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Synthesis and Antibacterial Activity of N-phenyl-3-(4-chlorophenyl)-5-(3,4-dimethoxy-phenyl) pyrazoline

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ABSTRACT. Compound of N-phenyl-3-(4-chlorophenyl)-5-(3,4-dimethoxy-phenyl) pyrazoline was synthesized by cycloaddition reaction. The structure of the product was chracterized by FTIR, ^{1}H-NMR and ^{13}C-NMR spectrometers. The pyrazoline was screened for antibacterial activity using agar diffusion method against *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtillis*, *Shigella flexnerri*, and *Escherichia coli*. The pyrazoline had been synthesized from chalcone with phenylhydrazine to give 52.90% yield. Antibacterial screening showed that pyrazoline was active against selected gram positive bacteria. The pyrazoline was found to exhibits an antibacterial activity and its zone of inhibition/concentration against S. aureus (8.75/300), B. cereus (7.75/1000), B. subtillis (6.50/1000), and E. coli (3.50/300). The result showed that pyrazoline which was subtituted with chloro and methoxy, was able to posse broad spectrum of the tested pathogenic bacteria.

Keywords: chalcone, pyrazoline, antibacterial

INTRODUCTION

Infectious diseases which caused by pathogenic bacteria are still a public health problem. WHO reported that infectious diseases are diseases with a high incidence rate and one of the biggest causes of death (World Health Organization, 2014). Antibiotics are the choice in dealing infectious diseases, especially caused by bacteria. Bacterial resistance to antibiotics was currently increasing and has become a major problem in overcoming infectious diseases in addition to the problems of toxicity and side effects (Murray et al., 2022). The development of new types of antibacterial agent needs to be done to solve this resistance problem. Indonesia is one country which has many natural products. Vanillin and its derivate is one of natural product that can used as basic material aldehyde source.

As a tropical country with numerous natural resources, Indonesia may be able to develop natural resources such as vanillin, fennel oil, clove oil, and patchouli oil as natural igredients that can be employed as basic materials in the production of chalcone compound intermediates. One of the raw materials that can be used is a natural component. Vanillin is used to make chalcone intermediates. Vanillin is a naturally occurring substance found in the Vanilla planifolia plant's fruit (Arya et al., 2021).

Electron-rich nitrogen containing heterocycles such as pyrazolines have been gaining considerable amount of attention due to their important role in drug discovery. Pyrazolines possess a broad spectrum of microbial activities (Matiadis & Sagnou, 2020; Matiadis & Sagnou, 2020; Saroja et al., 2021), antidepressant activity (Popova et al., 2021; Sharma et al., 2021; Fatmayanti et al., 2024; Bhakare et al., 2025), anti-inflammatory and analgesic agents (Cuartas et al., 2020; Ouyang et al., 2021; Yasar & Zaheer, 2021; Shalaby et al., 2023; Stessel et al., 2023), anticancer activity (Matiadis & Sagnou, 2020; Tjitda et al., 2022; Fatmayanti et al., 2024), antitubercular activity (Vaddiraju et al., 2021; Gurav et al., 2022; Kumar et al., 2022; Zala et al., 2025), antioxidant activity (Lakshminarayanan et al., 2020; Mantzanidou et al., 2021; Cahyono et al., 2022; Balamon et al., 2023), anticonvulsant activity (Ray et al., 2023; Chauhan et al., 2024), antimalarial (Tiwari et al., 2021; Andhare et al., 2022), antidiabetic activity (R. S. Kumar et al., 2023; Kafali et al., 2024) and antihepatotoxic activity (Sathiya et al., 2020).

Antibiotics are the first line of defense in the fight against infectious diseases, particularly those caused by bacteria. In addition to the difficulties of toxicity and side effects, Muteeb et al. (2023) says that

bacterial resistance to antibiotics is currently increasing and is a serious difficulty in combating infectious diseases. To combat the problem of antibacterial resistance, new forms of antibacterials must be developed.

