Synthesis *N*-Benzylisatin Hybrid of 4-Methylumbelliferone

Arif Fadlana), Landaeta Yolga Pratama, Winda Seviani and Heni Masitoh

Department of Chemistry, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember

Kampus ITS Sukolilo, Surabaya 60111, East Java, Indonesia

a) Corresponding author: afadlan@its.ac.id

**Abstract.** Coumarins and their derivatives have the potential for various therapeutic applications. In this study, the coumarin acetohydrazide was produced from the alkylation of 4-methylumbelliferone using ethyl chloroacetate followed by a reaction with hydrazine hydrate. The reaction of acetohydrazide with 1-benzylindoline-2,3-dionafforded the *N*-benzylisatin hybrid of 4-methylumbelliferone, *N’*-(1-benzyl-2-oxoindolin-3-ylidene)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide **11**, in 75% yield. The synthesized compounds were characterized using spectroscopic methods (NMR, MS, IR).

# INTRODUCTION

Coumarin containing six-membered lactone ring and a 2H-1-benzopyran-2-one nucleus is grouped as phenylpropanoid compounds [1,2]. A coumarin with hydroxyl group at the C7 position known as umbeliferone is polar and forms intermolecular hydrogen and intramolecular oxy bonds [3]. Coumarins are found in numerous plant species, especially in the Rutaceae and Apiaceae families [4]. This compound can also be found as warfarin, scopoleptin, armillarisin A, and geiparvarin with medicinal purposes (**FIGURE 1**) [2].



**FIGURE 1.** Structure of (a) coumarin, (b) umbelliferone, (c) warfarin, (d) scopoletin, (e) armillarisin A, and (f) geiparvarin

4-Methylumbelliferona or 7-hydroxy-4-methyl-2H-chromen-2-one (**FIGURE 2a**) contains coumarin skeleton substituted with methyl and hydroxyl groups at C4 and C7, respectively [5]. The modification of 4-methylumbeliferona can be accomplished by alkylation, arylation, and halogenation of the hydroxyl group to obtain derivatives with improved biological activity. Eldeen et al. (2018) described the synthesis of 7-(*p*-chlorobenzoyl)-methyl-4-methylcoumarin (**FIGURE 2b**), 7-(2-(aryl)-1-(*p*-chlorobenzoyl)-vinyl-1-yloxo)-4-methylcoumarin (**FIGURE 2c**), and 7-(2-(bromoaryl)-1-(*p*-chlorobenzoyl)-vinyl-1-yloxo)-4-methylcoumarin (**FIGURE 2d**). The antibacterial assay against *Staphylococcus aureus* as Gram-positive and *Escherichia coli* as Gram-negative indicated that the three compounds had fairly good activity against *S. aureus* bacteria, but showed negative result against *E. coli* bacteria [6].



**FIGURE 2.** Structure of 4-methylumbelliferone and derivatives

Isatin containing nitrogen atom, carbonyl groups, and cyclic rings exhibits various biological and pharmacological activities [7]. The structure of isatin has been extensively modified at N1, C2, C3, and aromatic ring through alkylation, halogenation, nitration, etc. [8,9]. Furthermore, the heterocyclic framework of isatin can be altered into various derivatives with different substituents to influence its biological activity [10].

In the last several years our group studied the synthesis of small molecule active compounds [11-15]. This paper reported the synthesis of 4-methylumbelliferone derivative **11** by molecular hybridization which is a valuable approach to obtain hybrid molecules [16,17]. The hybrid of 4-methylumbelliferone **11** was obtained by reaction of the acetohydrazide of 4-methylumbelliferone **7** and benzylated isatin **10**.

# EXPERIMENTAL

**General**

The reaction progress was monitored by using pre-coated silica gel plates (0.20 mm, 60 F254) (Merck, Darmstadt, Germany). The measurement of melting points were performed on a Fischer John apparatus (Cole Parmer, Illionis, USA) and uncorrected. Infrared (FTIR) spectra (4000-400 cm-1) were recorded on Shimadzu 8400S spectrophotometer (Kyoto, Japan) using KBr disks. The NMR spectra were obtained from a Jeol Delta2 ECA 500 MHz (JEOL Ltd., Tokyo, Japan) (1H, 500 MHz; 13C, 125 MHz) in DMSO-d6 with TMS as internal standard. The mass sepctra (HRMS) were recorded on a ESI Waters LCP Premier XE (Waters, Hertfordshire, UK). Chemicals were supplied from Merck (Darmstadt, Germany) or Sigma Aldrich (Massachusetts, United States) and used as purchased.

