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Research

Synthesis Characterization, *In Vitro* Antidiabetic and Antioxidant Activity Evaluation of Heteroaryl para chloro N-acetyl pyrazoline derivatives

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Abstract: In medicinal chemistry, pyrazoline structure was found to be an advantaged moiety due to its broad spectrum of pharmacological properties. The study aims on the synthesis, characterization, and in vitro antidiabetic and antioxidant activity evaluation of heteroaryl para chloro N-acetyl pyrazoline derivatives. The synthesis begins with the reaction of previously synthesized heteroaryl chalcone derivatives and hydrazine hydrate in presence of acetic acid using reflux method for 4hrs. The synthesized derivatives were purified using thin layer chromatography, obtained in a good yield and characterized using FT-IR, 1HNMR and 13CNMR spectroscopies. The in vitro antidiabetic was assessed using α-amylase inhibitory assay utilizing acarbose as reference standard. The result indicates that among the synthesized derivatives only compound 3b shows inhibition against α-amylase with IC50 value 90.49 ± 0.19 µM though higher compared to acarbose control standard with IC50 value 34.37 ± 0.14 µM and the result were statistically significant at ($p < 0.05$). Whereas the in vitro antioxidant activity was evaluated using DPPH assay employing ascorbic acid as reference standard. The result shows that all the synthesized heteroaryl para chloro N-acetyl pyrazoline derivatives gives negative or no radical scavenging activity due to the high lipophilic nature of the derivatives. In conclusion the heteroaryl para chloro N-acetyl pyrazoline derivatives were synthesized efficiently and the in vitro antidiabetic and antioxidant activities were assessed; it was found that only compound 3b inhibits α-amylase among the derivatives while none of the derivative show antioxidant activity. Other antidiabetic like α-glucoside and antioxidants like ABS are recommended for the synthesized derivatives in the preceding research.

Keywords: Antidiabetic, Antioxidant, N-acetyl, Pyrazoline.

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1.0 Introduction

A dihydro derivative of pyrazole with one endocyclic double is pyrazoline, which exist in three different forms, as 1-pyrazoline, 2-prazoline, and 3-pyrazoline and are identified based on the position of the endocyclic double bond. Among which 2-pyrazoline has been the more stable and most studied due to its numerous pharmacological properties (Bhattacharjee and Chandra, 2010; Weber et al., 2017; Matiadis and Sagnou, 2020; Shekhar et al., 2024). Pyrazole and its derivatives are subjected to nucleophilic attack at 3 and 5 positions while selectively sustain an electrophilic substitution reaction at 4 positions, as they are aromatic heterocyclic and N-heteroaromatic π-excessive compounds (Karrouchi et al., 2018; Shehu et al., 2026). Pyrazoline have confirmed to be the most useful scaffold for biological activities among the nitrogen five membered containing heterocycles and have attracted the attention of many researchers in the field of organic and medicinal chemistry (Gol et al., 2014). In medicinal chemistry, pyrazoline structure was found to be an advantaged moiety due to its broad spectrum of pharmacological properties and are reported as potential anticancer, antioxidant, antidiabetic, antimicrobial, analgesic, antipyretic, anti-endogenic, and anticoagulant activity (Palanisamy et al., 2015; Peerzade et al., 2020; Sathiya et al., 2020; Çapan et al., 2022; Shehu et al., 2026). Pyrazoline derivatives fused with thiophene moieties was reported to have potent antiproliferation activity as well as inhibitory effect on tubulin polymerization (Yang et al., 2021).

In the same way, an important organic compound that possesses a broad spectrum of biological activities is the α, β-unsaturated ketone, as they are readily accessible starting materials for the synthesis of many heterocyclic compounds and steroids modified with heterocyclic rings (Zheng et al., 2011; Çapan et al., 2022).

In our previous studies, thiophenyl and pyridinyl α, β-unsaturated ketone was synthesized from substituted para chloro acetophenone. Herein we report the synthesis of heteroaryl N-acetyl para chloro pyrazoline derivative and evaluate their antidiabetic inhibitory and antioxidant scavenging activity utilizing α-amylase and DPPH assays.

2.0 Materials and Methods

All chemicals, reagents and solvents used were of analytical grade and obtained from commercial suppliers (Sigma- Aldrich BDH) and were used without further purification. Weighing was carried out on electronic analytical balance. TLC analysis were carried out on silica-gel precoated plate (aluminum-packed silica gel 60 F254 plates), Fourier Transform Infrared (FT-IR) was recorded on SHIMADZU, Japan, were recorded in