Some of pyrazoline derivatives which were subtitued with *para* chloro, *para* nitro and hydroxy in pyrazoline ring C3 position had role increase antimicrobial (Farooq & Ngaini, 2022). The most popular method to synthesize pyrazolines is carried out by under acidic solvent such as using acetic acid (Saleh et al., 2020; Matiadis, 2023; Anita et al., 2024; Novaković et al., 2024). The synthesis of *N*-phenyl pyrazoline of veratradehyde through cyclization reaction from phenylhydazine and α,β-unsaturated ketones in acidic solvent (Mironov et al., 2021; Annes et al., 2023). The electron-donating substituents obtained from veratraldehyde were introduced to evaluate antibacterial activity by *in-vitro* assay.

The reaction of chalcone molecules with 2-phenylhydrazine can be used to make pyrazoline compounds, according to the retrosynthetic strategy. The Claisen-Schmidt condensation reaction can produce chalcone compounds as intermediates from aryl aldehyde compounds with aryl ketones. The Claisen-Schmidt condensation process follows a simple procedure that involves alkaline stirring.

EXPERIMENTAL SECTION

General remarks

All starting materials and solvents were commercially available without further purification. Melting points were measured on a Electrothermal 9100 and are uncorrected. The ^{1}H and ^{13}C-NMR spectra of the obtained compounds were analyzed by JEOL JNMECA 500 MHz (^{1}H) and 125 MHz (^{13}C) spectrometers use internal standard tetramethylsilane. IR spectra (KBr pellets) were recorded by Shimadzu prestige-21 spectrophotometer.

Synthetic procedure and characterization data

Procedure synthesis of chalcones

The aqueous sodium hydroxide (5 mL, 30%) was added into mixture of 5 mmol 4-chholoroacetophenone and 5 mmol veratraldehyde in ethanol and the resulting stirred for 4 h under room temperature. The precipitation was collected and crystallized by from the appropriate solvents.

1-(4-chlorophenyl)-3-(3,4- dimetoxyphenyl)-1-propenon **(3).** Yield: 79.07%; mp: 99 °C; ν_{max} (KBr)/cm^{-1}: 987 (C=C *trans*); 2731&2839 (C-H aldehyde), 1658 (C=O), 1157&1026 (Ar-Cl). ^{1}H-NMR (500 MHz, $CDCl_3$, TMS) δ: 3.93 (3H, s, -OCH_3), 3.94 (3H, s, -OCH_3), 6.89 (1H, d, J = 8.40 Hz, Ar-H), 7.14 (1H, d, J = 1.95 Hz, Ar-H), 7.23 (1H, dd, J = 8.45 & 1.95 Hz, Ar-H), 7.33 (1H, d, J = 15.5 Hz, C=C trans), 7.46 (2H, dd, J = 8.75 & 2.00 Hz, Ar-H), 7.76 (1H, d, J = 15.5 Hz, C=C trans), 7.95 (2H, dd, J = 6.50 & 1.95 Hz, Ar-H). ^{13}C-NMR (125 MHz, $CDCl_3$, TMS) δ: 56.14 (OCH_3), 56.17 (OCH_3), 123.50 & 145.71 (C=C trans), 189.4 (C=O), 110.26, 111.29, 119.59, 127.82, 128.57, 130.01, 136.92, 139.12, 149.44, 151.78 (Ar).

General procedure for synthesis of N-Phenyl pyrazoline (**4**)

A solution of intermediate product (chalcone) 0.76 mmol in acetic acid glacial and phenylhydrazine (0.76 mmol) was refluxed for 4 h. The mixture was poured in crushed ice and cooled in refrigerator for 24 h. The precipitated was filtrated off, washed with aquadest and ethanol, respectively. No further purification was required.

