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Synthesis and Bioactivity of New Pyrazoline Derivative: N-carbamide-3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)pyrazoline

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Abstract

Pyrazoline is an alkaloid class rarely found in nature. The pyrazoline possesses biological activities such as anti-inflammatory, antibacterial, antioxidant and antidiabetic. Pyrazoline has potential as candidate of new drug molecules in pharmacy. This study aims to synthesize new pyrazoline derivative and with the preliminary test through their toxicity and antibacterial activity to know its potential as a new drug candidate. The synthesis of N-carbamide-3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)pyrazoline was conducted from 2',4'-dichloro-4-hydroxy-3-methoxy chalcone and semicarbazide through cyclization by refluxing for 8 hours. It was then characterized by TLC, UV-Vis, ¹H-NMR, ¹³C-NMR and LC-Mass Spectroscopy.

The toxicity test was carried out by Brine Shrimp Lethality Test (BSLT) and antibacterial activity screened by Agar Diffusion method against *Staphylococcus aureus* and *Escherichia coli* bacteria. Based on this study, the LC₅₀ value was 96,96 ppm to *Artemia Salina* Leach which shows its potential as an anticancer agent. Antibacterial activity against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 was classified as moderated-strong inhibition.

Keywords: Synthesis, pyrazoline, n-carbamide, toxicity, antibacterial.

Introduction

The researchers are now making progress towards creating various new drugs. By modifying the molecular structure of compounds to know the biological activity, new compounds can be obtained with higher activity, more selectivity and more stability with lower toxicity or side effects¹. Pyrazoline is a dihydro pyrazoline derivative which is anazole group compound with five heterocyclic structures containing two nitrogen atoms².

Several studies have reported that pyrazoline derivatives have a broad spectrum of biological activity such as anti-inflammatory, antimicrobial, antibacterial, antidiabetic, antioxidant, insecticides and antipyretics³. Some of the common methods used in pyrazoline synthesis are

condensation of chalcone with hydrazine and thiosemicarbazide derivatives under acidic conditions and the addition of cyclic from nitrilamine. α , β unsaturated ketones can be used as precursors in the synthesis of pyrazoline derivatives. The reaction of hydrazine and its derivatives with ketones α , β epoxy is one of the preparative methods to synthesize pyrazoline⁴. 3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl) pyrazoline compound from chalcone was substituted by -Cl, -OCH₃, -OH and -NH groups and hydrazines have antibacterial activity with 7-11 mm inhibition zone, IC₅₀ of 6.21 ppm and LC₅₀ of 80.1 ppm.

In this study the synthesis of N-carbamide-3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)pyrazoline II was conducted from 2',4'-dichloro-4-hydroxy-3-methoxychalcone I with the yield of 91,57% and bioactivity of chalcone produced resulted in the selection of chalcone as an intermediate of pyrazoline II⁶. In the view of the therapeutically potential of new pyrazoline derivatives, this study also evaluated their toxicological profile using *Artemia Salina* Leach and continues with antibacterial activity.

This research was of interest because of the modification of pyrazoline compounds with the presence of substituent amides and ketones in the side chains of heterocyclic pyrazoline rings known for a molecular docking approach. Carbazone groups derived from O and N atoms can interact with certain amino acids, thus proving the existence of biological effects that can be given by the presence of C = O with N-H groups⁷.

Material and Methods

Instruments: The instruments used in this study are UVGL-55 Handheld UV Lamp | 254/365 nm, Dynamica Halo DB-20S UV/Visible Double Beam Spectrophotometer, JEOL Resonance NMR 400 MHz and XevoTM QT of Mass Spectrometer.

Chemicals: The materials used are silica gel 60 GF₂₅₄ (0.2-0.5mm), (Merck) plate Thin Layer Chromatography (TLC) coated with silica gel G 60 F₂₅₄ (Merck), 2,4-dichloroacetophenone (Merck), 4-hydroxy-3-methoxybenzaldehyde (Merck), semicarbazide hydrochloride (Merck), sodium hydroxide (Merck), hydrochloric acid (Merck), ethanol (Merck), methanol (Merck) (Merck), n-hexane (Merck), ethyl acetate (Merck), chloroform (Merck), universal pH indicators (Merck), sodium bicarbonate (Merck), aquadest, *Artemia Salina*

Leach larvae, seawater, yeast, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, Nutrient Agar, NaCl 0.9 %, Whatmann Antibiotic Discs 6mm.

