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Short Note

(*E*)-3-[4-(1*H*-Imidazol-1-yl)phenyl]-1-(3-chloro-4-fluorophenyl)prop-2-en-1-one

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Abstract: Imidazole-containing chalcones have been shown to be effective against *Aspergillus fumigatus*, the pathogenic agent for pulmonary aspergillosis. Claisen-Schmidt condensation of 4-(1*H*-imidazol-1-yl)benzaldehyde with 3′-chloro-4′-fluoroacetophenone using aqueous sodium hydroxide in methanol yielded the novel compound (*E*)-3-[4-(1*H*-imidazol-1-yl)phenyl]-1-(3-chloro-4-fluorophenyl)prop-2-en-1-one in good purity after purification by silica gel column chromatography. This novel compound is suitable for testing the antifungal properties of the combined pharmacophores against *Aspergillus* and other pathogenic fungi.

Keywords: chalcone; synthesis; aldol; pulmonary aspergillosis; imidazole

1. Introduction

Pulmonary aspergillosis (PA) is a category of respiratory illnesses caused by *Aspergillus* that significantly impacts the lives of immunocompromised individuals. *Aspergillus* conidia (asexual spores) are easily dispersed into the air and readily found in the environment, and therefore commonly inhaled by humans [1,2]. Immunocompromised individuals, such as those with cystic fibrosis, neutropenia, and corticosteroid-induced immunosuppression, are unable to induce mucociliary clearance and macrophage and neutrophil defense mechanisms to eliminate *Aspergillus* conidia from the respiratory tract [1]. Mild symptoms of PA include fatigue, difficulty breathing, and hemoptysis, whereas severe symptoms include respiratory failure, neurological conditions, and dissemination to other organs [2]. New classifications of secondary infections like influenza-associated aspergillosis (IAA) and COVID-associated pulmonary aspergillosis (CAPA) exacerbate matters by expanding the demographic beyond the immunocompromised [3,4]. As millions are affected yearly, with mortality rates ranging from 20–90%, antifungal resistant strains of *Aspergillus* are reducing the efficacy of current therapeutic treatments, making it imperative to develop novel medicines to combat this evolving disease [1,5,6].

Chalcones and imidazoles are current pharmacophores used to treat PA that possess a wide range of biological activities such as antidiabetic, anticancer, anti-inflammatory, antifungal, antimicrobial, antioxidant, antiparasitic, antitubercular, analgesic, and anti-HIV activities [7,8]. As antifungal agents, chalcones inhibit enzymes that catalyze the biosynthesis of β(1,3)-glucan and chitin polymers and imidazoles that interfere with ergosterol biosynthesis by inhibiting lanosterol 14α-demethylase—both of which disrupt the structure and function of the fungal cell wall and membrane [9,10]. Recent literature demonstrated that chalcones and imidazoles can be synthesized in novel ways and have the potential to be successful antifungal agents in conjunction [11–13]. Our objective was to synthesize chalcone and imidazole moieties into a novel, dual-pharmacophore compound to target *Aspergillus* as a potential treatment for pulmonary aspergillosis.

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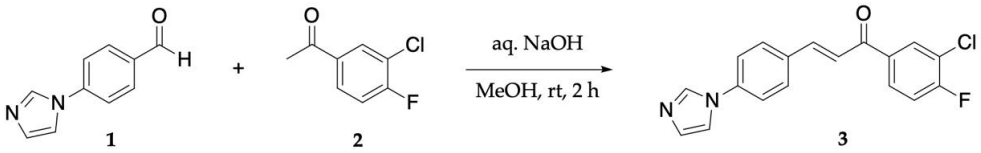
2. Results

(*E*)-3-[4-(1*H*-imidazol-1-yl)phenyl]-1-(3-chloro-4-fluorophenyl)prop-2-en-1-one **3** was synthesized via a Claisen-Schmidt condensation (Scheme 1). The reaction was performed by adding 4-(1*H*-imidazol-1-yl)benzaldehyde **1**, 3′-chloro-4′-fluoroacetophenone **2**, and methanol to a round-bottom flask at room temperature. Aqueous NaOH was added and allowed to stir for 2 h. The crude product was purified by silica gel column chromatography, resulting in a yield of 78%.



Scheme 1. Claisen-Schmidt condensation to form chalcone **3**.

3. Discussion

The purified compound exhibited spectroscopic signals that confirmed the successful synthesis of chalcone **3**. Using Figure 1 as a reference, the ^{1}H-NMR spectrum shows notable confirmatory assignments such as the trans vinylic hydrogens H6 (7.82 ppm) and H7 (7.48 ppm), which were the only two doublets with an integration of one hydrogen. The *J*-values of 15.61 Hz and 16.76 Hz (respective to H6 and H7), represent the trans alkene geometry. H10 was identified as the multiplet at 7.93–7.94 ppm due to its $^{3}J/^{4}J$ couplings to H8 (8.10 ppm), H9 (7.27 ppm), and the fluorine. Furthermore, H8 (8.10 ppm) was identified as the double doublet because of its ^{4}J couplings to both H10 (7.93–7.94 ppm) and F. A noteworthy substantiating ^{13}C-NMR signal is the α,β-unsaturated carbonyl peak (C10) at 187.2 ppm being more upfield than a non-conjugated ketone carbonyl. HSQC was then used to assign all carbons bearing protons.