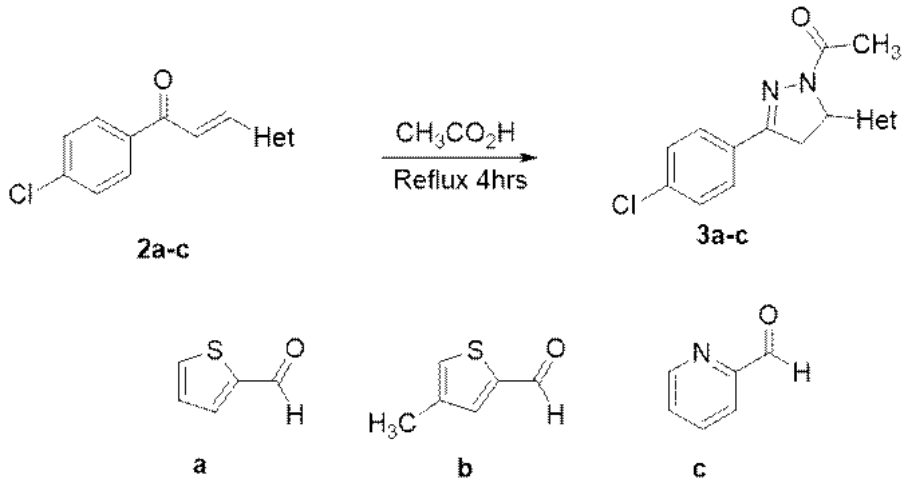
frequency range 3500-400 cm^{-1} on ATR, ^{1}H NMR and ^{13}C NMR spectra were recorded on Brunker 500 MHz and 125 MHz spectrometers (Brunker, USA) in $CDCl_3$ as solvent. Melting points were determined using Stuart melting point apparatus SMP10 (Staffordshire, UK) at temperature range 25 ^{0}C to 300 ^{0}C and were uncorrected, Micro Plate Reader MPR-96 microplate reader (Halo, Dynamica, Australia), SHIMADZU UV-2600 UV-Vis. All reactions were performed in dried glassware under ice. Liquid transfers were performed with standard syringes. Unless otherwise stated, the chemicals and reagents used were of the highest purity. Chemical shifts were referenced to TMS or the residual solvent ($CDCl_3$ = 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C spectroscopy).

2.1 Chemicals and Reagents

4 - Chloro - acetophenone, 2 - Thiophene carboxaldehyde, 3 – Methyl - 2 - thiophene carboxaldehyde, 2 - Pyridine carboxaldehyde, Hydrazine hydrate, Acetic acid, Methanol, Chloroform, n-Hexane, Chloroform D ($CDCl_3$), Dichloromethane, Distilled water, deionize water, Acarbose, porcine pancreatic α-amylase, 3,5-dinitrosalicylic acid (DNSA), sodium hydroxide, anhydrous sodium sulfate Na_2SO_4, sodium potassium tartrate, dimethyl sulfoxide (DMSO), 2,2-diphenyl – 1 - picrylhydrazyl, ascorbic acid.

2.2 General Procedure for the Synthesis of heteroaryl para chloro N-acetyl pyrazoline derivatives 3a-c

To the corresponding (0.7mmol, 0.15g) heteroaryl para chloro chalcone derivatives 2a-c in 6ml acetic acid were added (2.10mmol, 0.1mL, 50%) hydrazine hydrate in dropwise. The mixture was refluxed for 4h, and the reaction progress was monitored with the help of TLC on precoated TLC plates. After completion of the reaction, the mixture was cooled to room temperature and extracted with dichloromethane 20 mL twice to collect the organic layer. Sodium sulphate Na_2SO_4 was added to the extract and filtered off, and the solvent was evaporated using a rotary evaporator. The crude product was recrystallized from ethanol and para chloro N-acetyl pyrazoline derivatives **3a-c** was obtained in good yield.



Scheme 1: Synthesis of heteroaryl p - chloro N-acetyl pyrazoline derivatives 3a-c

2.3 Biological activity

2.3.1 Inhibition of the α-Amylase Enzyme

In this assay, the procedure of Abu Bakar *et al.* was adopted with slight modifications m (Bukhari et al., 2015; Abu Bakar et al., 2020; Saad et al., 2022; Phongphane et al., 2023; Azmi et al., 2024). The DNS reagent was prepared according to the protocol demonstrated previously by Nyambe 2015(Holmes et al., 2015). First, 2 M sodium hydroxide solution was prepared by dissolving 8 g NaOH in 100 mL deionized water. Then, 5.3 M sodium potassium tartrate solution was prepared by dissolving 150 g of sodium potassium tartrate in 100 mL of 2 M sodium hydroxide solution with stirring at 80 °C. Subsequently, 96 mM 3,5-dinitrosalicylic acid (DNS) solution was prepared by dissolving 2.19 g of DNS in 100 mL deionized water. DNS reagent was prepared by mixing 20 mL of 5.3 M sodium potassium tartrate solution, 8 mL of 96 mM DNS solution and 12 mL warm deionized water. As for test samples, A 1000 µM of test samples was prepared in DMSO and diluted to various concentrations (16 – 500 µM) by serial dilution.