Synthesis of Chalcone (2',4'-dichloro-4-hydroxy-3-methoxychalcone) (I): 2,4-dichloroacetophenone (5mmol) compound dissolved with 10 mL absolute methanol is put into Erlenmeyer flask and stirred until constant and then add with 5 mL of 40% NaOH. 4-hydroxy-3-methoxy benzaldehyde (5mmol) solution was added slowly and constantly mixed for 24 hrs at room temperature and the reaction is controlled by TLC. After 24 hours, 10 mL of cold distilled water and HCl of 10% solution until pH is 7. The product is filtered, washed with cold distilled water and then stored in a desiccator⁶.

Synthesis of Pyrazoline (N-carbamide-3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)pyrazoline) (II):

2', 4'-dichloro-4-hydroxy-3-methoxychalcone (I) (2 mmol) and semicarbazide (2 mmol) are dissolved in 10 mL absolute ethanol. 2', 4'-dichloro-4-hydroxy-3-methoxychalcone (I) (2 mmol) solution is put into the synthesis flask and semicarbazide solution (2mmol) was added slowly. The mixture was refluxed under constant stirring for 8 hours. The reaction is controlled with TLC. After the reaction process is complete, the mixture is cooled, add 10% cold sodium bicarbonate and leave in the refrigerator for 24 hours until a precipitate is formed. The solid separated was filtered and dried. It was purified by column chromatography performed on silica gel (0,2-0,5 mm, Merck) using ethyl acetate and hexane mixture as a mobile phase.

N-carbamide-3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)pyrazoline(II): Yield 29,8%, purplish pink solid ; ¹H-NMR (400 MHz, CDCl₃, ppm) δH (3.31, dd: J = 5.2; 18 Hz; H_{4a}) (3.91; dd: J = 8.4; 13.2 Hz; H_{4b}); (1H, 5.44, dd: J = 5.2; 11.6 Hz; H₅); (1H, 7.44; d: J = 2.4 Hz; H₃'); (1H, 7.28, dd: J = 8.2; 2.2 Hz; H₅); (1H 7.63, d: J = 8.4 Hz; H₆); (6.74; J = 2 Hz; H₂); (1H, 6.86; d: J = 8 Hz; H₅); (2H, 6.76; s; H₆); (3H, 3.87; s; OCH₃); ¹³C-NMR (100 MHz, CDCl₃, ppm) δ 128.5 (C-1'); δ 133.9 (C-2'); δ 127.4 (C-3'); δ 136.3(C-4'); δ 121.3 (C-5'); δ 131.2 (C-6'); δ 130.8 (C-1''); δ 108.7 (C-2''); δ 146.7 (C-3''); δ 137.0 (C-4''); δ 114.7 (C-5''); δ 118.2 (C-6''); δ 156.1(C-3); δ 45.7 (C-4); δ 60.5 (C-5); δ 170.9 (C=O); δ 56.0 (OCH₃); ESI-TOF-MS (positive ion mode); [M+H]⁺ m/z 380.0856; 320.0055; 212.9628; 214.9559; 215.2316; 216.9830; 179.0402; 178.2630; 151.0236.

Toxicity: This test is carried out by making a solution of 1000 ppm N-carbamide pyrazoline (II) in 25 mL. A series of concentrations of 30 ppm, 60 ppm, 90 ppm, 120 ppm and 150 ppm were tested in vials calibrated in 10 mL. The control solution was made with tween 80. After that, 10 *Artemia salina* Leach shrimp larvae were inserted into each vial and add seawater until 10 mL. Tests were carried out five times with the same treatment in each concentration.

Then incubate for 24 hours. The data obtained were analyzed by determining the LC₅₀ value with the Reed and Muench analysis method¹⁰.

Antibacterial activity: This test is based on agar diffusion method and is carried out by making five variations of the concentration of pyrazoline compounds and negative controls (ethanol). Then, inoculate suspension of gram-positive *Staphylococcus aureus* ATCC 25923 and gram-negative *Escherichia coli* ATCC 25922 aseptically in each NA medium in the Petri dish. Paper disk is dipped into each variation of the concentration of the test compound and negative control.