**Synthesis 4-Methylumbelliferone 3**

In a round bottom flask, concentrated sulfuric acid (50 mL) in an ice bath (5°C) was mixed with a solution of resorcinol **1** (3.7481 g, 34 mmol) in ethyl acetoacetate **2** (4.5 mL, 34 mmol). After stirring for 60 minutes (TLC monitoring), the mixture was poured into crushed ice. The resulting precipitate was filtered, dried, and dissolved in 1 M aqueous sodium hydroxide. The reprecipitation was carried out by addition of concentrated sulfuric acid and the solid was washed with cold distilled water, dried, and purified by recrystallization from ethanol [18]. The product **3** was isolated a pink solid (3,8228 g, 64%). mp 222-224ºC. FTIR (KBr) v cm-1: 3500, 3119, 2953, 1670, 1606, 1276. 1H-NMR (DMSO-*d6*, 500 MHz): δ 2.36 (d, *J* = 1.0 Hz, 3H), 6.12 (d, *J* = 1.5 Hz, 1H), 6.70‒6.81 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 10.52 (s, 1H). 13C-NMR (DMSO-*d6*, 125 MHz): δ 18.6, 102.6, 110.7, 112.5, 113.3, 127.1, 154.0, 155.3, 160.8, 161.6. HRESIMS [Found: *m*/*z* 177.0567 (M+H)+, calcd for C10H9O3: (M+H)+, 177.0552].

**Synthesis Ethyl 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetate 5**

4-Methylumbelliferone **3** (1.0572 g, 6 mmol) in DMF (25 mL) was stirred at 0°C for 15 minutes. K2CO3 (0.9684 g, 7 mmol) was added to the mixture. After stirring for 30 minutes, ethyl chloroacetate **4** (1.1 mL, 10 mmol) was added and the reaction mixture was further stirred at 0°C for 1 h, followed by 3 hours at room temperature. The reaction mixture was poured into crushed ice and the solid was filtered, dried, and purified by recrystallization from ethanol [19]. The product **5** was obtained as white solid (0,9033 g, 57%). mp 118-120ºC (dec). FTIR (KBr) v cm-1: 3001, 2918, 1764, 1616, 1226. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 1.23 (t, *J* = 7.7 Hz, 3H), 2.40 (d, *J* = 1.0 Hz, 3H), 4.19 (q, *J =* 7.0; 7.5 Hz, 2H), 4.93 (s, 2H), 6.23 (d, *J =* 1.0 Hz, 1H), 6.99-7.00 (m, 2H), 7.70 (d, *J* = 9.5 Hz, 1H). 13C-NMR (DMSO-*d6*, 125 MHz): *δ* 14.5, 18.6, 61.3, 65.4, 102.0, 112.0, 112.8, 114.2, 127.0, 153.8, 155.0, 161.1, 160.5, 168.7. HRESIMS [Found: *m*/*z* 263.0911 (M+H)+, calcd for C14H15O5: (M+H)+, 263.0919].

**Synthesis** **2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide 7**

The compound **5** (0.6554 g, 2.5 mmol) and hydrazine hydrate **6** (0.4 mL, 7.5 mmol) were placed in a round-bottomed flask and dissolved in ethanol (12.5 mL). After a clear mixture was obtained by stirring, reflux was set for 5 hours (TLC monitoring). The solid was filtered, dried, and purified by recrystallization from ethanol. The product **7** was yielded as white solid (0.5887 g, 95%) [20]. mp 246-248ºC. FTIR (KBr) v cm-1: 3331, 3269, 3082, 2958, 1726, 1610, 1284, 1074. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 2.40 (s, 3H), 4.36 (d, *J =* 3.5 Hz, 2H), 4.62 (s, 2H), 6.23 (s, 1H), 6.97-7.02 (m, 2H), 7.70 (d, *J* = 8.5 Hz, 1H), 9.42 (s, 1H). 13C-NMR (DMSO-*d6*, 125 MHz): *δ* 18.6, 67.0, 102.0, 111.9, 113.0, 114.0, 126.9, 153.9, 155.0, 161.2, 160.6, 166.5. HRESIMS [Found: *m*/*z* 249.0878 (M+H)+, calcd for C12H13N2O4: (M+H)+, 249.0875].

