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Synthesis, Characterization and Antimicrobial Activity of New 4-aminoantipyrine Derivatives Using Ultrasonic Mediation

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Abstract

A straightforward, one-pot, three-component reaction between substituted aromatic aldehydes, 2-naphthol and 4- aminoantipyrine have been used to synthesis a series of new 4-(((2-hydroxynaphthalen-1-yl) (phenyl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one derivatives (A1- A5). This reaction was carried out with zirconyl chloride (ZrOCl2.8H2O) as an efficient catalyst under the condition of ultrasound irradiation. The fact that these derivatives have the potential to act as building blocks in the production of new compounds makes them very essential 4-(1-phenyl-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)- 1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one derivatives (A6, A7 and A8). Likewise, the MCRs that resulted in the formation of hetero cyclic compound (1,3-naphthoxazine) and included 4-aminoantipyrine, formaldehyde, and 2-naphthol in a mole ratio of 1:2:1 have been employed to generate 4- (1H-naphtho [1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1, 5-dimethyl-1,2-dihydro-3H-pyrazol-3-one (A9). This reaction begins with the introduction of ZrOCl2-K2CO3 catalyst system and proceeds through condensation and cyclization. All produced compounds were analyzed through IR, 1H NMR, and 13C NMR spectra data to illustrate each of these distinct structures. Using the broth microdilution and disc diffusion method, the antibacterial and anti-fungal activities of the compounds were evaluated against Gram-positive, Gram-negative, in comparison to conventional medicines (Ampicillin, Ciprofloxacin and Amoxycilline). The synthesized compounds had a wide range of action, with MIC values of 200, 600 and 1000 µg/ml against the investigated bacteria, as determined by microbiological analysis.

Keywords: Multicomponent reaction, 1, 3-Naphthoxazine, One pot synthesis, Ultrasound irritation, Zirconyl chloride.

Introduction

Multicomponent reactions (MCR) have revolutionized organic synthesis by enabling the construction of diverse and intricate organic compounds with remarkable synthetic efficiency and stereo selectivity. Unlike traditional two-component reactions, MCRs offer several advantages, such as the ability to perform one-pot processes and the generation of structurally diverse products[1]. The key feature of MCRs lies in the multiple tandem bond formation processes, which contribute to their synthetic power. By bringing together three or more reactants in a single reaction vessel, MCRs facilitate the simultaneous formation of multiple bonds, leading to the rapid assembly of complex molecular frameworks[2]. One-pot multicomponent reactions (MCR) have gained considerable significance in

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recent years within organic synthesis. These reactions allow for the production of target molecules in a single operation without the need for intermediate compound separation. This streamlined approach reduces reaction duration, energy input, and the consumption of raw materials, resulting in significant time and resource savings[3]. MCRs have now established themselves as a recognized and highly valuable method in organic chemistry.

They provide a rapid and straightforward route for the synthesis of a wide range of molecules, enabling chemists to access diverse compound libraries efficiently. The broad applicability of MCRs has made them a valuable tool in various fields, including pharmaceutical research, material science, and the development of functional organic materials[4].The synthesis of 2-naphthyl-amine derivatives[5], is a typical MCR since these compounds are easily converted to physiologically active derivatives by amide hydrolysis[6]. These advantageous molecules are also capable of being converted into 1,3-oxazines with possibly diverse biological effects[7], including antibacterial, analgesic, anticancer, anticonvulsant, antihypertensive, and antirheumatic characteristics[8]. Due to the importance of 1-amidoalkyl-2-naphthol in biology, medicine, and pharmacology. However, some of their proposed procedures, which include both amino derivatives and hydroxyl groups, suffer from drawbacks such as lengthy reaction duration, toxic and corrosive solvents, high reaction temperatures (greater than 100 ^{o}C), and the requirement to employ microwave or ultrasonic irradiation in certain scenarios. Anti-inflammatory properties are one of 4-aminoantipyrine's many applications in clinical practice. Compounds containing pyrazole nuclei have shown strong anthelmintic and antibacterial action[9], as well as analgesic, antipyretic, and different chemotherapeutic agents, according to research that have been published[10]. The alteration of a potentially useful parent molecule at the molecular level continues to be an important search strategy for innovative medications. Molecular rearrangement is the process of combining distinct groups of molecules that have comparable activities into a single product[11]. This is accomplished by removing or adding new moieties to the parent chemical. 4-Aminoantipyrine is a valuable precursor in the production of pharmaceutical drugs as well as an important component of natural products. 1,3-Oxazines have been an essential component in the production of a wide variety of compounds with important physiological functions[12], including those with anticonvulsant [13], herbicidal, fungicidal[14] and anticancer properties, photochemical transformation and other derivatization of oxazines to other heterocyclic structures and chiral intermediates play a crucial role in the synthesis of a large number of medicinal drugs[15]. For instance, the antimicrobial medication levofloxacin incorporates this structural motif[16]. In recent years, there has been a significant lot of interest in synthesis[17], and as a consequence of active research into the synthesis of oxazines[18,19] , various unique techniques have been established[20]. In the field of synthetic organic chemistry, the use of ultrasonic irradiation is on the rise due to the numerous advantages it offers over more traditional methods. These advantages include shorter reaction times, milder reaction conditions, higher yields, higher selectivity, and cleaner reactions overall[21]. As a consequence of this green technique's reaction being done at a lower external temperature than standard thermal processes, the probability of unexpected reactions is reduced, and the work up is aided by the cleaner reaction.

In the initial phase of this research, it was judged desirable to synthesis derivatives of 4-(((2-hydroxynaphthalen-1-yl) (phenyl) methylene) amino)-1, 5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_1-A_5). Throughout the course of our research on Lewis acid catalyzed organic reactions, we discovered that zirconyi chloride is a catalyst that is both affordable and readily available in commercial settings. This catalyst is capable of catalyzing the one-pot, three-component process in an efficient manner. The one-pot MCR of 2-naphthol, substituted aromatic aldehydes, and 4-aminoantipyrine in the presence of $ZrOCl_2.8H_2O$ at 25 °C and ultrasonic irradiation is described Scheme1. In the second part of this study, we present a technique for synthesizing novel derivatives of 4-(1-phenyl-1H-naphtho[1,2-e][1,3]oxazin-2(3H)-yl)-

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1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_6, A_7 and A_8). This synthetic method involves a one-pot reaction between compounds (designated as A_1, A_3, and A_4) and formaldehyde, using K_2CO_3 as a base and zirconyl chloride as a catalyst, while employing ultrasound in the reaction setup. Scheme 2 illustrates the reaction pathway. The third section of this research explores various pathways to obtain substituted 1,3-naphthoxazine, focusing primarily on the cyclic condensation of 4-aminoantipyrine with formaldehyde and 2-naphthol. This reaction is catalyzed by zirconium chloride, and potassium carbonate is employed as a base under ultrasound irradiation. Scheme 3 illustrates the diverse mechanisms involved. The current combination of $ZrOCl_2.8H_2O$ and K_2CO_3 has proven to be an efficient, environmentally friendly, readily available, and cost-effective catalyst system for the synthesis of 4-(1H-naphtho[1,2-e][1,3]oxazin-2(3H)-yl)-2-phenyl-1,5-dimethyl-1,2-dihydro-3H-pyrazol-3-one.

Materials and Methods

Chemicals and Apparatus

Merck and Aldrich provided high-purity chemical reagents, which were employed without further purification. The melting points of open capillaries were determined using an Electro thermal SPM10 apparatus. The ^{1}HNMR and ^{13}CNMR spectra were collected using a Bruker DRX-400 spectrometer at 400MHz and 100MHz, respectively, with $CDCl_3$ solvent and chemical shifts reported in parts per million (ppm) using TMS as the internal standard. FT-IR spectra of potassium bromide pellets were obtained using an IRaffinity -1s spectrometer in the 400-4000 cm^{-1} region. TLC and UV spectroscopy were used to assess the purity of the chemicals produced. For ultrasonic irradiation, a multi-wave ultrasonic generator (Ultrasonic Cleaner Jaken PS-40A) with a maximum power output of 240W was used. TLC analysis was performed on metal sheets (Merck, Kieselgel 60 F254, Thickness 0.2 mm).

General Procedure for Synthesis of 4-(((2-hydroxynaphthalen-1-yl) (phenyl)methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one Derivatives (A_1 –A_5)[6]

A combination of 4-aminoantipyrine (0.203g, 1 mmol), substituted aromatic aldehydes (0.01mol), and 2- naphthol (0.1441g, 1 mmol) was dissolved in (10 mL) of 95% ethanol in a one pot and irradiated at room temperature in the presence of zirconyl chloride (0.0178g, 0.1 mmol) for (1-5 minutes) As mobile phase, a combination of ethyl acetate and hexane (1:3) was used to monitor the completion of the reaction by TLC. After the reaction was complete, the liquid was poured over ice granules. On a Buchner funnel, the crude product and catalyst were filtered and collected. To get the pure product, the crude product was refined by re-crystallization from hot ethanol.

4-(((2-hydroxynaphthalen-1-yl) (phenyl)methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_1); Pink crystals, yield:473.1mg,(95%) ; mp. 180-181 ℃; IR (KBr, cm^{-1}): 3460 (–OH), 3068-3053 (Ar–H), 2970-2890 (–CH_3) 1681 (C=O),1588(C=N) .^{1}H NMR ($CDCL_3$, ppm) δ 9.80 (s, 1H, -OH), 7.87– 7. 91 (m, 6H, ArH), 7.48 – 7.54 (m, 5H, ArH), 7.3 4 – 7.44 (m, 5H, ArH), 2.51 (s, 3H, -CH_3), 3.17 (s, 3H, N-CH_3).^{13}CNMR ($CDCL_3$, ppm) δ 118.58, 160.87, 118.50, 130.21, 122.9, 129, 124.63, 126.91, 127.8, 128.94, 134.79, 128.55, 129.77, 128.54, 134.51, 152.11, 10.16, 35.86, 124.38, 129.21 [10].

4-(((2-chlorophenyl) (2-hydroxynaphthalen-1-yl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_2); Yellow crystals, yield:458mg,(97%) ;mp. 195-197 ℃; IR (KBr, cm^{-1}): 3460 (–OH), 3068-3053 (Ar–H), 2975-2910 (–CH3) 1680 (C=O), 1570 (C=N),720 (C–Cl). ^{1}H NMR ($CDCL_3$, ppm) δ 10.21 (s, 1H, OH), 7.44– 8.27 (m, 6H, ArH), 7.36 – 7.41 (m, 4H, ArH), 7.32-7.36 (m, 5H, ArH), 2.49 (s 3H, -CH_3), 3.14 (s, 3H, N-CH_3). ^{13}CNMR ($CDCL_3$, ppm) δ 124.49, 154.59, 118, 130.93, 126.66, 127.93, 127.03, 153.59, 129.9, 129.23, 130.90, 139.93, 10.16, 35.72, 127.3.