After the NA medium was almost solidified, a paper disk was placed on top of the surface. Tests were carried out three times with the same treatment in each concentration. Then incubate for 24 hours at 37°C. Observe inhibition zones that are formed and measure them.

Results and Discussion

Synthesis of N-carbamide pyrazoline (II) was carried out through 2 steps: the first step was intermediate chalcone (I) and second was cyclization of chalcone (I) and semicarbazide shown in figure 1. Chalcone formation (I) is prepared from the starting material 2,4-dichloroacetophenone and 4-hydroxy-3-methoxy benzaldehyde via condensation for 24 hours with 40% NaOH as a catalyst.

The reaction was observed by TLC with n-hexane: ethyl acetate (8:2) eluent which showed a single spot and compare the Rf value with Rf chalcone compound (I) according to Meilinda's research⁶. From that synthesize N-carbamide pyrazoline (II) with cyclization reaction of chalcone (I) and semicarbazide by refluxing for 8 hours and continue with column chromatography with the gradient system of n-hexane: ethyl acetate eluent.

After that the results of the column were observed by TLC showing single spot with Rf value 0,25 with n-hexane: ethyl acetate eluent obtained in the form of purplish pink solids with a yield of 29,8%.

N-carbamide pyrazoline (II) was characterized using UV-Vis, ¹H-NMR, ¹³C-NMR and LC-Mass Spectroscopy. The UV-Vis spectrum shows maximum absorption at 270.8 nm, 260 nm and 257.2 nm showing a shift in the wavelength to the hypochromic direction when compared with chalcone wavelength that shows a maximum absorption of the typical carbonyl group on the chalcone at 291.6 ppm. This also shows that chalcone (I) has reacted with semicarbazide and formed N-carbamide pyrazoline (II).

¹H-NMR spectrum of N-carbamide pyrazoline (II) showed a typical peak with the ABX system of the pyrazoline ring, namely the proton H_{4a}, H_{4b} and H₅. Proton H_{4a} appears at δ 3.31 ppm with a signal doublet of doublets.

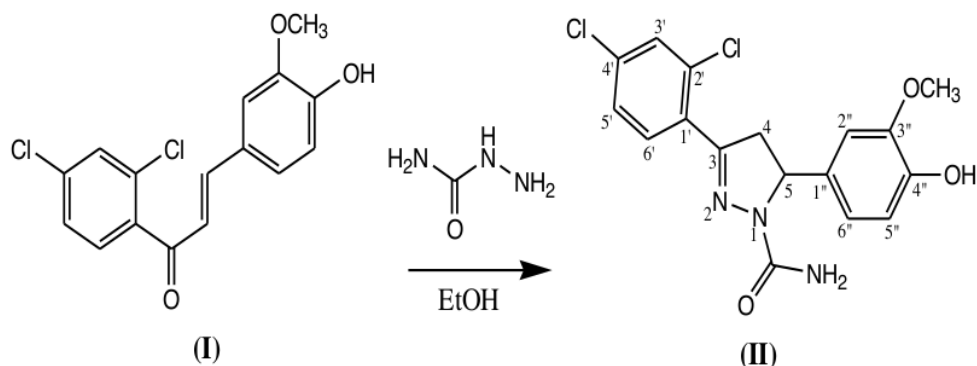


Fig. 1: Synthesis of N-carbamide pyrazoline

This proton has a geminal coupling with proton H4b and a vicinal coupling with proton H5 ($J = 18 \text{ Hz}; 5.2 \text{ Hz}$). Proton H4b appears at $\delta 3.91 \text{ ppm}$ with a signal doublet of doublets by coupling with proton H4a and proton H5 ($J = 13.2 \text{ Hz}; 8.4 \text{ Hz}$). Proton H4a and H4b are on the same carbon atom but have different chemical shifts. Proton H4a is in the upfield area compared to H4b because the proton H4a is more protected (shielding) than H4b (deshielding).

This is because the proton H4a has an equatorial position while the proton H4b has an axial position on the pyrazoline ring so that the interaction of the H4b proton with two nitrogen atoms on the pyrazoline ring is greater. Proton H5 appears at $\delta 5.44 \text{ ppm}$ with a signal doublet of doublets. This proton has a vicinal coupling with protons H4a and H4b ($J = 5.2 \text{ Hz}$ and $J = 11.6 \text{ Hz}$).