In the 96 well microplate, 20 µL of 4U/mL of α-amylase enzyme and 20 µL of the test samples were added into 96 well microplate. Then, the solution was then pre-incubated at 37 °C for 15 min prior to an addition of 20 µL of 1% starch solution followed by a further incubation cycle for 30 min at 37 °C. As the end of the incubation was reached, 20 µL of DNS reagent was added to the 96 well microplate. The 96 well microplate was then placed in a boiling water bath for 15 min at 85 °C. Subsequently, the 96 well microplate was diluted with 150 µL of distilled water in preparation for the absorbance measurement at 540 nm using a microplate reader (Perkin Elmer, Victor X5, Waltham, Massachusetts,

USA). The same procedure was used for positive control, negative control and blank, using acarbose, 1% DMSO and the phosphate buffer solution instead of the test sample, respectively. The inhibitory activity of α-amylase was determined using the following formula:

$$Percentage\ Inhibition\ (\%) = \frac{Abs\ control - Abs\ sample}{Abs\ control} \times 100$$ Equation (1)

2.3.2 Radical scavenging activity using DPPH

The reagents used for this analysis are ascorbic acid (Merck), which serves as a positive control, 2,2-diphenyl-2-picrylhydrazyl (DPPH) and freshly prepared distilled water. The free radical scavenging potency of the samples was assessed by using the DPPH assay (sHarun-Or-Rashid et al., 2023) with some modification. The DPPH solution was prepared by dissolving 3.94 mg of DPPH in 100 mL methanol making a solution of 0.1 mM.

1 mg ascorbic acid were dissolved in 100 mL methanol to 10 µg/mL, the prepared 10 µg/mL were serially diluted to 5 µg/mL, 2.5 µg/mL, 1.25 µg/mL, 0.625 µg/mL and 0.3125 µg/mL.

1 mg of the synthesized compounds were dissolved in 25 mL methanol to make a concentration of 40 µg/mL, the prepared 40 µg/mL were serially diluted to 20 µg/mL, 10 µg/mL, 5 µg/mL, 2.5 µg/mL 1.25 µg/mL.

750 µL of the sample solution at varying concentrations from 1.25 µg/mL to 40 µg/mL was added to 1500 µL of the DPPH solution. The absorbance of the mixed solution was assessed at 517 nm after 30 minutes of incubation at room temperature. While methanol served as a negative control. The same procedure was used for ascorbic acid standard. The capacity to scavenge DPPH was computed using Equation.

$$Percentage\ scavenging\ (\%) = \frac{Abs\ C - Abs\ S}{Abs\ C} \times 100$$ Equation (2)

Where Abs C is the absorbance of DPPH and Abs S is the absorbance of the sample. The concentration of the sample needed to scavenge 50 % of the DPPH radical (IC_{50}) was assessed using the ascorbic acid calibration curve (0–10 µg/mL). All experiments were performed in triplicate.

2.4 Statistical Analysis

All data are expressed as mean ± SD of triplicate experiments. Statistical analysis was performed by one-way analysis of variance (ANOVA) using GraphPad Prism 5.0. Values of $*p < 0.05$ were considered significant.

3.0 Results and Discussion

3.1 Characterization of heteroaryl para chloro N-acetyl pyrazoline derivatives 3a-c

The FT-IR, ^{1}H and ^{13}C NMR was carried out at Natural Product and synthetic Organic (NPSO) research laboratory, University Sains Malaysia USM and the compounds were obtained in good to excellent yield.

3.1.1 1-acetyl-3-(4-chlorophenyl)-5-(thiophen-2-yl)-4,5-dihydro-*1H*-pyrazole 3a: Brown crystals (0.1g, yield 81.3%, m.p 136-139^{0}C);); **IR ν_{max} (ATR, cm^{-1}):** 3122-3071 (C-H aromatic stretching), 2967-2924 (C-H aliphatic stretching), 1660 (C=O stretching), 1588 (C=N/C=C stretching), 1436 (C-C aromatic stretching), 1326 (C-N stretching), 1093 (N-N stretching), 810 (C-Cl stretching), 718 (C-S stretching); **^{1}H NMR ($CDCl_3$, 500MHz, δ, ppm) δ_H:** 7.68 (d, J = 8.6Hz, H-2″, H-6″, CH, 2H), 7.40 (d, J = 8.6Hz, H-3″, H-5″, CH, 2H), 7.18 (d, J = 1.0Hz, H-5′, CH, 1H), 7.01 (d, J = 3.3Hz, H-4′, CH, 1H), 6.92 (dd, J = 3.6Hz, H-3′, CH, 1H), 5.91 (dd, J = 4.0Hz, H-5, CH, 1H), 3.70 - 3.31 (dd, J = 11.5Hz, J = 4.1Hz, H-4, CH_2, 2H), 2.39 (s, H-6, CH_3, 3H); **^{13}C NMR ($CDCl_3$, 125MHz, δ, ppm) δ_C:** 169.0 (C=O), 152.7 (C-3), 144.1 (C-2′), 136.4 (C-4″), 129.8 (C-1″), 129.1 (C-3″, C-5″), 127.8 (C-2″, C-6″), 126.8 (C-3′), 124.8 (C-4′), 124.7 (C-5′), 55.4 (C-5), 42.0 (C-4), 22.0 (C-6).