4-(((2-hydroxynaphthalen-1-yl) (4-methoxyphenyl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_3); Cream crystals, yield:412.3 mg,(88%) ;mp. 174-175°C; IR (KBr, cm^{-1}): 3446 (–OH), 3060-3045 (Ar–H), 2985-2920 (–CH_3), 1667 (C=O), 1570 (C=N). ^{1}HNMR ($CDCL_3$, ppm) δ 9.77(s,1H, –OH), 7.50–7.83 (m,6H, ArH), 7.50-7.83 (m,4H, ArH), 7.01-7.44 (m,5H, ArH), 2.50 (s, 3H, –CH_3), 3.14 (s, 3H, N-CH_3), 3.89 (s,3H, -OCH_3), ^{13}CNMR ($CDCL_3$, ppm) δ 118.85, 161.4, 114.33, 132, 129.44, 122,8, 124.23, 126.77, 129.06, 161.04, 161.47, 130.84, 129.16, 114, 153.59, 151.68, 10.19, 36, 134.9.

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4-(((2-hydroxynaphthalen-1-yl) (o-tolyl) methylene) amino)-1, 5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_4); Purple crystals, yield:407.2 mg,(90%) ;mp. 177-179 ℃; IR (KBr, cm^{-1}): 3566 (–OH), 3066 -3047(Ar–H), 2971-2920 (–CH_3), 1687 (C=O), 1568 (C=N). ^{1}HNMR ($CDCL_3$, ppm) δ 10.13(s,1H, –OH), 7.49–8.15 (m,6H, Ar), 7.43 -7.45 (m,4H, Ar), ,7.20-7.36 (m,5H, Ar) 2.48 (s,3H, –CH_3), 2.58 (s,3H, N-CH_3),3,19 (s,3H, -CH_3).^{13}CNMR ($CDCL_3$,ppm) δ 119, 155.80, 131.81, 126.36, 126, 125.94, 126.97, 129.96, 138.38, 133.70, 135.71, 129.25, 124.45, 160.9, 10.2, 35.83, 135.71, 10.40.

4-(((2-hydroxynaphthalen-1-yl) (3-nitrophenyl) methylene) amino)-1-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_5); Pale orange crystals, yield:474 mg,(98%) ;mp. 221-222 ℃; IR (KBr, cm^{-1}): 3429 (–OH), 3069 -3050(Ar–H), 2975-2870 (–CH_3), 1690 (C=O), 1570 (C=N), 1568(-NO_2). ^{1}HNMR ($CDCL_3$, ppm) δ 9.79 (s,1H, –OH), 7.36-7.52 (m,5H, Ar),7.58–7.62 (m,6H, Ar),7.62 -8.75 (m,4H, Ar), 2.57 (s, 3H, –CH_3), 3.24 (s,3H, N-CH_3), ^{13}CNMR ($CDCL_3$, ppm) δ 121.52, 160.44, 117.67, 129.34, 124.80, 133.93, 152.32, 124.41, 148.74 , 124.21, 129.49 , 153.60, 10.16, 35.53, 139.76.

General Procedure for Synthesis of 1,3-naphthoxazine Derivatives (A_6,A_7 and A_8)[20]

Into a 100 ml round bottle flask dissolved (1mmol) of (A_1, A_3 and A_4) and formaldehyde (0.036g, 1.2 mmol) in DMF (5 ml) irradiated in ultrasonic bath till solution becomes transparent. Then, this solvation was combined with potassium carbonate (0.0138 g, 0.1 mmol) and zirconyl chloride (0.0178g, 0.01 mmol) and irradiated in an ultrasonic bath at 60 ºC for (50-60) minutes; the reaction was analyzed by thin-layer chromatography. Subsequently, the solvent was evaporated at reduced pressure. The residue was extracted with ethyl acetate (20 ml)) after 10 ml of saturated brine was added. The organic layer was washed with 5 ml of brine solution, dried with anhydrous sodium sulfate, and filtered. The filtrate was evaporated at low pressure, and the resulting residue was purified by hot ethanol.

4-(1-phenyl-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)- 1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_6); White crystals, yield:461mg,(86%) ;mp. 190-192 ℃; IR (KBr, cm^{-1}): 3037 (Ar–H)), 2998 (-CH_3), 2941-2930 (-CH_2), 1824 (C=O), 1298 (C-O-C),1246 (C-N-C). ^{1}HNMR ($CDCL_3$, ppm) δ 2.20 (s,3H, –CH_3), 3.01 (s,3H, N-CH_3),5.22 (s,2H, -CH_2),4.81 (s,1H, -CH), 7.12-7.36 (m,5H, ArH),7.63–7.82 (m,6H, ArH),7.37-7.52 (m,5H, ArH). ^{13}CNMR ($CDCL_3$, ppm) δ118.97, 151.81, 123.65, 128.11, 129.11, 128.56, 126.62, 123.45, 80.73, 47.93, 131.14, 128.98, 148.52, 126.31, 10.64, 36.77, 135.03, 126.32.

4-(1-(4-methoxyphenyl)-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_7); White crystals, yield:516 mg,(90%) ;mp. 201-203 ℃; IR (KBr, cm^{-1}): 3051 (Ar–H)), 2995 (–CH_3), 2958-2936 (-CH_2), 1680 (C=O), 1283 (C-O-C),1213 (C-N-C). ^{1}HNMR ($CDCL_3$, ppm) δ 2.20 (s, 3H, –CH_3), 3.27 (s, 3H, N-CH_3), 3.79 (s,3H, O-CH_3),5.22 (s,2H, -CH_2),4.81 (s,1H, -CH), 7.48-7.72 (m,4H, ArH),7.80–7.89 (m,6H, ArH),7.25-7.44 (m,5H, ArH). ^{13}CNMR ($CDCL_3$, ppm) δ 118.64, 153.40, 126.90, 124.90, 129.89, 81.73, 57.93, 134.64, 129.23, ,160.61, 135.02, 10.13, 35.70, 135, 124.50, 55.7.

4-(1-(o-tolyl)-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)- 1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_8); Pale yellow crystals, yield:487 mg,(88%) ;mp. 188-189 ℃; IR (KBr, cm^{-1}): 3045 (Ar–H)), 2994 (–CH_3), 2952-2930 (-CH_2), 1685 (C=O), 1290 (C-O-C),1250 (C-N-C). ^{1}HNMR ($CDCL_3$, ppm) δ 2.19 (s, 3H, –CH_3), 2.90 (s, 3H, N -CH_3), 3.01 (s,3H, 2-CH_3),5.22 (s,2H, -CH2),4.80 (s,1H, -CH), 7.43 -7.47 (m,4H, Ar),7.48-8.03 (m,6H, Ar),7.26--7.38 (m,5H, Ar). ^{13}CNMR ($CDCL_3$, ppm) δ118.96, 153.40, 128.12, 128.56, 126.37, 123.57, 126.63, 121.23, 129.10, 80.73, 47.73, 118.64, 129.23. 129.1, 134.64, 10.63, 36.66, 36.72.

General Procedure for Synthesis of 4-(1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1,5-dimethyl-1,2-dihydro-3H-pyrazol-3-one (A_9)[16]

In a 100 ml round bottle flask, 1,4-dioxane (15 ml), formaldehyde (0.06g, 2 mmol), and potassium carbonate (0.0138 gm,0.1 mmol) were added. The mixture was irradiated in an ultrasound bath for 1 minute until a clear solution appeared, and then 4-aminoantipyrine (0.203g, 1 mmol) and zirconyl chloride (0.0178g, 0.01 mmol) were added. After adding 2-naphthol (0.1441g, 1 mmol), the mixture was irradiated in an ultrasonic bath at 40^0Cfor thirty minutes. TLC was used to monitor the progression of

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the reaction, and the insoluble potassium carbonate was filtered to separate. The filtrate was concentrated under vacuum to acquire raw materials, then dried and recrystallized from ethanol to produce white crystals. (363 mg, 97.8%), m.p (178-179 ºC); IR (KBr, cm^{-1}): 3045 (Ar–H)), 3010 (–CH_3), 1289 (C-O-C), 1230 (C-N-C), 2920 (-CH_2), 1645 (C=O). ^{1}HNMR ($CDCL_3$, ppm): 2.20 (s,3H, –CH_3), 3,01 (s,3H, N -CH_3), 5.22 (s,2H, O -CH_2-),4.81 (s,2H, N –CH_2-),7.68-7.84 (m,6H, Ar),7.35-7.54 (m,5H, Ar). 13CNMR (CDCL3, ppm) δ118.96, 151.80, 128.56, 128.11, 126.34, 123.54, 126.62, 121.23, 129.10, 80.73, 47.93, 163.17, 10.63, 36.75, 131.14, 128.99, 135.01.

Microbiology Test

Antimicrobial Analysis

Using agar well diffusion and minimum inhibitory concentration techniques, the antibacterial activity of chemically synthesized materials was evaluated against Gram-positive, Gram-negative bacteria and fungus, Staphylococcus aureus, Escherichia coli, and Candida albicans.

Preparing the Inoculum

The discovered bacterial pathogens were cultivated for 24 hours at 37 °C on nutrient agar. The culture was then inoculated into nutrient broth and kept undisturbed at 4ºC. The turbidity of the culture was corrected to 0.5 McFarland standards after extracting overnight-grown cultures from the broth. Around 0.2 mL of cultured microorganisms at a concentration of 105–107 CFU/mL and an optical density of 0.1 at 600 nm were added to 20 mL of sterile nutritive broth.

Agar Well Diffusion Assay

The Agar well diffusion test was performed as prescribed[22]. Plates of Mueller Hinton agar were consistently cultivated using a sterile cotton swab from a saline solution containing bacterial and fungal strains that had been inoculated. The dishes were placed on the bench in order to absorb the surplus liquid. A sterile, eight-millimeter-diameter cork borer was used to create 4-millimeter-deep wells in the sealed agar media. The wells of the plates were filled with one hundred and fifty µl of each chemical substance generated at three distinct concentrations (1000, 600, and 200 µg/µL) using a micropipette. Positive controls [Ciprofloxacin (5 µg/µL) and negative controls [sterile distilled water] were evenly dispensed into each well. The plates were incubated for 24 hours at 37°C. Using a caliper, the diameters of each sample's inhibitory zones, including the wells, were measured in millimeters, and the findings were recorded appropriately. All tests were performed in duplicate Table .2.