**Synthesis** **1-Benzylindoline-2,3-dion 10**

Isatin **8** (0.4475 g, 3 mmol) in a round-bottomed flask was dissolved in DMF (25 mL). After stirring at 0°C for 15 minutes, K2CO3 (0.4859 g, 3.5 mmol) was added, and the mixture was further stirred for 30 minutes. Benzyl chloride **9** (0.57 mL, 5 mmol) was added to the flask and the reaction mixture was stirred again at 0°C for 1 hours and at room temperature for 3 hours. A solid was formed after pouring the reaction mixture into crushed ice which was then filtered, dried, and purified by recrystallization from ethanol [19]. The product **10** was produced as orange solid (0.4383 mg, 62%). mp 154-155ºC. FTIR (KBr) v cm-1: 1750, 1620, 1468. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 4.91 (s, 2H), 6.97 (d, *J =* 8.5, 1H), 7.12 (t, *J =* 7.5, 1H), 7.28 (t, *J =* 7.5, 1H), 7.35 (t, *J =* 7.5, 2H), 7.43 (d, *J =* 7.5, 2H), 7.58 (t, *J =* 7.5, 2H). HRESIMS [Found: *m*/*z* 238.0866 (M+H)+, calcd for C15H12NO2: (M+H)+, 238.0868].

**Synthesis** ***N’*-(1-Benzyl-2-oxoindolin-3-ylidene)-2-((4-Methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide 11**

1-Benzylindolin-2,3-dione **10** (0.1186 g, 0.5 mmol) and 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide **7** (0.1251 g, 0.5 mmol) was dissolved in ethanol (10 mL). Then, glacial acetic acid (0.1 mL) was added, and the reaction mixture was stirred at 78°C for 5 hours. The solid was filtered and washed with cold ethanol [21]. The product **11** was obtained as yellow solid (0.1761 g, 75%). mp 296-297ºC. FTIR (KBr) v cm-1: 3071, 1714, 1610, 1267, 991. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 2.41 (s, 3H), 4.98 (s, 2H), 5.31 (s, 2H), 6.23 (s, 1H), 6.97-7.17 (m, 4H), 7.27-7.39 (m, 6H), 7.71 (d, *J =* 8.5, 1H), 8.18 (s,1H), 11.55 (s, 1H). HRESIMS [Found: *m*/*z* 468.1559 (M+H)+, calcd for C27H22N3O5: (M+H)+, 468.1559].

# RESULTS AND DISCUSSION

Pechmann condensation between phenol and a carboxylic acid or ester containing β-carbonyl is a prevalent method for preparing coumarin and derivatives [22]. Knoevenagel reaction involving carbonyl compounds (aldehydes or ketones) and a base catalyst which also acts as a solvent and Perkin reaction associated with salicylaldehyde to anhydrous carboxylic acid in the presence of a base catalyst are also work for coumarin synthesis. But they show several drawbacks i.e. the solvents are dangerous or carcinogenic and the difficult recovery of the catalysts [23,24]. Pechmann reaction working by transesterification, intramolecular hydroxylation, and dehydration is usually performed in dimethyl sulfoxide, methanol, butanol, dichloromethane, tetrahydrofuran, and dioxane and acidic condition with the addition of concentrated sulfuric acid, phosphorous pentaoxide, trifluoroacetic acid, aluminum chloride catalysts[25,26].The recent development of this reaction entails the use of solvent-free, microwave, ultrasound irradiation techniques [27,28]. This paper utilizes the conventional Pechmann reaction in acidic conditions to produce coumarin.

In the present study, 4-methylumbelliferone **3** was synthesized as a previously reported procedure [18]. The target *N*-benzylisatin hybrid of coumarin **11** was obtained by *O*-alkylation of 4-methylumbelliferone **3** with ethyl chloroacetate **4** [18], followed by a reaction of the product **5** with hydrazine hydrate **6** [29] to give the key intermediate **7**. Next, alkylation of isatin **8** was achieved by using benzyl chloride **9** to afford 1-benzylindoline-2,3-dion **10** [18]. Finally, the coupling of acetohydrazide **7** with compound **10** yielded the *N*-benzylisatin hybrid of 4-methylumbelliferone **11** [18].



**FIGURE 1.** Synthetic pathway of compound **11**. Reagents/conditions: (i) ice bath 60 min, 1M aq NaOH, H2SO4 c, 64%; (ii) ethyl chloroacetate **4**, K2CO3, DMF, 0°C 1h to rt 3h, 57%; (iii) hydrazine hydrate **6**, ethanol, reflux 5 h, 95%; (iv) benzyl chloride **9**, K2CO3, DMF, 0°C 1h to rt 3h, 62%; (v) **10**, glacial acetic acid (cat.), reflux 5 h, 75%.