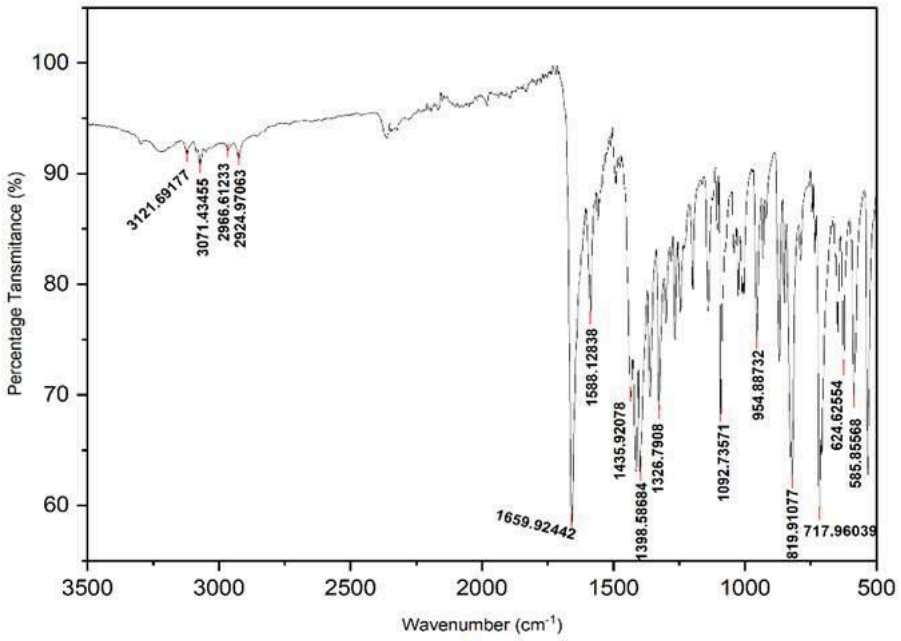


Figure 1: FT-IR spectra of compound 3a

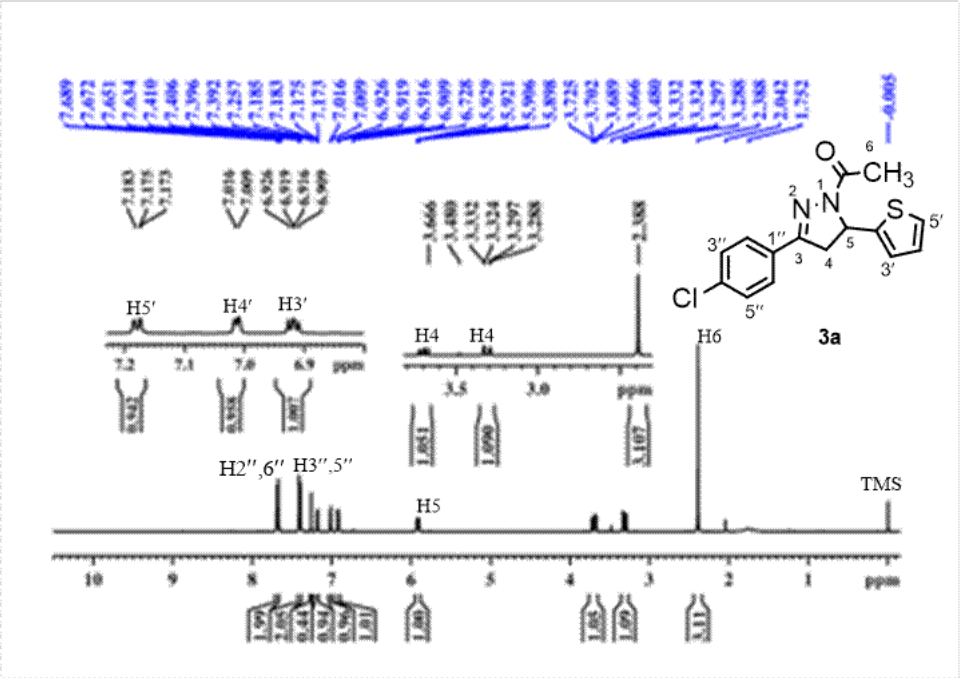


Figure 2: ^{1}H NMR Spectra of compound 3a

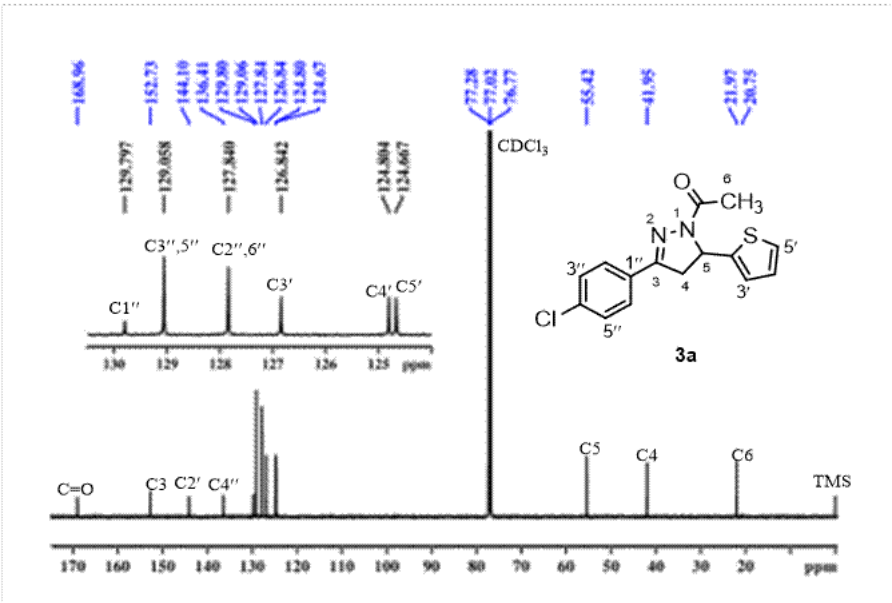


Figure 3: ^{13}C NMR Spectra of compound 3a

3.1.2 1-acetyl-3-(4-chlorophenyl)-5-(3-methylthiophen-2-yl)-4,5-dihydro-*1H*-pyrazole 3b: Yellow powder (0.11g, yield 90.8%, m.p 141-144^{0}C); **IR ν_{max} (ATR, cm^{-1}):** 3122 (C-H aromatic stretching), 2964-2923 (C-H aliphatic stretching), 1661 (C=O stretching), 1587 (C=N/C=C stretching), 1416 (C-C aromatic stretching), 1325 (C-N stretching), 1009 (N-N stretching), 823 (C-Cl stretching), 727 (C-S stretching); **^{1}H NMR ($CDCl_3$, 500MHz, δ, ppm) δ_H:** 7.68 (d, J = 8.6Hz, H-2″, H-6″, CH, 2H), 7.40 (d, J = 8.6Hz, H-3″, H-5″, CH, 2H), 7.04 (d, J = 5.1Hz, H-5′, CH, 1H), 6.74 (d, J = 5.1Hz, H-4′, CH, 1H), 5.86 (dd, J = 4.5Hz, H-5, CH, 1H), 3.70 - 3.20 (dd, J = 11.7Hz, J = 4.6Hz, H-4, CH_2, 2H), 2.38 (s, H-6, CH_3, 3H), 2.31 (s, H-7, CH_3, 3H); **^{13}C NMR ($CDCl_3$, 125MHz, δ, ppm) δ_C:** 168.9 (C=O), 152.5 (C-3), 137.9 (C-2′), 136.3 (C-4″), 134.1 (C-3′), 130.2 (C-4′), 129.9 (C-1″), 129.0 (C-3″, C-5″), 128.8 (C-2″, C-6″), 122.6 (C-5′), 54.2 (C-5), 42.0 (C-4), 22.0 (C-6), 13.9 (C-7).