^{13}C -NMR spectrum shows that the number of carbon atoms corresponding to the number of carbon atoms synthesized all appearing 17 as carbon atoms. Specific carbon atoms that bind directly to the chloro group are observed at $\delta 133.9 \text{ ppm}$ and $\delta 136.3 \text{ ppm}$. $\delta 146.7 \text{ ppm}$ showed carbon that binds directly to the methoxy group while $\delta 137.0 \text{ ppm}$ indicates carbon binding to the hydroxy group.

In addition, the most important group in the pyrazoline compound seen at $\delta 56.0 \text{ ppm}$ indicated carbon in the OCH_3 . $\delta 45.7 \text{ ppm}$ shows methylene carbon ($-\text{CH}_2$), at $\delta 60.5 \text{ ppm}$ it was observed as carbon methine ($-\text{CH}$). $\delta 156.1 \text{ ppm}$ was observed as carbon that binds N atoms to form imine ($\text{C}=\text{N}$) on the pyrazoline ring. The presence of $\text{C}=\text{O}$ group at $\delta 170.9 \text{ ppm}$ showed more deshielding compared to other carbon.

Based on the NMR experiment of ABX system and NH_2 typical peak from pyrazoline signals were found $\delta 3.02 \text{ ppm}$ (dd, 1H, H4a, $J = 5.1 \text{ Hz}; 18.0 \text{ Hz}$); $\delta 3.76 \text{ ppm}$ (dd, 1H, H4b, $J = 12.0 \text{ Hz}; 18.0 \text{ Hz}$); $\delta 5.36 \text{ ppm}$ (dd, 1H, H5, $J = 5.1 \text{ Hz}; 12.0 \text{ Hz}$); $\delta 6.51 \text{ ppm}$ (s, 2H, N-H). ^{13}C NMR spectra signals in the $\delta 43.0$ and $\delta 59.0 \text{ ppm}$ corresponded to (C-4) and (C-5) carbons. The pyrazoline structure has a similar proton with this experiment and has a substituent $-\text{CONH}_2$

in pyrazoline ring side. This study shows N-carbamide pyrazoline (II) made with the typical ABX system peaks belonging to N-carbamide pyrazoline (II) and not the appearance of the enon group peak in chalcone (I). Evenly a typical peak of NH_2 and OH proton was not found in this experiment. This happens because the solvent used in NMR was CDCl_3 which affects the appearance of NH_2 and OH protons at ^1H -NMR analysis⁹. However, the presence of NH_2 and OH in the pyrazoline structure can be proved by Mass spectroscopy.

Mass analysis of N-carbamide pyrazoline (II) was shown by the mass spectrum with molecular ion peak $[\text{M}+\text{H}]^+ m/z 380.0586$ calculated as $\text{C}_{17}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_3$ with a molecular mass of 379 g/mol and it was a structured target with the addition of H^+ ions. The location of OH and NH_2 groups in Mass Spectroscopy was shown by the fragmentation observed with $[\text{M}-\text{CH}_3\text{NO}_2]^+ m/z 320.0055$ which shows the formation of OH and CONH_2 group radicals. This fragmentation also shows that the synthesized compound forms five-membered rings instead of 6 membered ring, which is a characteristic of pyrazoline compound. This is because the formation of CONH_2 radical was a substituent that binds to the pyrazoline ring.

N-carbamide pyrazoline (II) was tested for toxicity using the Brine Shrimp Lethality Test (BSLT) method. This method was chosen because this method has the advantage of being cheap, fast, easy to process and the results can be trusted⁶. The BSLT method can be used as a preliminary test for compounds that have the potential as anticancer agents.