**FIGURE** 1 depicts the synthetic pathway of the *N*-benzylisatin hybrid of 4-methylumbelliferone **11**. The classical Pechmann condensation between resorcinol **1** and ethyl acetoacetate **2** using concentrated sulfuric acid as a catalyst was utilized to give 4-methylumbelliferone **3** in 64% yield [22]. A solution of resorcinol **1** in ethyl acetoacetate **2** was cautiously added (dropwise) to sulfuric acid in an ice bath. Sodium hydroxide solution was then used for redissolving the formed precipitate. After that, concentrated sulfuric acid was added to the solution to precipitate the product **3**. The next reaction was conversion of coumarin **3** into ester **5** by using ethyl chloroacetate **4**. The hydroxyl group of 4-methylumbelliferone **3** is deprotonated by potassium carbonate and the nucleophilic substitutes the chlorine atom of ester **4** [30]. The reaction was performed in DMF at 0ºC to room temperature and yielded the product ethyl 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetate **5** in 57% yield. Further reaction of ester **5** with hydrazine hydrate **6** afforded the intermediate 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide **7** in 95% yield. The nucleophilic addition by hydrazine hydrate **6** combined with the elimination of alcohol comprises the acyl substitution and gives the product **7** [31]. The alkylation of isatin **8** with benzyl chloride **9** was accomplished in DMF in the presence of K2CO3 to give 1-benzylindoline-2,3-dion **10** (62% yield) [30]. The hybridization of acetohydrazide **7** with 1-benzylindoline-2,3-dion **10** in ethanol with a catalytic of glacial acetic acid gave *N’*-(1-benzyl-2-oxoindolin-3-ylidene)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide **11** as the *N*-benzylisatin hybrid of 4-methylumbelliferone in 75% yield. The reaction of amine **7** and ketone **10** includes a nucleophilic addition catalyzed by acid [32]. The expected signals for the structure of all compounds were found from the spectra of 1H & 13C NMR, FTIR, and HRMS.

The data analysis was then used for elucidating the structure of 7-hydroxy-4-methylcoumarin **3**. The hydroxyl and carbonyl groups in the structure of **3** were clarified by the presence of absorption peaks at 3500 and 1670 cm-1 in the IR spectrum. This was supported by the appearance of a singlet signal at 10.52 ppm in the 1H NMR spectrum of **3** for hydroxyl proton. Signals at 18.6 and 161.6 ppm in the 13C NMR spectrum of **3** correlated with methyl and carbonyl carbon. The HRESIMS spectrum of coumarin **3** revealed the molecular ion peak at m/z 177.0567 (M+H)+ relating to its relative mass (m/z 177.0552). The structure of ethyl 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetate **5** was established by IR, 1H NMR, 13C NMR and MS spectral data. For example, the IR spectrum of **5** contains no absorption peak for hydroxyl group present in the spectrum of precursor **3**, but it has the CO ester absorption bands in the region of 1226–1198 cm-1. The 1H NMR spectrum of **5** then displays a quartet signal at δ 4.19 ppm (*J*=7.0;7.5 Hz, 2H) for methylene protons and its carbons appear at δ 61.3 and 65.4 ppm in the 13C NMR spectrum, respectively. The spectrum also consist of carbons of carbonyl at *δ* 160.5 and 168.7 ppm. The molecular ion peak at m/z 263.0911 (M+H)+ in the mass spectrum corresponding to a relative mass of **5** (m/z 263.0919). Further, the structure of 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide **7** was deduced from the absorption peaks of NH group found at 3269 and 3331 cm-1 in the IR spectrum. The 1H NMR spectrum indicates the singlet signals for protons =NH-NH2 at δ 4.36 and 9.42 ppm. The methylene and carbonyl carbons appeared at 67.0, 160.6 and 166.5 ppm in the 13C NMR spectrum. The molecular ion peak m/z 249.0878 (M+H)+ in the HRESIMS spectrum of coincides with the relative mass of **7** (m/z 249.0875). For **10** and **11**, the carbonyl groups appeare at 1750 and 1714 cm-1, respectively, in the IR spectra. The 1H NMR of **11** comprise of singlet signal at δ 11.55 ppm for NH proton and at δ 4.98 and 5.31 ppm for methylene protons. The relative masses of **11** (m/z 468.1559) fit to the molecular ion peak of **11** (m/z 468.1559, (M+H)+) in the HRESIMS spectrum. The analytical data of **3**, **5**, **7**, **10**, **11** are shown in **TABLE 1** and **TABLE 2**.