N-phenyl-3- (4-chlorophenyl) -5-(3,4-dimethoxy-phenyl) (4)

Yield 52.9%; as a yellow solid; m.p. 143-144 °C. IR: ν_{max} (KBr)/cm^{-1}: 1597 (C=N), 1242 (C-N), 1465 & 1496 (aromatic C=C), 1381 (C-O-C Methoxy). ^{1}H-NMR (500 MHz, $CDCl_3$, TMS) δ: 3.10 (1H, dd, J = 17.00, 7.80 Hz, CH_2), 3.78 (1H, dd, J = 17.25, 12.35 Hz, CH_2), 3.81 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.20 (1H, dd, J = 12.32, 7.80 Hz, CH), 6.81 (1H, m, ArH), 6.87 (1H, dd, J = 8.45, 1.95 Hz, ArH), 7.08 (2H, d, J = 7.75 Hz, ArH), 7.18 (2H, t, ArH), 7.35, 7.64 (4H, d, ArH). ^{13}C-NMR (125 MHz, $CDCl_3$, TMS) δ: 29.53 (CH_2), 29.87 (CH), 55.83 & 56.04 (CH_3-O), 104.60, 111.52, 121.62, 122.85, 125.70, 127.49, 129.01, 129.16, 131.56, 133.99, 140.07, 144.79, 148.72, 149.30 (Ar), 150.78 (C=N).

Antibacterial activity

The pyrazoline **4** was *in vitro* assayed by cup plate method for antibacterial activity against *Bacillus Subtillis* FNCC 0041, *Bacillus Cerreus* FNCC 0040, *Staphylococcus Aureus* FNCC 0047, *Escherichia Coli* FNCC 0091, *Shigella Flexnerrii* ATCC 12022 obtained from Biotechnology laboratory, Universitas Gadjah Mada Yogyakarta, Indonesia. The tested solutions were prepared by dissolving the compound in DMSO at 100, 300, 500, 1000 μg/mL concentrations. DMSO used as a control test to be inactive. The tested solution series were added into cup of plate and incubated at 37 ºC for 24 h. The inhibition zones were measured.

RESULTS AND DISCUSSION

Chemistry

The synthesis of N-phenyl-3-(4-chlorophenyl)-5-(3,4-dimethoxy-phenyl) (**4**) was accomplished by cyclo-condensation of chalcones **3** (**Figure1**). The chalcones **3** has been synthesized from the halogenated acetophenone and veratraldehyde by Claisen-Schmidt condensation. The structures of chalcones were supported by several spectral. Thus, IR spectra showed the appearing band at 972 cm^{-1} indicated C=C *trans*. The absence bands at 2746 and 2846 cm^{-1} indicated the vibration of C-H aldehyde. ^{1}H-NMR spectra indicated the appearance of duplets signals (~7.20-7.70 ppm). New signals

corresponded to the allylic trans hydrogens by calculating coupling constant (J = 15.5 Hz); corresponding signals were also observed in ^{13}C-NMR spectra.

The compound **4** has been achieved by hetero cyclo-condensation between chalcone **3** and Phenyl hydrazine. The reactions was performed using acetic acid glacial. Cyclization of chalcone to N-Phenyl pyrazoline was proved by important spectral changes. Thus, IR spectroscopy showed the absence of the carbonyl adsorption bands (~1600 cm^{-1}) and of the double bond allylic trans (~972cm^{-1}) and the presence of new adsorption band (~1597 cm^{-1}) of heterocyclic ring. In the ^{1}HNMR spectra, the presence of new signals corresponded to the methylene and methine of hetero ring (~3.80 & ~5.12 ppm). ^{13}CNMR spectra confirmed the absence signals of the carbonyl and allylic trans (~189.5 and ~123.7 & ~ 145.9 ppm) and showed new signals at ~ 43.80 & ~56.48 ppm corresponding to the methylene and methine of hetero ring.

Biology

The compound was tested against Gram-Positive bacteria: *B. cereus* FNCC 0040, *B. Subtillis* FNCC 0041 and *S. Aureus* FNCC 0047 and against Gram-Negative bacteria: *E. Coli* FNCC 0091 and *S. Flexnerii* ATCC 12022 using agar diffusion method. The inhibitor zone values of these compounds against these bacteria are presented in **Table 1** tetracycline as known commercially antibiotic was also tested. The result showed that the compound exhibited antibacterial activities. The best of inhibition zone value was obtained against Gram-Positive bacteria *S. aureus* at 300 μg mL^{-1}. Antibacterial screening showed that chloropyrazoline was active against selected gram positive bacteria. The pyrazoline was found to exhibits an antibacterial activity and its zone of inhibition/concentratio n against *S. aureus* (8.75/300), *B. cereus* (7.75/1000), *B. subtillis* (6.50/1000), and *E. coli* (3.50/300). The result showed that the pyrazoline which was subtituted with chloro and methoxy, was found to exhibits an antibacterial activity.