Minimum Inhibitory Concentration (MIC)

The Minimum Inhibitory Concentration (MIC) was measured using the broth micro dilution technique. To assess the lowest concentration of antibacterial activity[23], cultures isolated for 18–24 hours were employed and their turbidity was compared to the 0.50 McFarland standards. The 96-well polystyrene microtiter plate was used to detect the MIC against the microorganisms tested. Thereafter, 100 L of manufactured chemical compounds with varied concentrations (1,600, and 200) g/mL were pipetted onto a series of microtiter plate wells. For comparison, 50 L of standardized inoculum suspensions were pipetted into each test well, whereas the negative control well contained just broth and the positive control well included microorganisms in addition to broth. The well of the microtiter plate was vortexed and incubated at 37°C for 24 hours. As comparison to the control wells, the clear wells had the lowest concentration of synthetic chemical substances that suppressed bacterial growth Table .3.

Results and Discussion

In the first approach, we present a unique methodology for synthesizing a sequence of 4-(((2-hydroxynaphthalen-1-yl) (3-phenyl) methyl) amino) 1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one derivatives (A_1-A_5) employing a catalytic quantity of $ZrOCl_2$ in the presence of ultrasound. (Scheme 1) depicts the one-pot synthesis, in a matter of seconds; 88–98% of the product was extracted by easy and routine procedures. All of the derivatives were supported by spectral data. The IR (Fig. 1,4,7,10,13,16,19,22,25) ^{1}HNMR (Fig. 2,5,8,11,14,17,20,23,26 and ^{13}CNMR (Fig.3,6,9,12,15,18,21,24,27) spectra corroborate the hypothesized structures. In the case of naphthol, the

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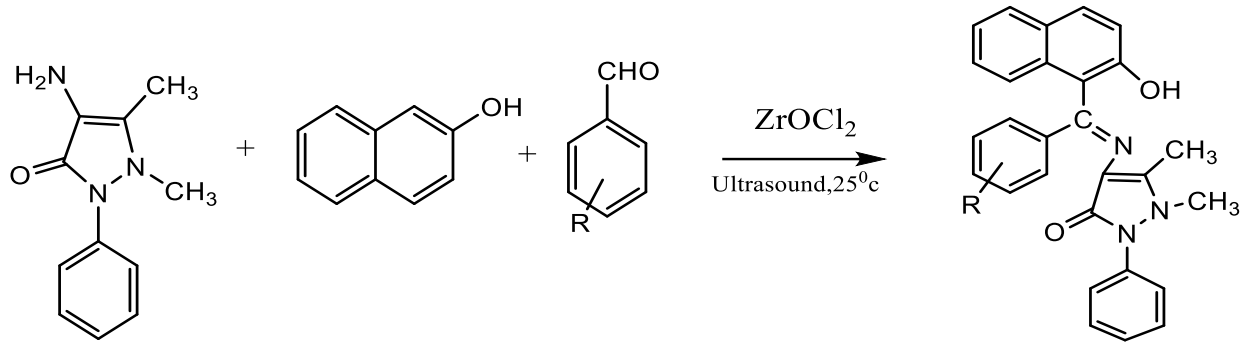
infrared spectra of these compounds show a unique OH group stretch between (3429 and 3566) cm-1, while the infrared spectra of pyrazolone show (C=O) stretching vibrations between (1667 and 1690) cm^{-1}. From the stretching frequencies between 1568 and 1599 cm^{-1}, the existence of C=N in the skeleton was established. The ^{1}HNMR results of all compounds indicate the existence of a singlet between 2.40 and 2.57ppm for the $–CH_3$ moiety. The occurrence of a singlet with a frequency ranging from 2.58 to 3.44ppm was cited as evidence of the presence of -N-CH_3 in the skeleton in the spectral data. The existence of a singlet with a frequency between 9.77 and 10.21 ppm suggests that there is O–H present in the ring. All of the isolated compounds have ^{13}CNMR spectra that display aliphatic–CH_3 signals, and all of the other signals are carbons. This is in line with the structures that they have been assigned.



R=H,2-Cl,4-OMe,2-Me, 3-NO_2 (A_1-A_5)

Scheme1. Synthesis of 4-(((2-hydroxynaphthalen-1-yl) (phenyl)methyl) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one derivatives (A_1-A_5) from 2-naphthol, 4-minoantipyrine and substituted benzaldehyde

In our early experiments, we explored the optimization of reaction conditions for the ecologically benign synthesis of 4-(((2-hydroxynaphthalen-1-yl) (3- nitro phenyl) methyl) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_5). First, 3-nitrobenzaldehyde, 4-aminoantipyrine, and 2-naphthol were selected as model substrates for the synthesis. Utilizing the $ZrClO_2.8H_2O$ catalyst system, it was then determined how to optimize the catalyst for the production of 1e. Different amounts of catalyst were investigated (0.05-0.25 mmol), as shown in Table .1, when the quantity of $ZrOCl_2$ grew from 0.05 mmol to 0.1 mmol, product yields increased; however, there was no discernible increase in product yields when the amount of $ZrOCl_2$ was raised to 2.5 mmol. The optimal quantity of $ZrOCl_2$ for subsequent reaction at 25^{o}C under ultrasonic stimulation for 1 minute was determined to be 0.1mmol.

Table 1. Optimization of reaction conditions in the synthesis of 4-(((2-hydroxynaphthalen-1-yl) (3-nitrophenyl) methyl) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_5)

Entry	Catalyst (mmol)	Temperature (°C)	Time (min.)	Yeild %
1	0.05	25	0.5	85
2	0.1	25	1	98
3	0.08	25	1	95
4	0.1	30	1	96
5	0.15	25	2	95
6	0.15	35	1	83
7	0.2	25	2.5	88
8	0.2	40	1	77
9	0.25	25	3	84
10	0.25	45	2	73

By optimizing the reaction conditions, we have broadened the scope of the approach to encompass several aldehydes with electron-donating or electron-withdrawing substituent. In each case, aromatic aldehydes containing substituent-carrying electron-withdrawing groups reacted well and generated large yields of the desired products. A process was hastened using ultrasound, which lowered energy

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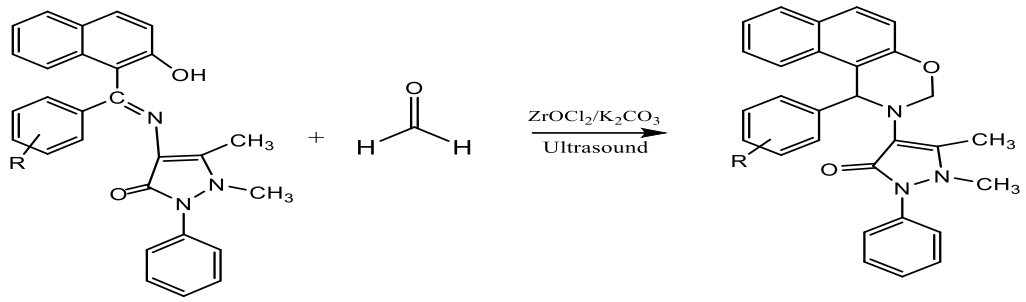
usage. In the second part of this approach novel compounds1,3-naphthoxazines (A_6, A_7 and A_8) were synthesized by the reaction of 4-(((2-hydroxynaphthalen-1-yl) (phenyl)methyl) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one derivatives (A_1, A_3 and A_4) with formaldehyde in DMF as solvent, in the presence of (K_2CO_3 and $ZrOCl_2$) Due to the low temperature, short reaction times (55-60 min), excellent yields (except for 2-chloroaldehyde and 3-nitroaldehyde), inexpensive, non-toxic, and commercially available catalyst, and simple work-up, this procedure is useful for the synthesis of a variety of 1,3-naphthoxazines under ultrasound irradiation Scheme 2.

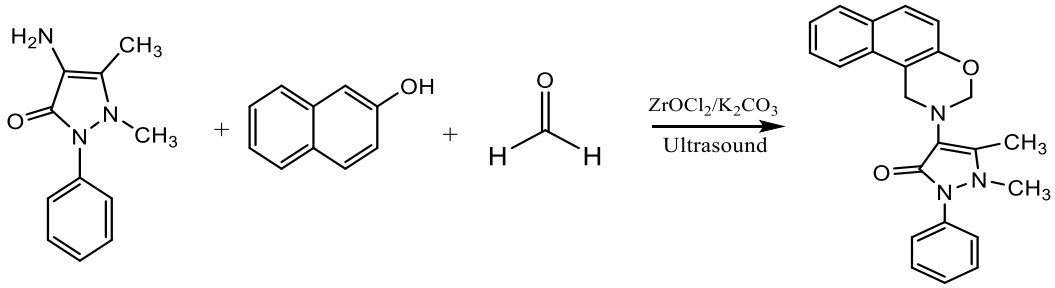


R=H, 4-OMe, 2-Me (A_6, A_7, A_8)

Scheme2. Synthesis of 4-(1-phenyl-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)- 1, 5-dimethyl-2-phenyl-,2-dihydro-3H-pyrazol-3-one derivatives (A_6, A_7, A_8).

Hence, we commenced our experiments with the reactions of 4-(((2-hydroxynaphthalen-1-yl) (3- nitro phenyl) methyl) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_5) and 4-(((2-chlorophenyl) (2-hydroxynaphthalen-1-yl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_2). These reactions did not generate the desired 1,3-naphthoxazine when performed using formaldehyde in the presence of DMF as a solvent for (60-80) minutes at 60°C under ultrasonic irradiation. The absence of a vibration peak for the CH_2 and CH groups of the oxazine ring in the infrared and ^{1}H NMR spectra of these compounds confirms that they are unreactive towards this reaction. All structures (A_6, A_7 and A_8) of the synthesized compounds have been validated by IR, ^{1}H NMR, and ^{13}C NMR, which have indicated the proper structure of the produced products.

To expand the preparative usefulness and wide applicability of this multicomponent reaction, formaldehyde, 4-aminoantipyrine, and 2-naphthol were used in a molar ratio of 1:2:1. Good yields of the matching 1,3-naphthoxazine were achieved Scheme.3 A possible mechanism for this cyclic condensation resulted in the elimination of two molecules of water indicating the formation 1,3-naphthoxazine the reaction processes are illustrated in scheme.4.