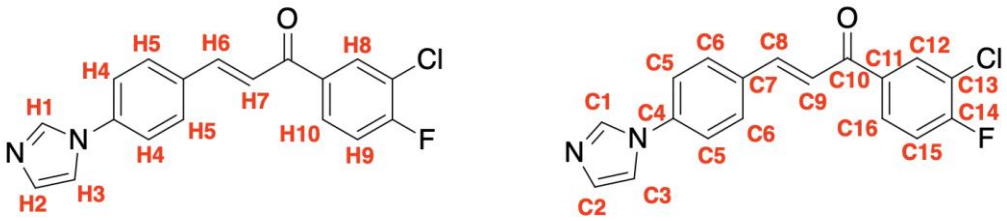


Figure 1. NMR assignment of chalcone **3**.

Assignments from the ^{1}H-NMR and ^{13}C-NMR that were validated by the HSQC were utilized in the HMBC to corroborate other assignments by analyzing the $^{2}J/^{3}J$ cross-peaks. For example, the carbonyl carbon (C10) was established by its cross-peaks to H8 (8.10 ppm), H10 (7.93–7.94 ppm), H6 (7.82 ppm), and H7 (7.48 ppm). Chemical shifts of the protons and carbons also agreed with predicted anisotropic and resonance effects. The aforementioned signals could then be used to substantiate other signals until all assignments were verified. FTIR exhibited a sharp carbonyl stretch at 1663 cm^{-1}, which is indicative of an α,β-unsaturated carbonyl. High-resolution mass spectrometry analysis found a M^{+} ion at 327.0697 m/z compared to a calculated mass of 327.0700.

4. Materials and Methods

All chemicals, reagents, and solvents used were obtained from commercial sources (Sigma Aldrich, St. Louis, MO, USA and Fisher Scientific, Waltham, MA, USA) and used without further purification. Thin layer chromatography (TLC) was used to monitor reactions and performed using aluminum sheets pre-coated silica gel 60 (HF_{254}, Merck, Waltham, MA, USA), and visualized with UV radiation (Fisher Scientific, Waltham, MA, USA). The product was characterized by ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, and

HMBC NMR, IR, HRMS, and melting point analysis. Spectra can be found in the supplementary information.

IR spectra were recorded on a ThermoFisher Nicolet Summit FTIR Spectrometer. The melting point was determined in open capillaries using a Stuart SMP3 melting point apparatus. ^{1}H- and ^{13}C-NMR spectra were collected using a 500 MHz Bruker AV-500 NMR spectrometer. HSQC and HMBC were collected using a 600 MHz Agilent DD2 600 MHz spectrometer. Spectra were referenced to residual $CHCl_3$. Chemical shifts were quoted in ppm and coupling constants (*J*) were recorded in hertz (Hz). High-resolution mass spectrum was acquired using an Agilent Technologies Series 6200 TOF spectrometer.

A solution of aqueous NaOH (0.25 mL, 3.75 mmol, 15 M) was added to a round bottom flask containing 4-(1*H*-imidazol-1-yl)benzaldehyde **1** (0.430 g, 2.50 mmol), 3′-chloro-4′-fluoroacetophenone **2** (0.431 g, 2.50 mmol), and methanol (7.5 mL). The mixture was stirred at room temperature for 2 h (monitored by TLC in 5% methanol/dichloromethane and visualized with UV radiation) during which a yellow-white precipitate formed. The mixture was diluted with water (10 mL) then cooled to 0 °C, and collected in vacuo, washed with an ice-cold solution of 10% methanol/H_2O (2.5 mL). The crude product was purified by silica gel column chromatography using a 3–5% MeOH/DCM gradient to yield pure chalcone **3** as light-yellow crystals (0.6393 g, 1.95 mmol, 78%).