Table 1. 1H NMR data of **3**, **5**, **7**, **10**, and **11**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Proton | Chemical Shifts (*δ*) (ppm) | | | | |
| **3** | **5** | **7** | **10** | **11** |
| -CH3 | 2.36 (d, *J*=1.0 Hz, 3H) | 1.23 (t, *J* = 7.7 Hz, 3H)  2.40 (d, *J* = 1.0 Hz, 3H) | 2.40 (s, 3H) |  | 2.41 (s, 3H) |
| -CH2 |  | 4.19 (q, *J =* 7.0; 7.5 Hz, 2H)  4.93 (s, 2H) | 4.62 (s, 2H) | 4.91 (s, 2H) | 4.98 (s, 2H)  5.31 (s, 2H) |
| -ArH | 6.12 (d, *J* = 1.5 Hz, 1H)  6.70‒6.81 (m, 2H)  7.58 (d, *J* = 8.5 Hz, 1H) | 6.23 (d, *J =* 1.0 Hz, 1H)  6.99-7.00 (m, 2H)  7.70 (d, *J* = 9.5 Hz, 1H) | 6.23 (s, 1H)  6.97-7.02 (m, 2H)  7.70 (d, *J* = 8.5 Hz, 1H) | 6.97 (d, *J =* 8.5, 1H)  7.12 (t, *J =* 7.5, 1H)  7.28 (t, *J =* 7.0; 7.5, 1H)  7.35 (t, *J =* 7.5, 2H)  7.43 (d, *J =* 7.5, 2H)  7.58 (t, *J =* 7.5, 2H) | 6.23 (s, 1H)  6.97-7.17 (m, 4H)  7.27-7.39 (m, 6H)  7.71 (d, *J =* 8.5, 1H)  8.18 (s,1H) |
| -NH |  |  | 9.42 (s, 1H) |  | 11.55 (s, 1H) |
| -NH2 |  |  | 4.36 (d, *J =* 3.5 Hz, 2H) |  |  |
| -OH | 10.52 (s, 1H) |  |  |  |  |

Table 2. 13C NMR data of **3**, **5**, and **7**

|  |  |  |  |
| --- | --- | --- | --- |
| Carbon | Chemical Shifts (*δ*) (ppm) | | |
| **3** | **5** | **7** |
| -CH3 | 18.6 | 14.5  18.6 | 18.6 |
| -CH2 |  | 61.3  65.4 | 67.0 |
| -ArC | 102.6  110.7  112.5  113.3  127.1  154.0  155.3  160.8 | 102.0  112.0  112.8  114.2  127.0  153.8  155.0  161.1 | 102.0  111.9  113.0  114.0  126.9  153.9  155.0  161.2 |
| -C=O | 161.6 | 160.5  168.7 | 160.6  166.5 |

# CONCLUSION

The *N*-benzylisatin hybrid of 4-methylumbelliferone, *N’*-(1-benzyl-2-oxoindolin-3-ylidene)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide **11**, was successfully synthesized in 75% yield. The structure of all synthesized compounds was determined by 1H & 13CNMR, FTIR, and HRMS spectroscopies.

# Acknowledgments

The authors gratefully acknowledge financial support from the Institut Teknologi Sepuluh Nopember for this work, under the project scheme of the Publication Writing and IPR Incentive Program (PPHKI) 2026.

# References

[1] M. Lončarić, D. Gašo-Sokač, S. Jokić, and M. Molnar, Biomolecules **10**, 151 (2020).

[2] S. Emami, and S. Dadashpour, Eur. J. Med. Chem. **102**, 611–630 (2015).

[3] V. D. Hiremani, S. Sataraddi, P. K. Bayannavar, T. Gasti, S. P. Masti, R. K. Kamble, and R. B. Chougale, SN Appl. Sci. **2**, 1877 (2020).

[4] E. Küpeli Akkol, Y. Genç, B. Karpuz, E. Sobarzo-Sánchez, and R. Capasso, Cancers **12**, 1959 (2020).

[5] D. V. Chistyakov, A. I. Nikolskaya, S. V. Goriainov, A. A. Astakhova, and M. G. Sergeeva, Int. J. Mol. Sci. **21**, 21 (2020).

[6] I. M. Eldeen, A. R. E. Mahdy, and M. S. Al-Saleem, Mens Agitat. **13**, 18–21 (2018).