(A_9)

Scheme 3. Synthesis of1,5-dimethyl-4-(1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A_9)

$ZrOCl_2.H_2O$ have been found to be an efficient and recyclable Lewis acid catalyst for the synthesis of 1,3-naphthoxathine, a Zr(IV) -based Lewis acid acts as an electron pair acceptor to increase the reactivity of substrate, 4-aminoantipyrine reacts with formaldehyde to form formaldehyde-aminoantipyrine quickly (scheme4, step1), then formaldehyde-aminoantipyrine reacts with 2-

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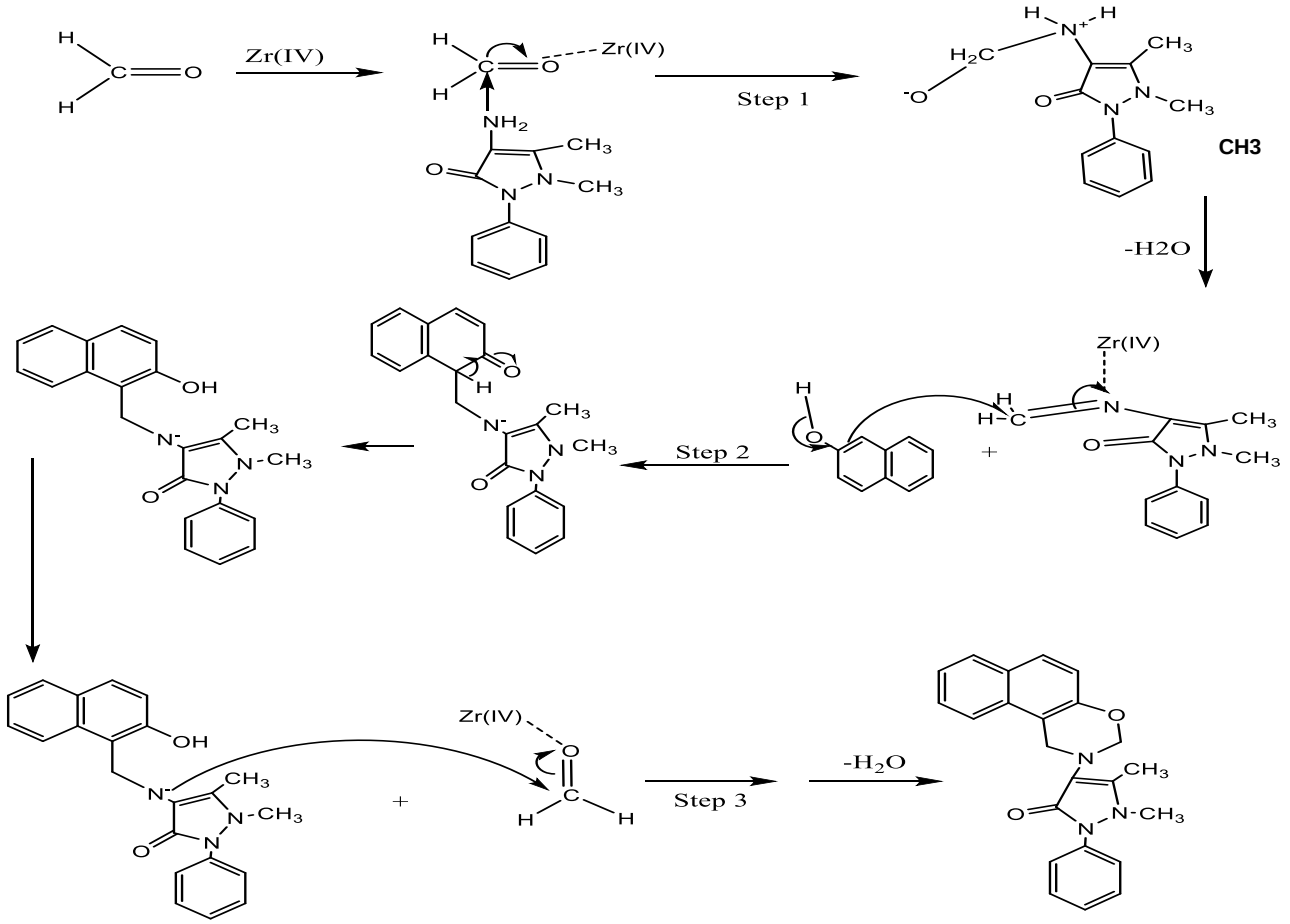
naphthol to obtained 4-((hydroxymethyl)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (mannich base) slowly (scheme 4, step2), 1,3-naphthooxazine is procured finally via the dehydration reaction between mannich base and formaldehyde scheme.4,step3. Here we report that the cyclic condensation of 4-((hydroxymethyl)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one to naphthoxazines can be performed in high yields and short reaction times by using combine catalyst ($ZrOCl_2.8H_2O$ / K_2CO_3), under ultrasound irradiation.



Scheme 4. The mechanism Reaction in the 1, 3-naphthoxazine synthesis from 2-naphthol, 4-aminoantipyrine and formaldehyde

We explain herein an effective and economical method for preparing 1,3-naphthoxazine (A_9). Using FT-IR, ^{1}H-NMR, and ^{13}CNMR, this novel chemical was studied. The IR spectrum revealed the disappearance of two stretching bands at (3373 cm-1) and (3262 cm^{-1}) corresponding to the $–NH_2$ group and the –OH group of 2-naphthol, as well as two other characteristic bands at (1289 cm^{-1}) and (1230cm-1) corresponding to the (C-O-C) and (C-N-C) stretching vibrations, indicating the cyclic grouping to obtain oxazine. The ^{1}HNMR spectrum exhibits chemical shifts (ppm) at 5.22 (s,2H, O -CH_2) and 4.81 (s,2H, N -CH_2), which correspond to the cyclic grouping -C-O-C-N- in the oxazine molecule. The ^{13}C-NMR spectra of compound exhibited the following carbon-atom-specific chemical shift signals (ppm): The chemical shifts of oxazine are (47.93) owing to the aliphatic carbon atom –N-CH_2- group and (80.75) due to the aliphatic carbon atom –O-CH_2- group.

The antibacterial activity of all produced compounds was evaluated using the disc diffusion technique. The preliminary screening findings for inhibitory zones are: Compounds ($A_1$and A_5) had the maximum activity against Staphylococcus aureus (G^+), while compounds (A_2 and A_7) exhibited less activity against this organism. Compounds A_3 and A_4 are less active against E. coli (G^-) than compounds A_1 and A_2. Although other compounds had only modest activity, compound (A_9) has no impact Table.2 Compounds

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A_1 and A_9 had the greatest efficacy against C. albicans.

Table 2. Zion of inhibition screening for synthesized compounds

Compounds	E.coli	S.aureus	C.albicans
A_1	++	+++	+++
A_2	++	+	++
A_3	+	-	-
A_4	+	-	-
A_5	++	+++	+
A_6	++	++	++
A_7	++	+	+
A_8	++	++	+
A_9	-	++	+++
St. drug	14	11	6
Ciprofloxacin	12	8	10
Amoxicillin			

- = Absence of inhibition = inactivity
+ = (5-9) mm = less active
++ = (10-15) mm = moderate active
+++ = (16-20 mm) = very active

Also, to test the antibacterial activity of the synthesized compounds, the two-fold serial dilution approach was used to Staphylococcus aureus Gram-positive, Escherichia coli Gram-negative, and C.andida species. All of the biological effects of the chemicals are detailed in Table .3 Compounds with MIC values of 200,600, and 1000 µg/ml shown antibacterial action against S. aureus, E.coli, and C.albicans, respectively. Compounds A_7 and A_9 were more potent than the others against E. coli, S. aureus, and C. albicans, with MIC values of 200 and 600 µg/ml, respectively. The synthesized compounds A_4, A_5, and A_8 demonstrated antibacterial activity with MIC values ranging from 600 to 1000 µg/ml against E. coli and Saureus, which were higher potent than the control medicines. Compound A_2 was determined to be the most effective derivative against all microorganisms with a MIC value of 600µg/ml of the substances evaluated, and had the same efficacy as Gentamycin.

Table 3. Antimicrobial activity of the synthesized compounds

Comp. no.	Minimum Inhibitory Concentration (Mic µg/ml)		
	Grame-Positive E.coli	Gram-Negative S.aureus	Funqi C.albicans
A_1	1000	1000	1000
A_2	600	600	600
A_3	1000	1000	1000
A_4	1000	600	1000
A_5	1000	1000	600
A_6	200	1000	200
A_7	600	200	200
A_8	1000	1000	600
A_9	200	200	600
Negative control	0.004	0.002	0.00
Positive control	0.496	0.249	0.254
Antibiotic control	0.17	0.13	0.181

Negative control: the well contain the Mueller Hinton broth; positive control: the well contain the Mueller Hinton broth inoculated with bacteria; antibiotic control: the well contains Mueller Hinton broth inoculated with bacteria and contain the Ampicillin at 50 µg/ml.

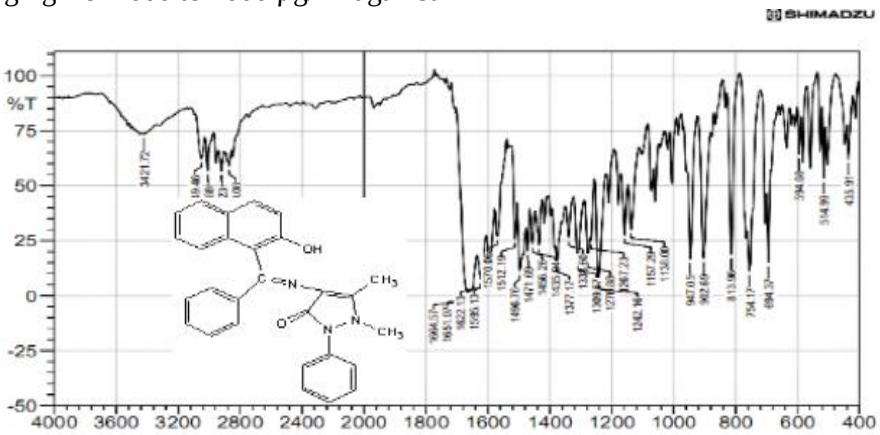

Figure 1. FT-IR spectrum for compound A_1

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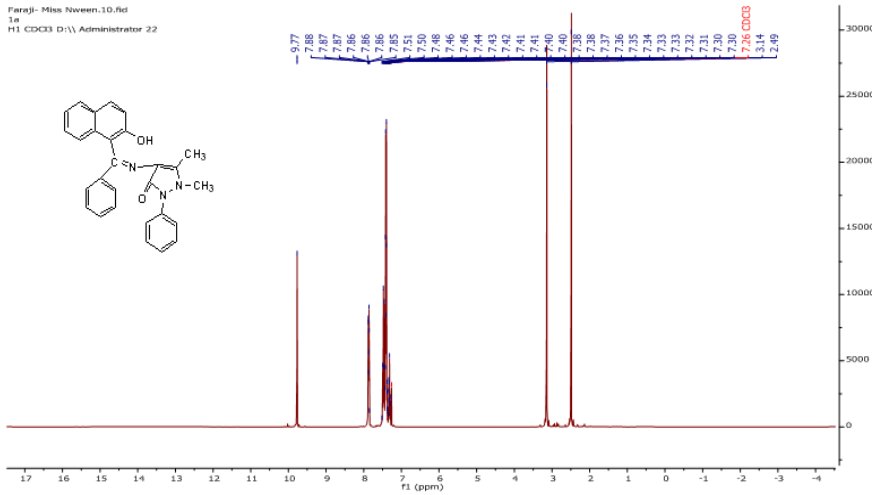