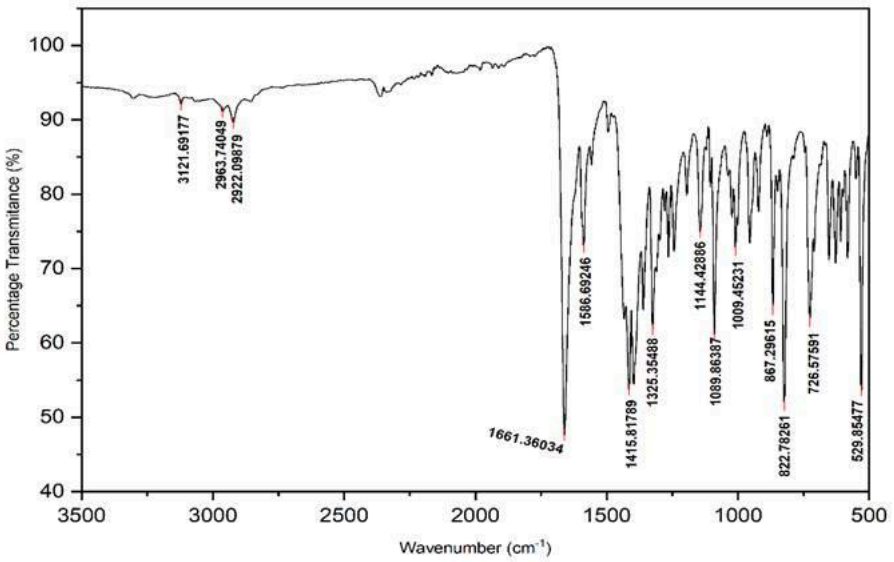


Figure 4: FT-IR spectra of compound 3b

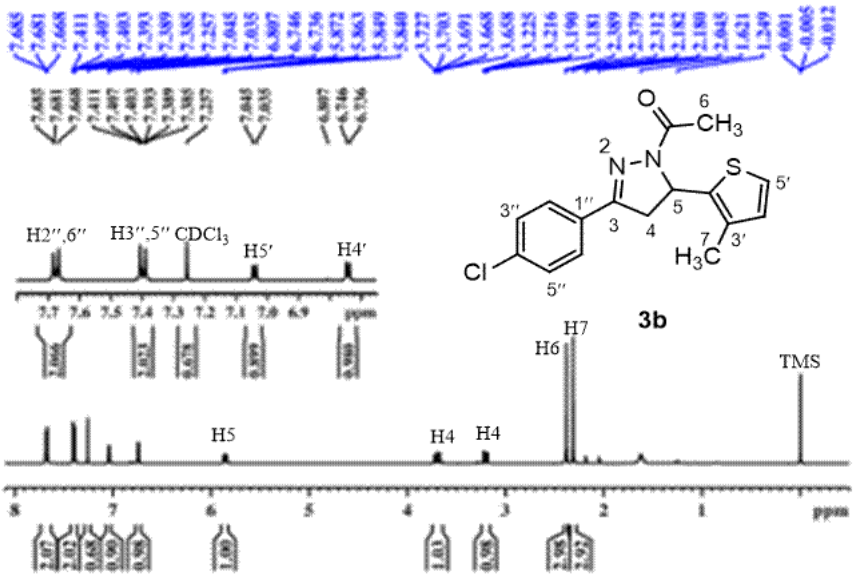


Figure 5: ^{1}H NMR Spectra of compound 3b

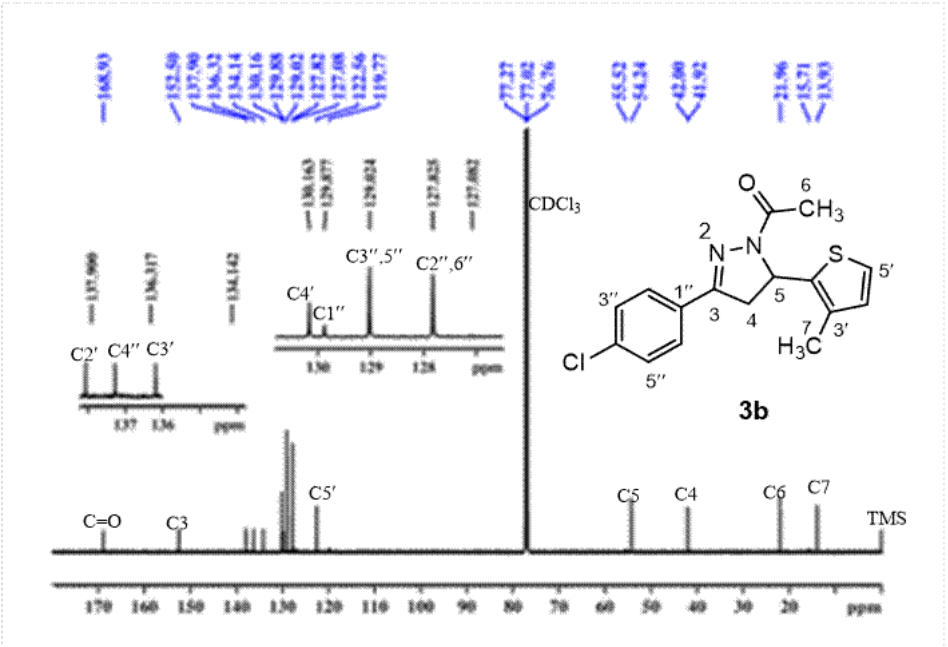


Figure 6: ^{13}C NMR Spectra of compound 3b

3.1.3 1-acetyl-3-(4-chlorophenyl)-5-(pyridin-2-yl)-4, 5-dihydro-*1H*-pyrazole 3c: Brown crystals (0.1g, yield 81.3%, 137-140^{0}C); **IR ν_{max} (ATR, cm^{-1}):** 3059-3008 (C-H aromatic stretching), 2934-2852 (C-H aliphatic stretching), 1647 (C=O stretching), 1590 (C=N/C=C stretching), 1475 (C-C aromatic stretching), 1322 (C-N stretching), 1012 (N-N stretching), 830 (C-Cl stretching); **^{1}H NMR ($CDCl_3$, 500MHz, δ, ppm) δ_H:** 8.55 (d, J = 5.6Hz, H-6′, 1H), 7.69 (d, J = 8.6Hz, H-2″, H-6″, CH, 2H), 7.65 (ddd, H-4′, CH, 1H), 7.38 (d, J = 8.7Hz, H-3″, H-5″, CH, 2H), 7.33 (d, J = 7.8Hz, H-5′, CH, 1H), 7.18 (m, H-3′, CH, 1H), 5.67 (dd, J = 5.3Hz, H-5, CH, 1H), 3.69 - 3.47 (dd, J = 11.9Hz, J = 5.3Hz, H-4, CH_2, 2H), 2.42 (s, H-6, CH_3, 3H); **^{13}C NMR ($CDCl_3$, 125MHz, δ, ppm) δ_C:** 169.3 (C=O), 159.2 (C-3), 153.4 (C-2′), 149.9 (C-6′), 136.8 (C-4′), 136.2 (C-4″), 129.9 (C-1″), 128.9 (C-3″, C-5″), 127.9 (C-2″, C-6″), 122.7 (C-3′), 121.8 (C-5′), 61.2 (C-5), 40.2 (C-4), 21.9 (C-6).