[7] M. G. A. Al-Khuzaie, M. M. Fahad, and A. J. Al-Safi, BCS. **1**, 3 (2022).

[8] K. Kaur, D. Utreja, N. K. Dhillon, R. K. Pathak, and K. Singh, Pestic. Biochem. Physiol. **171**, 104736 (2021).

[9] V. Kumar, M. Singh, P. Singh, A. Paul, and K. Lal, J. Mol. Struct. **1312**, 138378 (2024).

[10] J. Rasgania, R. Gavadia, S. Nimesh, L. Loveleen, S. Mor, D. Singh, and K. Jakhar, J. Mol. Struct. **1294**, 136464 (2023).

[11] M. Zulqurnain, M. R. G. Fahmi, A. Fadlan, and M. Santoso, IOP Conf. Ser. Mater. Sci. Eng. **833**, 012057 (2020).

[12] M. Zulqurnain, N. P. Aijijiyah, F. A. Wati, A. Fadlan, A. Azminah, and M. Santoso, J. Appl. Pharm. Sci. **13**, 170-177 (2023).

[13] B. Ardiansah, N. Rohman, M. A. F. Nasution, H. Tanimoto, A. H. Cahyana, A. Fadlan, and T. Ariyani, Chem. Pharm. Bull. **71**, 342-348 (2023).

[14] M. Santoso, M. R. G. Fahmi, Y. S. Kurniawan, T. Ersam, S. Fatmawati, F. Martak, and A. Fadlan, Trends Sci. **18**, 39 (2021).

[15] B. Ardiansah, A. Farhan, A. Firdaus, T. Ariyani, M. A. F. Nasution, A. Fadlan, A. H. Cahyana, E. E. Prabandari, and J. C. Menendez, J. Saudi Chem. Soc. **28**, 101826 (2024).

[16] X.-F. Song, J. Fan, L. Liu, X.-F. Liu, and F. Gao, Arch. Pharm. **353**, e2000025 (2020).

[17] A. Puerta, A. Gonzalez-Bakker, P. Brandao, M. Pineiro, A. J. Burke, E. Giovannetti, M. X. Fernandes, and J. M. Padron, Biochem. Pharmacol. **222**, 116059 (2024).

[18] L. Pan, X. Li, Z. Yan, H. Guo, and B. Qin, Plant Physiol. Biochem. **97**, 272–277 (2015).

[19] A. K. Jain, V. Ravichandran, M. Sisodiya, and R. Agrawal, Asian Pac. J. Trop. Med. **3**, 471–474 (2010).

[20] S. H. Alotabi, Arab. J. Chem. **13**, 4771–4784 (2020).

[21] W. M. Eldehna, M. A. E. Hassab, N. A. Abdelshafi, F. A. Sayed, M. Fares, S. T. Al-Rasood, Z. M. Elsayed, M. M. Abdel-Aziz, E. B. Elkaeed, M. Elsabahy, and N. G. Eissa, Int. J. Pharm. **612**, 121369 (2022).

[22] S. M. EL-Dafrawy, S. M. Hassan, and M. Farag, JMR&T. **9**, 13–21 (2020).

[23] P. Verdía, F. Santamarta, and E. Tojo, Molecules **16**, 4379–4388 (2011).

[24] J. Jumal, and N. Sakinah, Malaysian J. of Sci. H. Tech. **7**, 62–68 (2021).

[25] A. M. Rakkasagi, S. M. Hiremath, S. S. Khemalapure, M. M. Basanagouda, S. S. Kulkarni, V. V. Koppal, and S. C. Jeyaseelan, J. Photochem. Photobiol. A. **444**, 114976 (2023).

[26] S. Li, X. Qi, and B. Huang, Catal. Today **276**, 139–144 (2016).

[27] P. Kalita, and R. Kumar, Micropor. Mesopor. Mat. **149**, 1–9 (2012).

[28] B. Borah, K. D. Dwivedi, B. Kumar, and L. R. Chowhan, Arab. J. Chem. **15**, 103654 (2022).

[29] A. A. Jamaludin, R. D. Siti, H. A. Tatang, H. I. Wiani, and Z. Achmad, Res. J. Chem. Environ. **22**, 91–96 (2018).

[30] T. W. G. Solomons, and C. G. Fryhle, John Wiley dan Sons, Inc. (2011).

[31] F. A. Carey, and R. M. Giuliano, McGraw-Hill. (2017).

[32] J. McMurry, Cengage Learning. (2016).