Figure 2. ^{1}HNMR spectrum for compound A_1

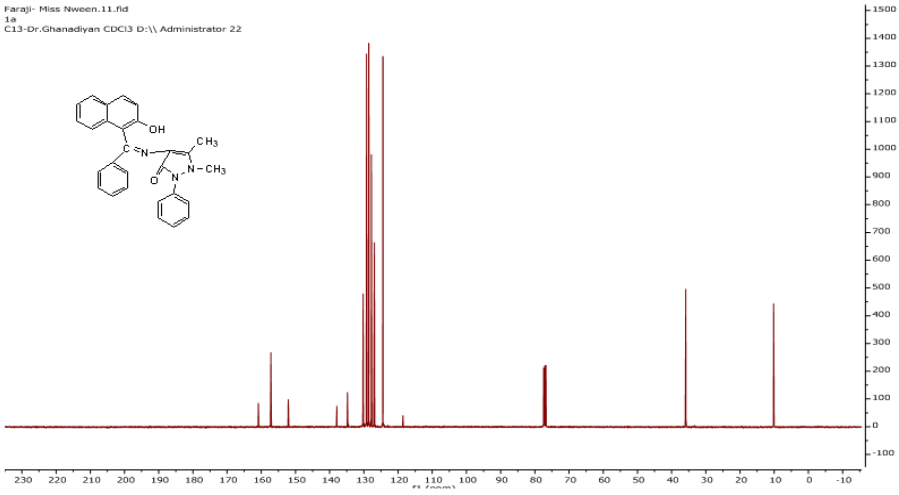

Figure 3. ^{13}CNMR spectrum for compound A_1

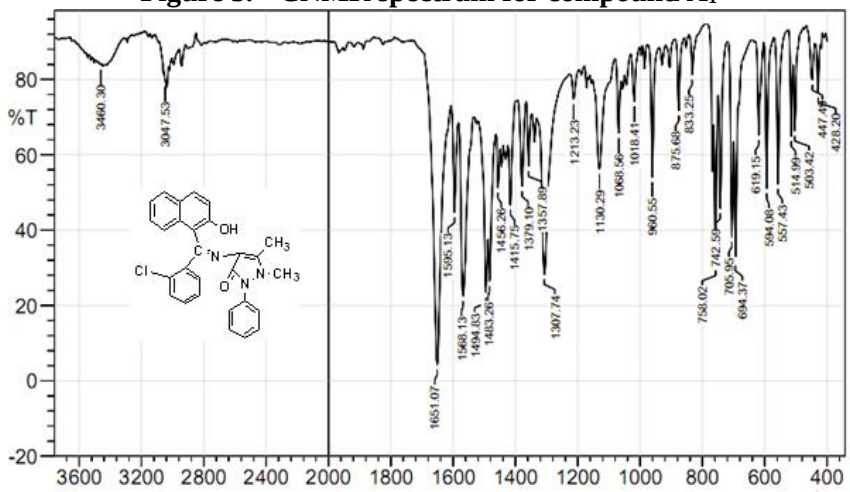

Figure 4. FT-Ir spectrum for compound A_2

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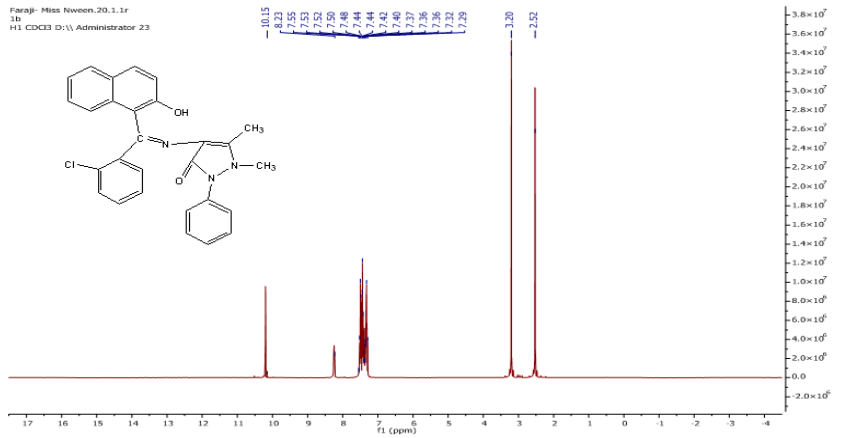

Figure 5. ^{1}HNMR spectrum for compound A_2

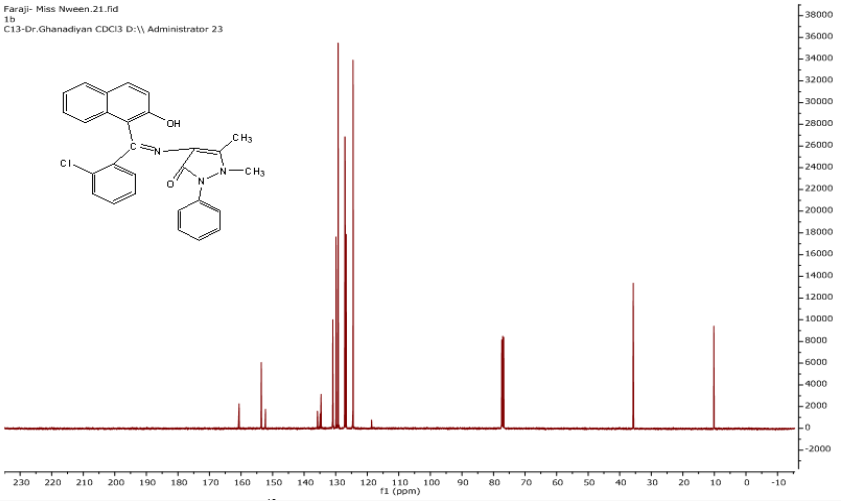

Figure 6. ^{13}CNMR spectrum for compound A_2

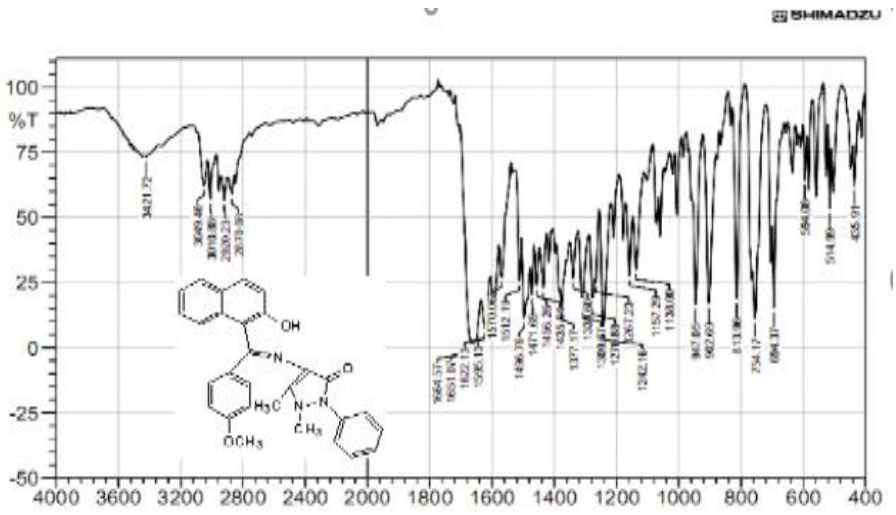

Figure 7. FT-IR spectrum for compound A_3

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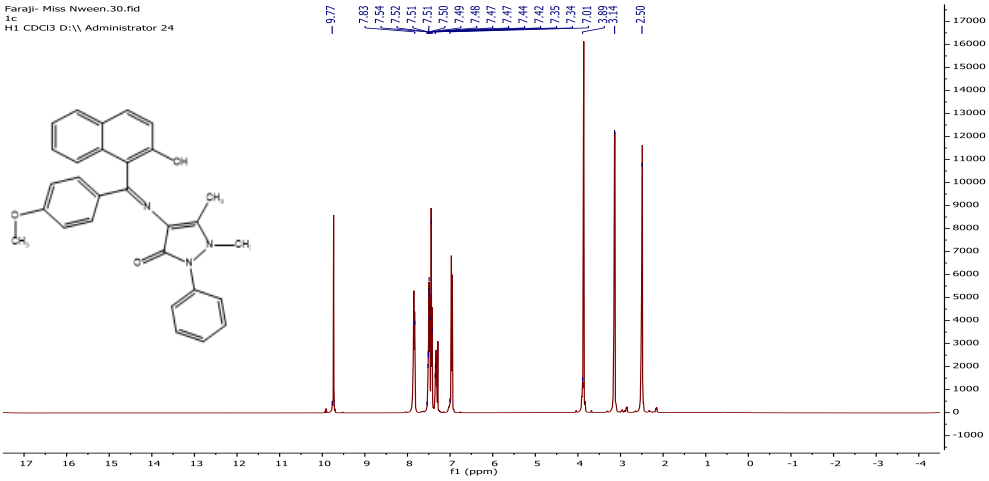