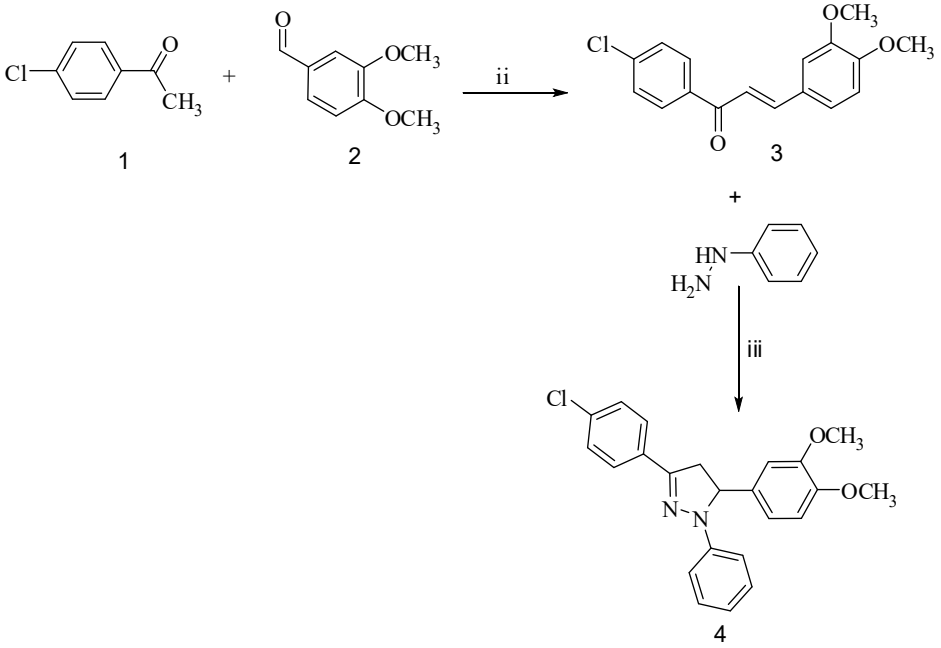

Figure 1. Cyclization of the chalcone (3) with phenylhydrazine in acetic acid glacial form N-phenyl pyrazoline (4). *Reagents and conditions*: (ii) ethanol, NaOH 30%, room temperature. (iii) CH_3COOH, $PhNHNH_2$, refluxed, 4 h.

Table 1. Antibacterial activity of the compound **4**

Compound	Concentration (μg mL^{-1})	Inhibition zone (mm)				
		S. *aureus*	B. *cereus*	B. *subtilis*	E. *coli*	S. *flexnerrii*
4	100	7.50	3.75	-	2.25	-
	300	8.75	2.75	-	3.50	-
	500	6.25	5.50	3.75	2.75	-
	1000	3.75	7.75	6.50	3.25	-
Tetracycline	100	20.75	20.25	20.25	12.25	14.25
DMSO	99.9%	0.75	-	-	-	-

Zone of Inhibition: -: < 1mm (no activity); +:1-4 (weak activity); ++:5-9 (moderate activity); +++:10-15 (strong activity), ++++: > 16 (Very strong activity)

CONCLUSIONS

The product of N-phenyl-3-(4-chlorophenyl)-5-(3,4-dimethoxy-phenyl) pyrazoline **4** was synthesized by cycloaddition reaction. The pyrazoline had been synthesized from derivate vanillin (veratraldehyde) to give 52.90% yield. Antibacterial screening showed that pyrazoline was active against selected gram positive bacteria. The pyrazoline was found to exhibits an antibacterial activity and its zone of inhibition/concentration against *S. aureus* (8.75/300), *B. cereus* (7.75/1000), *B. subtillis* (6.50/1000), and *E. coli* (3.50/300). The result showed that pyrazoline **4** which was subtituted with chloro and methoxy, was able to posse broad spectrum of the tested pathogenic bacteria. of the tested pathogenic bacteria.

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