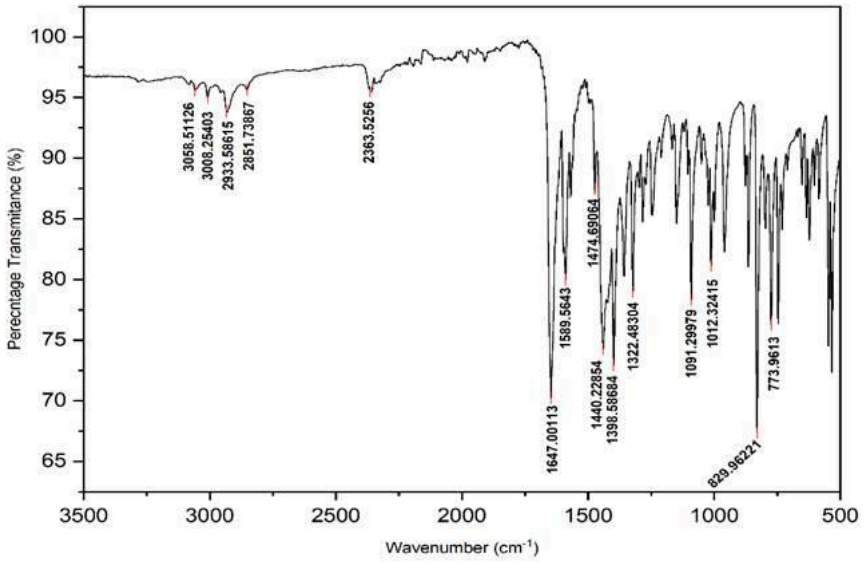


Figure 7: FT-IR spectra of compound 3c

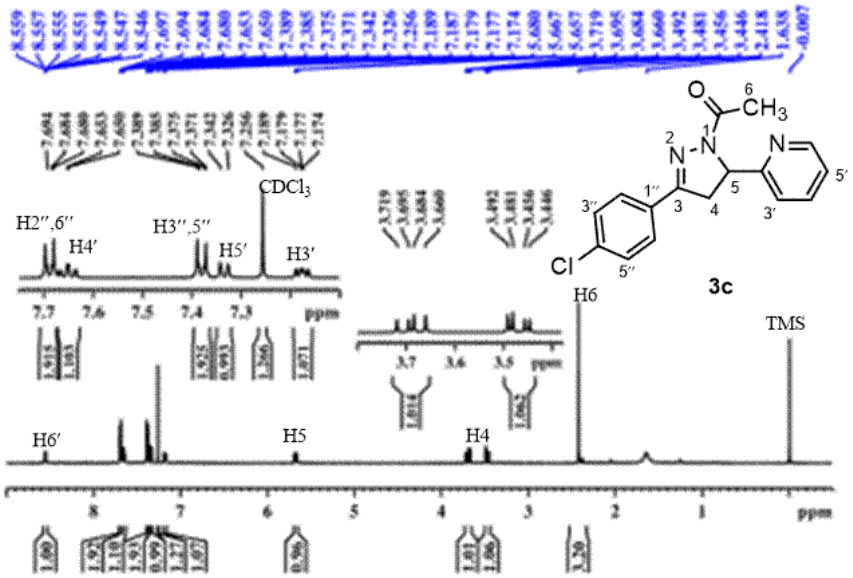


Figure 8: 1H NMR Spectra of compound 3c

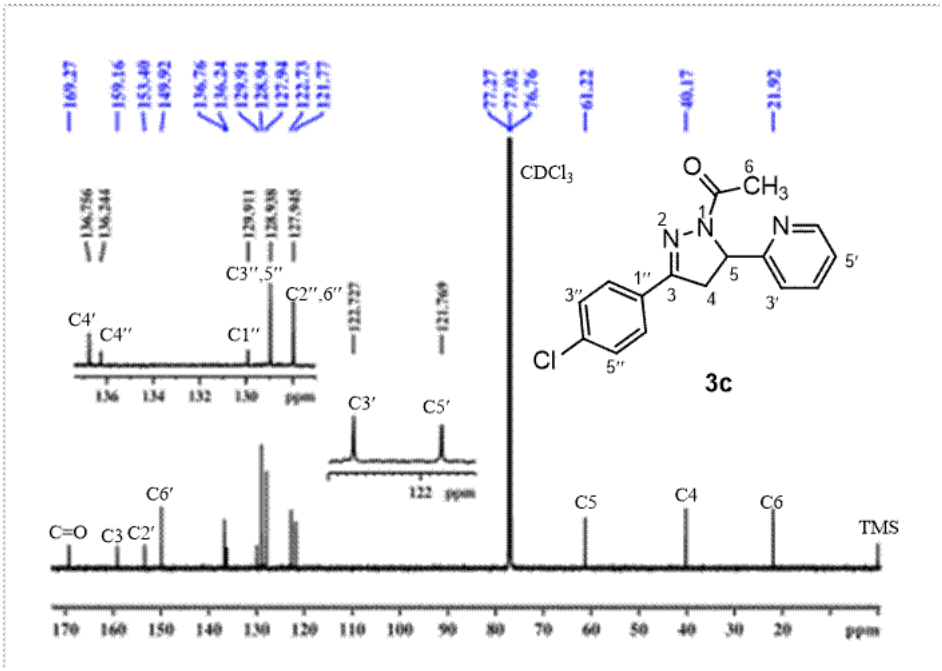


Figure 9: ^{13}C NMR Spectra of compound 3c

3.2 Biological Assay

3.2.1 In Vitro α-Amylase Inhibitory Activity

The *α*-amylase inhibitory activity of the synthesized heteroaryl N-acetyl pyrazoline derivatives was conducted and compared with the acarbose control standard inhibitor. Result of *α*-amylase inhibition were presented in table 1. The compounds synthesized with the control standard acarbose, were evaluated in vitro for *α*-amylase inhibition at different concentrations (16.0-500.0 µM).

Table 1: α - Amylase inhibitory activity (IC_{50} value) of active N-acetyl pyrazoline derivatives

Compounds	IC_{50} (µM)
8b	90.49±0.19
Acarbose (control)	34.37±0.14

Results are expressed as mean ± SD (n=3) of at least three independent experiments

From the results obtained, it can be observed that only compound **3b** with a methyl group at position 3 of the thiophene ring attached to C-5 of the pyrazoline core inhibit *α*-amylase among the synthesized derivatives, though with higher IC_{50} compared to acarbose control standard which implies low activity, with the remaining derivatives show no activity against *α*-amylase. This may be because N-acylation reduces hydrogen donor

ability there by missing either the key hydrogen bond donor or acceptor, so if the enzyme requires the free pyrazoline N as a hydrogen donor and its missing or displaced, then acylated derivatives could lose potency and H-bond geometry may be changed by different electronic effects from 4-chloro substituent. The results were statistically difference compared to the control ($P < 0.05$).

3.2.2 Radical scavenging activity