Figure 8. ^{1}HNMR Spectrum for compound A_3

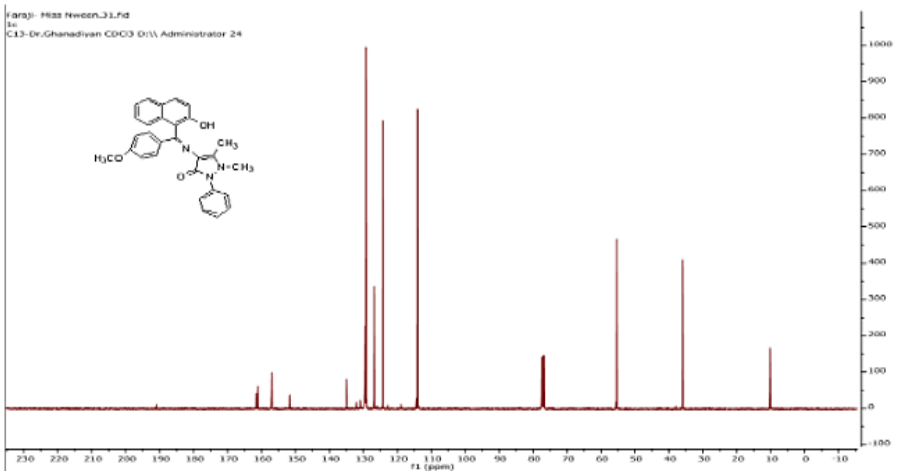

Figure 9. ^{13}CNMR spectrum for compound A_3

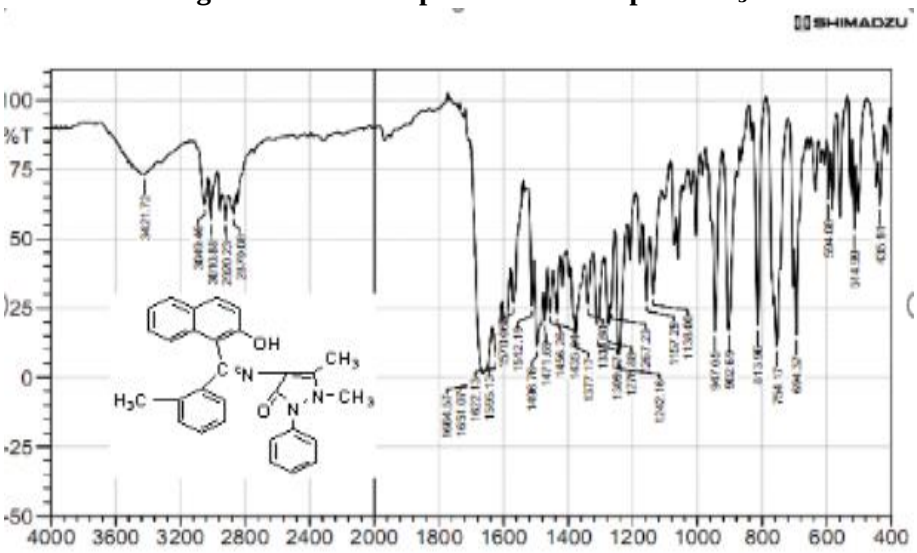

Figure 10. Ft-IR spectrum for compound A_4

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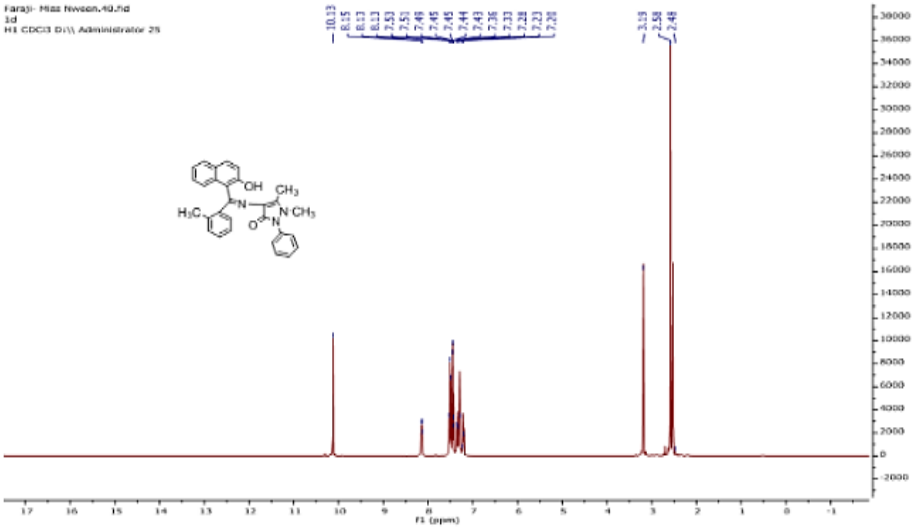

Figure 11. ^{1}HNMR spectrum for compound A_4

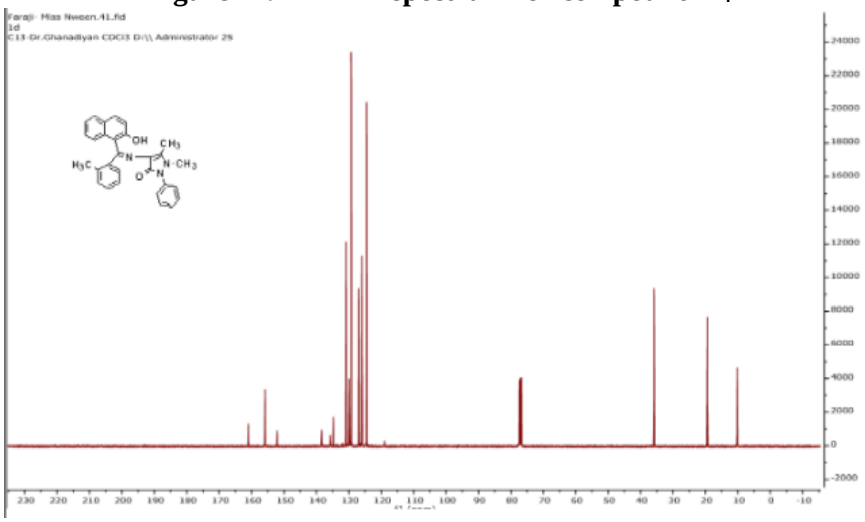

Figure 12. ^{13}CNMR spectrum for compound A_4

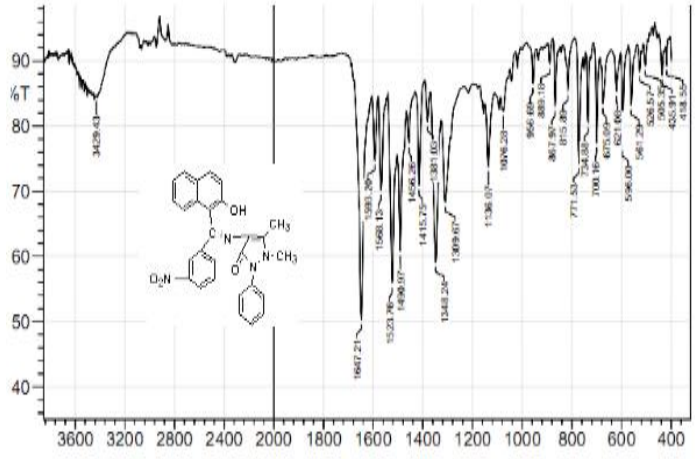

Figure13. FT-IR spectrum for compound A_5

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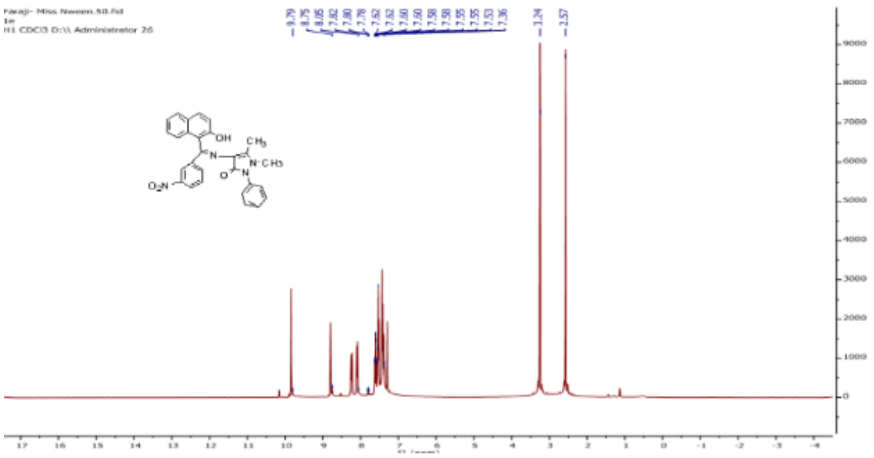

Figure 14. ^{1}HNMR spectrum for compound A_5

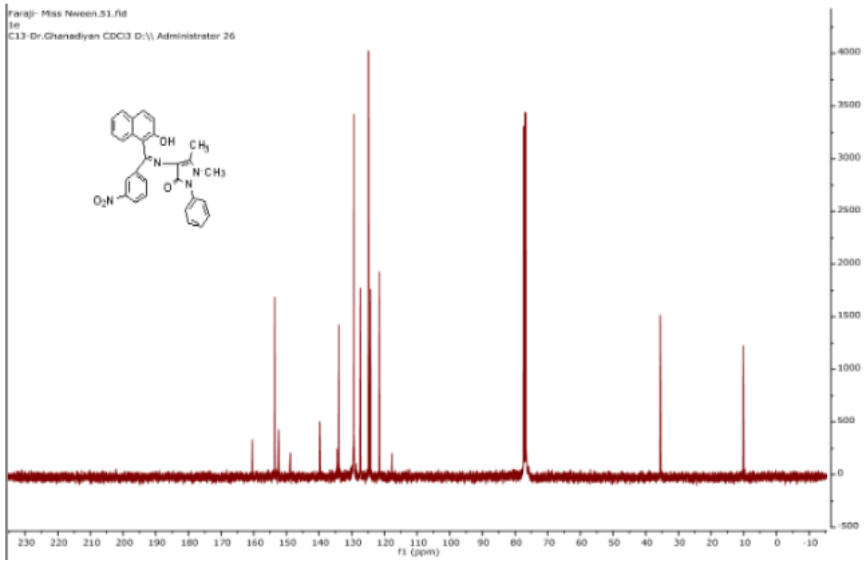

Figure 15. ^{13}CNMR spectrum for compound A_5

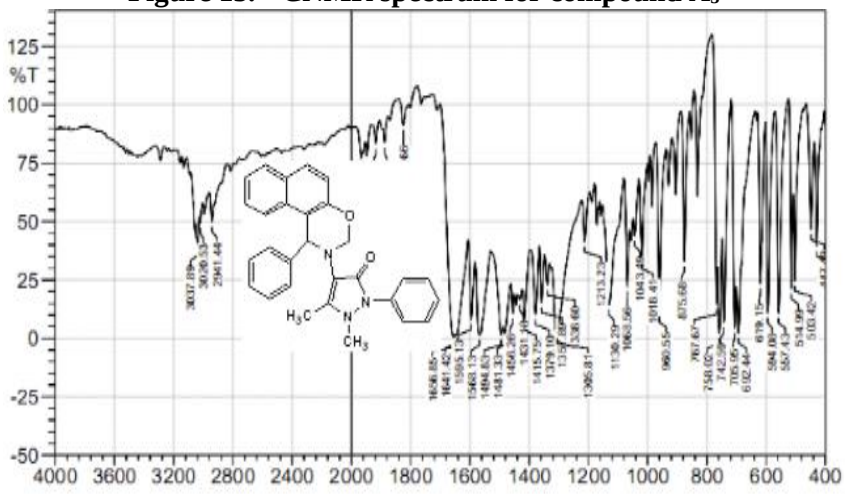

Figure 16. FT-IR spectrum for compound A_6

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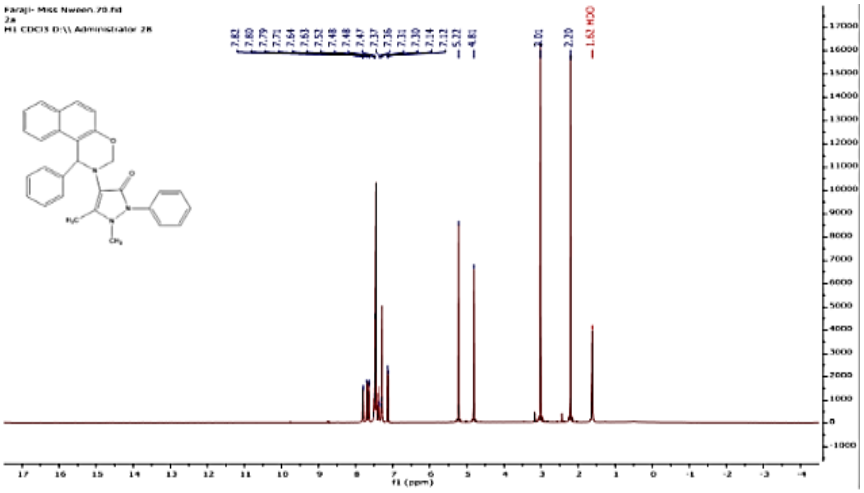