(*E*)-3-[4-(1*H*-imidazol-1-yl)phenyl]-1-(3-chloro-4-fluorophenyl)prop-2-en-1-one (**3**): mp 156–157 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.10 ppm (1H, dd, *J* = 5.26 Hz, H8), 7.95 ppm (1H, s, H1), 7.93–7.94 ppm (1H, m, H10), 7.82 ppm (1H, d, *J* = 15.61 Hz, H6), 7.76 ppm (2H, d, *J* = 8.35 Hz, H5), 7.47 ppm (1H, d, *J* = 16.76 Hz, H7), 7.45 ppm (2H, d, *J* = 7.76 Hz, H4), 7.33 ppm (1H, s, H2), 7.27 ppm (1H, t, *J* = 16.99 Hz, H9), 7.23 ppm (1H, s, H3); ^{13}C-NMR ($CDCl_3$, 125 MHz): 187.2 ppm (1C, s, C10), 160.9 ppm (1C, d, *J* = 257.17 Hz, C14), 143.9 ppm (1C, s, C8), 138.8 ppm (1C, s, C4), 135.3 ppm (1C, s, C1), 135.0 ppm (1C, d, *J* = 3.23 Hz, C13), 133.6 ppm (1C, s, C7), 131.3 ppm (1C, s, C12), 130.8 ppm (1C, s, C3), 130.1 ppm (2C, s, C6), 128.8 ppm (1C, d, *J* = 8.31 Hz, C16), 121.9 ppm (1C, d, *J* = 18.19 Hz, C11), 121.4 ppm (1C, s, C9), 121.4 ppm (2C, s, C5), 117.8 ppm (1C, s, C2), 116.9 ppm (1C, d, *J* = 21.61 Hz, C15); FTIR 3127 cm^{-1} (C-H_{Ar}), 3040 cm^{-1} (C-H_{Ar}), 1663 cm^{-1} (C=O), 1599 cm^{-1} (C=C), 1521 cm^{-1} (C=C); HRMS *m*/*z* calc for $C_{18}H_{12}ClFN_2O$ is 327.0700; found is 327.0697.

Supplementary Materials: The following supporting materials are available online: Copies of the ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC, FTIR, and HRMS spectra.

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Sample Availability: Samples of the compounds are not available from the authors.

References

1. Dagenais, T.R.T.; Keller, N.P. Pathogenesis of *Aspergillus fumigatus* in Invasive Aspergillosis. *Clin. Microbiol. Rev.* **2009**, *22*, 447–465. [CrossRef] [PubMed]
2. Bazaz, R.; Dening, D.W. Aspergillosis: Cause, types and treatment. *Pharm. J.* **2019**, *303*, 7927.
3. Waldeck, F.; Boroli, F.; Suh, N.; Wendel Garcia, P.D.; Flury, D.; Notter, J.; Iten, A.; Kaiser, L.; Schrenzel, J.; Boggian, K.; et al. Influenza-Associated Aspergillosis in Critically-Ill Patients A Retrospective Bicentric Cohort Study. *Eur. J. Clin. Microbiol. Infect. Dis.* **2020**, *39*, 1915–1923. [CrossRef]
4. Marr, K.A.; Platt, A.; Tornheim, J.A.; Zhang, S.X.; Datta, K.; Cardozo, C.; Garcia-Vidal, C. Aspergillosis Complicating Severe Coronavirus Disease. *Emerg. Infect. Dis.* **2021**, *27*, 18–25. [CrossRef]
5. Latgé, J.P.; Chamilos, G. *Aspergillus fumigatus* and Aspergillosis in 2019. *Clin. Microbiol. Rev.* **2019**, *33*, e00140-18. [CrossRef] [PubMed]
6. Tischler, B.Y.; Hohl, T.M. Menacing Mold: Recent Advances in Aspergillus Pathogenesis and Host Defense. *J. Mol. Biol.* **2019**, *431*, 4229–4246. [CrossRef] [PubMed]
7. Salehi, B.; Quispe, C.; Chamkhi, I.; El Omari, N.; Balabib, A.; Sharifi-Rad, J.; Bouyahya, A.; Akram, M.; Iqbal, M.; Docea, A.O.; et al. Pharmacological Properties of Chalcones: A Review of Preclinical Including Molecular Mechanisms and Clinical Evidence. *Front. Pharmacol.* **2020**, *11*, 592654. [CrossRef] [PubMed]
8. Verma, A.; Joshi, S.; Singh, D. Imidazole: Having Versatile Biological Activities. *J. Chem.* **2013**, *2013*, 329412. [CrossRef]
9. Gupta, D.; Jain, D.K. Chalcone derivatives as potential antifungal agents: Synthesis, and antifungal activity. *J. Adv. Pharm. Technol. Res.* **2015**, *6*, 114–117. [CrossRef] [PubMed]
10. Hu, C.; Zhou, M.; Wang, W.; Sun, X.; Yarden, O.; Li, S. Abnormal Ergosterol Biosynthesis Activates Transcriptional Responses to Antifungal Azoles. *Front. Microbiol.* **2018**, *9*, 9. [CrossRef] [PubMed]
11. Bailey, N.; Atanes, A.; Ashburn, B.O. (*E*)-3-(4-chlorophenyl)-1-(2-fluoro-4-methoxyphenyl)-2-propen-1-one. *Molbank* **2021**, *2021*, M1184. [CrossRef]
12. Amato-Ocampo, J.; Carrillo, R.; Kae, H.; Ashburn, B.O. Synthesis and Antimicrobial Evaluation of a Series of Chlorinated Chalcone Derivatives. *IJPPR Hum.* **2018**, *13*, 112–119.
13. Bailey, N.; Ashburn, B.O. (*E*)-3-[4-(1*H*-imidazol-1-yl)phenyl]-1-(4-methylphenyl)prop-2-en-1-one. *Molbank* **2021**, *2021*, M1269. [CrossRef]