DPPH radical scavenging assay was used to evaluate the antioxidant activity of the synthesized pyrazoline derivatives by noticing its colour change from purple to yellowish which occurs due to the free radical's reduction. The activity was evaluated at the maximum absorption wavelength of 517nm. The change in colour was mainly due to the quenching of the DPPH radical, which acted as an indicator of the scavenging capability of the tested compounds.

The result shows that all the synthesized heteroaryl para chloro N-acetyl pyrazoline derivatives gives negative or no radical scavenging activity due to the high lipophilic nature of the derivatives, as they tend to aggregate or became insoluble during the assay. These often lead to precipitation or formation of coloured oxidation adducts that interfere with the DPPH reading. The combination of increased lipophilicity by the 4-chloro group and the extra bulk added by the acetyl group make these compounds more likely to clump, fall out of the solution or generate coloured by product that distort the spectral results.

Conclusion

Heteroaryl para chloro N-acetyl pyrazoline derivatives were successfully synthesised by the reaction of previously synthesized chalcones obtained via Claisen Smidt condensation of para chloro acetophenone and three heteroaromatic aldehydes, followed by the reaction of hydrazine hydrate in presence of acetic acid. The synthesized derivatives were purified and characterised by FT-IT, ^{1}H NMR, and ^{13}C NMR spectroscopy. The α-amylase inhibitory activity indicated that, only derivative derived from 3 – methyl - 2 - thiophene show inhibition against α-amylase among the synthesized derivatives, though less activity compared to acarbose control, but the results were statistically difference compared to the control ($P < 0.05$). The radical scavenging activity of the synthesised derivatives were evaluated, and it was found that all the derivatives have no radical scavenging activity against DPPH.

Acknowledgement

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