Figure 2 shows the linearity curve of toxicity test for concentration of N-carbamide pyrazoline in ppm (X-axis) against % mortality (Y-axis) of *Artemia salina* Leach and linear regression analysis done showing equation ($y = 0.677x - 14.21$) and $R^2 = 0.9942$ value obtained for it. The results of the toxicity test of the N-carbamide pyrazoline (II) are based on Reed and Muench analysis having $\text{LC}_{50} 96.96 \text{ ppm}$. From the toxicity assay, N-carbamide pyrazoline (II) has an $\text{LC}_{50} < 200 \text{ ppm}$ that has the potential as an anticancer agent¹⁰⁻¹²

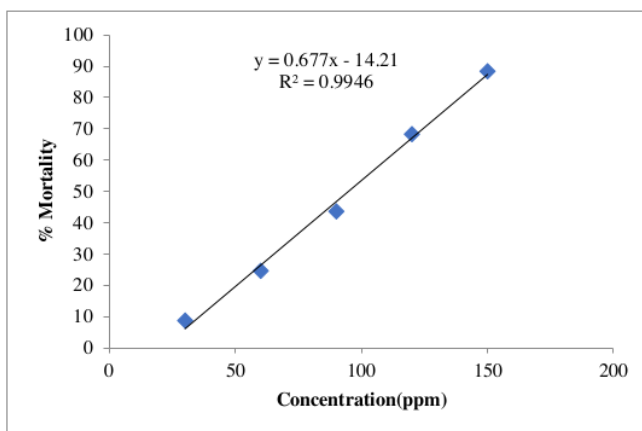


Fig. 2: Linearity Curve % Mortality of N-carbamide pyrazoline (II)

Table 1
Average Diameters of the Inhibition Zone of N-carbamide pyrazoline (II)

Concentration %	Average Diameters of the Inhibition Zone (mm) ± Standard Deviation	
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>
2%	9,97±0,342	11,61±0,224
4%	10,40±0,230	12,04±0,102
6%	11,01±0,061	12,77±0,131
8%	11,42±0,241	13,31±0,138
10%	12,18±0,327	13,89±0,237
Control (-)	0	0

Based on table 1, antibacterial activity of N-carbamide pyrazoline (II) against *Staphylococcus aureus* shows clear zones 11-13 mm and *Escherichia coli* bacteria with clear zones ranging from 9-12 mm. N-carbamide pyrazoline (II) shows better activity against gram-positive bacteria than gram-negative bacteria. The antibacterial activity given by N-carbamide pyrazoline (II) is due to the presence of heterocyclic rings with two nitrogen-based substituents which may be responsible for their biological activity⁵. Also, it is strengthened by N-carbamide pyrazoline (II) substituents (-CONH₂), which can be hydrogen donors and acceptors with bacterial amino acids. This is what causes the pyrazoline compound to have the ability to inhibit the growth of all bacteria used in the antibacterial activity test.

The main difference between gram-positive and gram-negative involves the thickness of the peptidoglycan layer surrounding the plasma membrane. Therefore, the inhibition of *Staphylococcus aureus* bacteria is greater because pyrazoline can penetrate cell walls easily. The difference in the inhibition zone between *Staphylococcus aureus* and *Escherichia coli* was due to the polarity of the N-carbamide pyrazoline (II). The structure of the pyrazoline compound shows the presence of an active NH₂ group that is polar so that it will make it easier to bond to the cell walls of gram-positive bacteria that have cell wall consisting of 90% peptidoglycan capable of polar binding compounds¹³.

Moreover, N-carbamide pyrazoline (II) is dissolved in ethanol which strengthens the binding capacity of positive bacteria. This is also reinforced according to researches. Teichoic acid as a constituent of gram-positive bacterial cell walls is a water-soluble polymer that functions as a positive ion transport to enter and exit.

The presence of an amine group in a positively charged in N-carbamide pyrazoline (II) will easily bind to teichoic acid which has a relatively negatively charged in hydroxide group causing peptidoglycan on the bacterial cell wall to be attracted. This is what causes changes in the permeability of bacterial cell membranes resulting in an imbalance in internal cell pressure and causing leakage of intracellular electrolytes, such as potassium and other low molecular weight proteins such as nucleic acids and glucose. This is what makes bacterial metabolism inhibited so that bacterial growth will be inhibited¹⁴.

Conclusion

Cyclization of 2',4'-dichloro-4-hydroxy-3-methoxycalcone (I) and semicarbazide has successfully yielded N-carbamide-3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl) pyrazoline (II) of 29,8%. Characterization results using UV-Vis, ¹H-NMR, ¹³C-NMR and LC-Mass Spectroscopy showed that synthesized structure was confirmed as the

structured target. N-carbamide pyrazoline has antibacterial activity and toxicity.

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