Figure 17. ^{1}HNMR spectrum for compound A_6

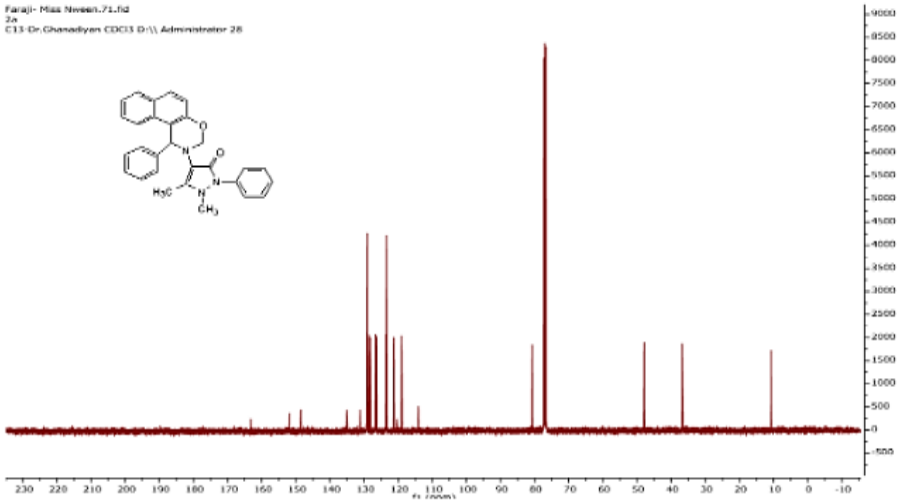

Figure18. ^{13}CNMR spectrum for compound A_6

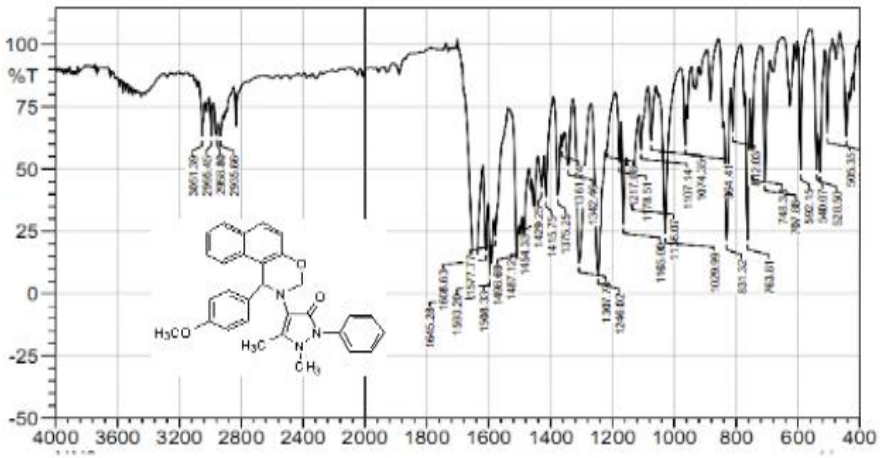

Figure19. FT-IR spectrum for compound A_7

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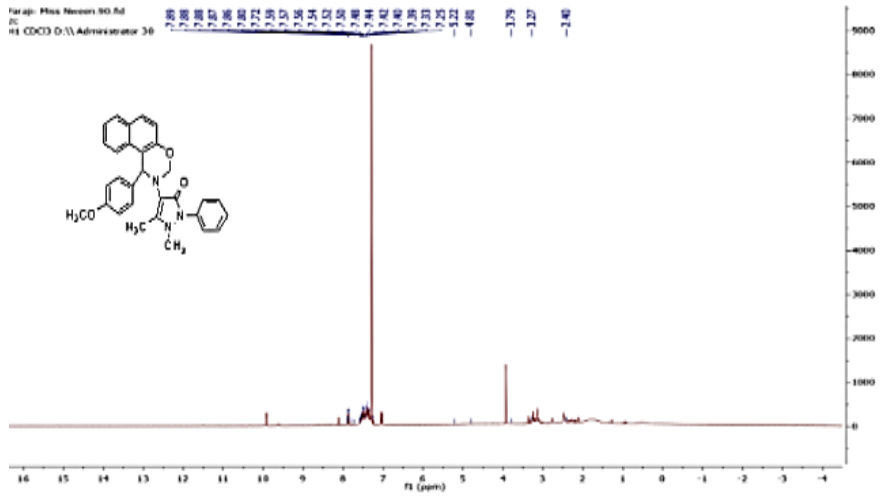

Figure 20. ^{1}HNMR spectrum for compound A_7

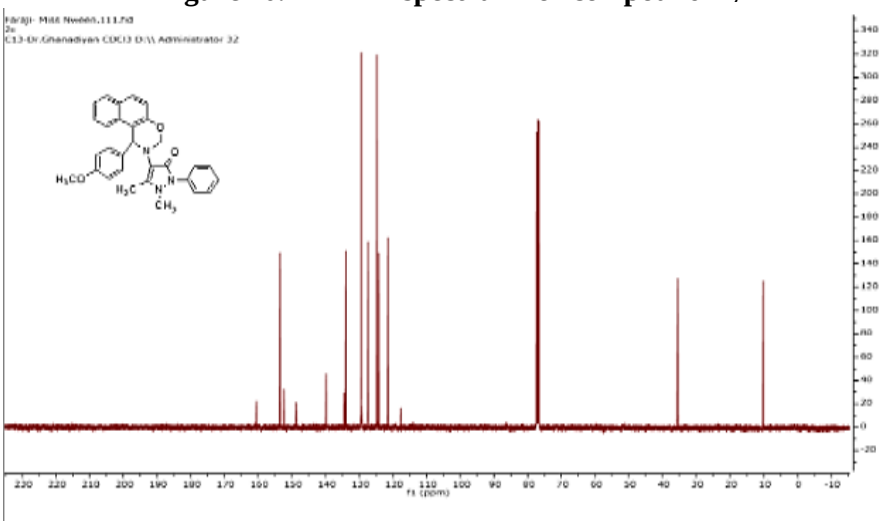

Figure 21 ^{13}CNMR spectrum for compound A_7

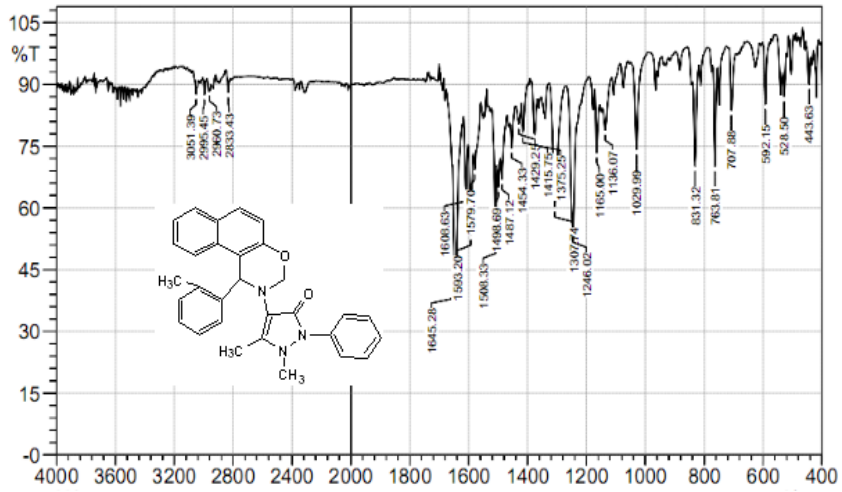

Figure 22. FT-IR spectrum for compound A_8

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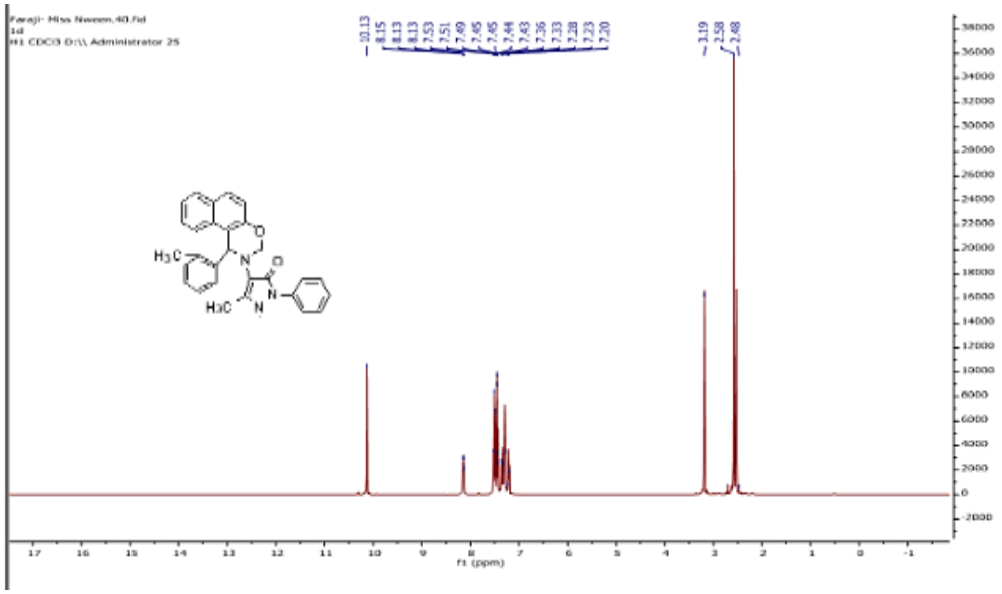

