan J. Chem.*, 13 (4), 2317–2324.

[27] Yang, J., Chen, J., Hao, Y., and Liu, Y., 2021, Identification of the DPPH radical scavenging reaction adducts of ferulic acid and sinapic acid and their structure-antioxidant activity relationship, *LWT*, 146, 111411.

[28] Kayukov, Y.S., Kayukova, O.V., Kalyagina, E.S., Bardasov, I.N., Ershov, O.V., Nasakin, O.E., and Tafeenko, V.A., 2011, Reactions of 2′-oxo-1′,2′-

dihydrospiro[cyclopropane-1,3′-indole]-2,2,3,3-tetracarbonitriles with nucleophiles, *Russ. J. Org. Chem*., 47 (3), 392–401.

[29] Kumar, N.S., Reddy, M.S., Kumar, S.T.S., Bheeram, V.R., Mukkamala, S.B., and Rao, L.C., 2019, A quantitative and rapid Knoevenagel condensation catalyzed by recyclable zeolite ımidazole frameworks, *ChemistrySelect*, 4 (4), 1188–1194.

[30] Lahari, K., and Sundararajan, R., 2020, Design and synthesis of novel isatin derivatives as potent analgesic, anti-inflammatory and antimicrobial agents, *J. Chem. Sci*., 132 (1), 94.

[31] Jun, M., Fu, H.Y., Hong, J., Wan, X., Yang, C.S., and Ho, C.T., 2003, Comparison of antioxidant activities of isoflavones from kudzu root (*Pueraria lobata* Ohwi), *J. Food Sci.*, 68 (6), 2117–2122.