Figure 23. ^{1}HNMR spectrum for compound A_8

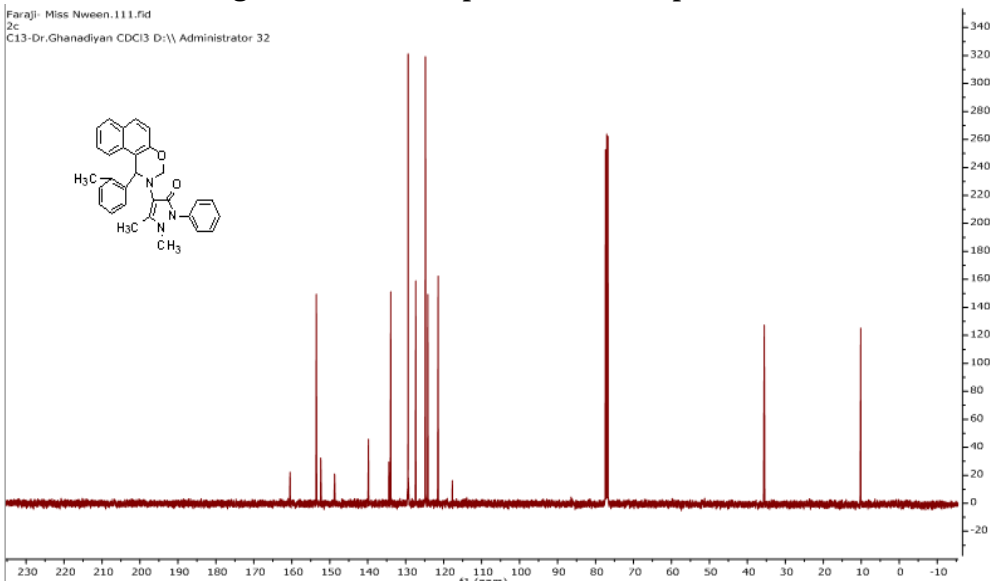

Figure 24. ^{13}CNMR spectrum for compound A_8

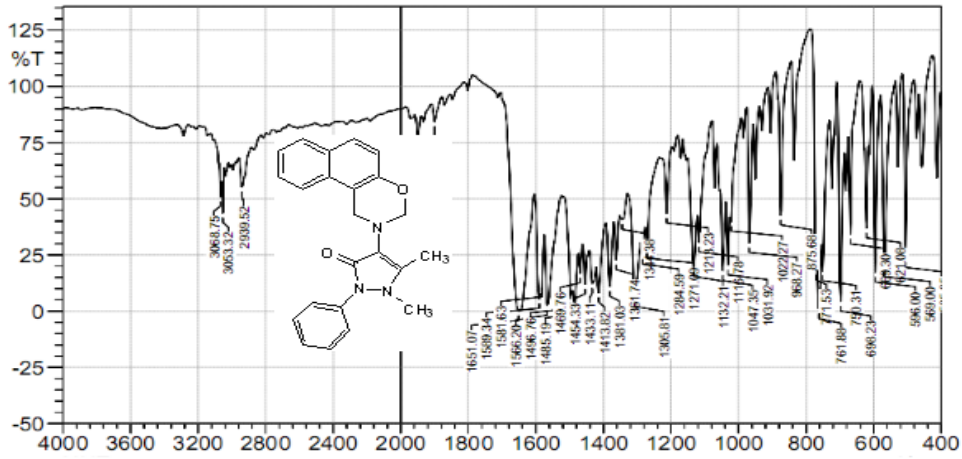

Figure 25. FT-IR spectrum for compound A_9

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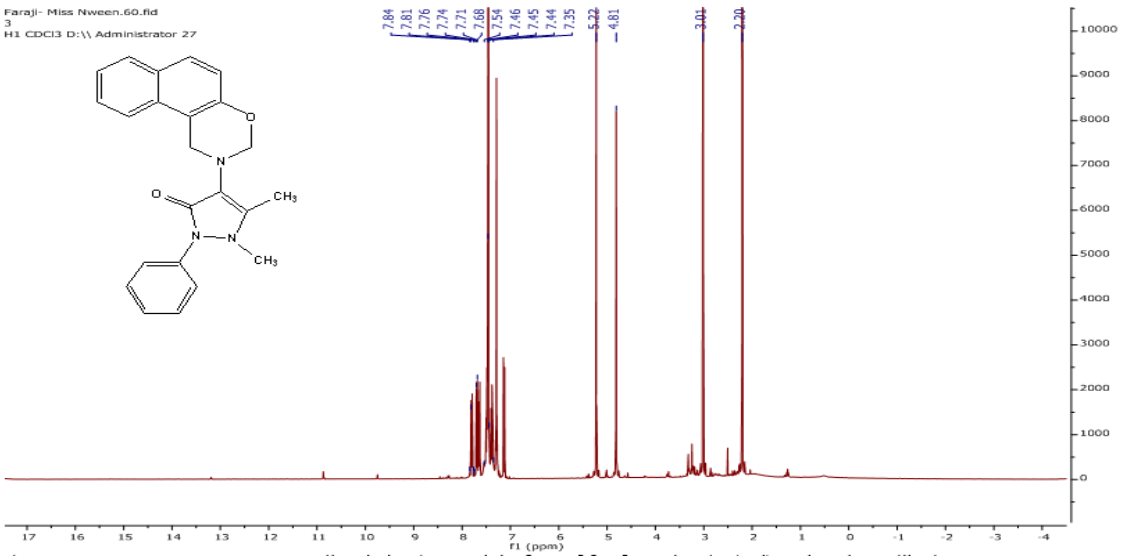

Figure 26. ^{1}HNMR spectrum for compound A_9

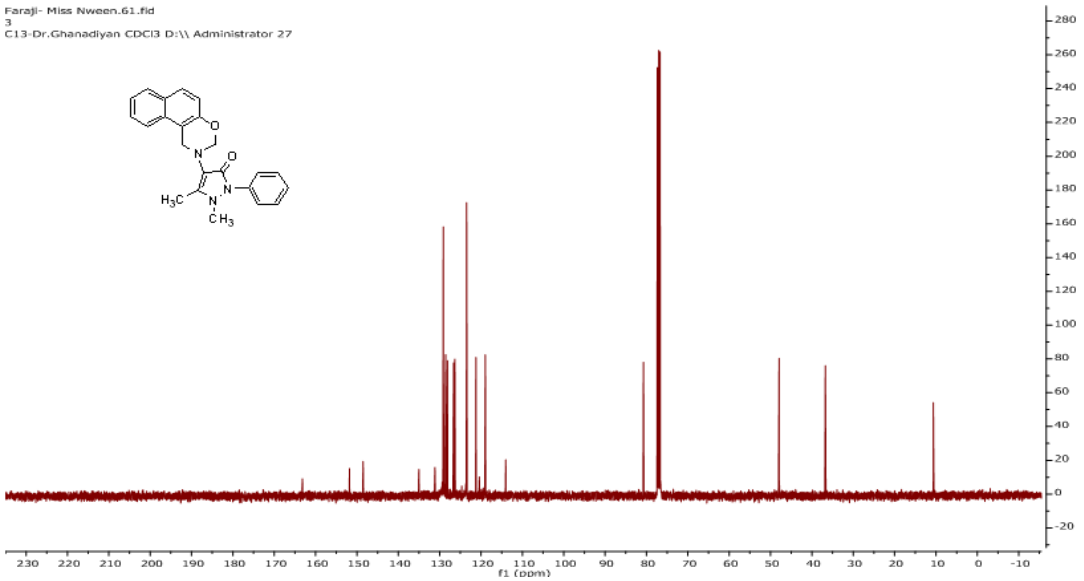

Figure 27. ^{13}CNMR spectrum for compound A_9

Conclusion

An alternative synthesis for the aforementioned compounds was developed using a one-pot procedure, multi-component reaction under ultrasound irradiation in the presence of $ZrOCl_2$, yielding 4-((2-hydroxynaphthalen-1-yl) (3-phenyl) methyl) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one derivatives (1a-e). It has been stated that $ZrOCl_2.8H_2O$ is an effective, recyclable, non-toxic, and cheap catalyst.The use of ultrasonic and MCR as a combined catalytic system ($ZrOCl_2/K_2CO_3$) for the synthesis of certain organic compounds of biological interest. These methods have a significant potential for application in organic synthesis, pharmacy, and industrial processes, and this paper paves the way for the implementation of a green strategy in organic process. This research is part of an ongoing investigation of ultrasonic/catalyst for green organic reactions. The synthetic product (A_9) of the reaction among 4-aminoantipyrin, formaldehyde and 2-naphthol in a 1:2:1 molar ratio was studied in detail and characterized. Initially, from the interaction of formaldehyde and 4-aminantipyrin, the crucial intermediate is produced, which may attack at the 1 position of 2-naphtho. The resulting product reacts quickly with the second mole of formaldehyde to produce 1.3-naphthoxazine.This findings of this study will aid in understanding the synthesis of 1, 3-

naphthoxazine and the design and creation of innovative naphthoxazine.

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The author would like to thank the Head and all of the Staff of the Chemistry Department.

Authors' Declaration

- Conflicts of Interest: None.
- I hereby confirm that all the Figures and Tables in the manuscript are mine. Furthermore, any Figures and images, that are not mine, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Salahaddin.

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تحضير، تشخيص والفعالية البايولوجية لبعض المشتقات الجديدة لـ 4- امينو انتي بييرين باستخدام الموجات فوق الصوتية

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الخلاصة

تم استخدام تفاعل المباشر, ذو وعاء واحد، ثلاثي المكونات بين الألديهايدات الاروماتيه المعوضه, 2-نافثول و4- أمينو أنتيبيرين لتخليق سلسلة جديده من 4-(((2-hydroxynaphthalen-1-yl) (phenyl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A1- A5) لقد أجريت هذا التفاعل بأستخدام كلوريد الزركونيل كمحفز فعال في حالة التشعيع بالموجات فوق الصوتية. في الحقيقة أن هذه المشتقات لديها قدره على العمل كمواد أساسية في تكوين مركبات جديده 4- (1H-naphtho [1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1, 5-dimethyl-1,2-dihydro-3H-pyrazol-3-one(A6, A7 and A8). وبالمثل, تم استخدام MCRs التي أدت إلى تكوين مركب حلقي غير متجانس (3،1-نافثوكسازين) وتضمنت تفاعل 4- أمينو أنتي بييرين, و الفورمالديهايد و 2-نافثول بنسبة مول 1: 2: 1 لتكوين 4-(1H-naphtho [1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1-5 dimethyl-1,2-dihydro-3H-pyrazol-3-one (A9) يبدأ هذا التفاعل بأدخال نظام محفزZrOCl2-K2CO3 ويستمر من خلال التكثيف وتكوين الحلقه. ثم تحليل جميع المركبات المنتجه من خلال بيانات أطياف IR و H1 NMR و C13 NMR لتوضيح عمل هذه المركبات المميزه. باستخدام طريقة التخفيف الدقيق للمرق وطريقة نشر القرص، تم تقييم الأنشطة المضادة للبكتيريا (إيجابية الجرام وسالبة الجرام) والفطريات و مقارنة بالأدوية التقليدية (امبيسلين, سيبروفلوكساسين و اموكسيسلين). كان للمركبات المحضرة مجموعة واسعة من التأثير بقيم MIC من 200 ,600 و 1000ميكروغرام / مل ضد البكتيريا التي تم فحصها ، كما هو محدد بواسطة التحليل الميكروبيولوجي.

الكلمات المفتاحية: تفاعل متعدد المكونات ، 3،1-نافثوكسازين ، تركيب وعاء واحد ، تشعيع الموجات فوق الصوتية، كلوريد زركونيل.