Ultrasonic mediation: Synthesis, spectral characterization and antimicrobial activity of new 4-aminoantipyrine based 1,3-naphthoxazines derivatives

Abstract

A straightforward, one-pot, three-component reaction between 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 (1a-e). This reaction was carried out with zirconyl chloride ($ZrOCl_2.8H_2O$) 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 1,5-dimethyl-2-phenyl-4-(1-phenyl-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)-1,2-dihydro-3H-pyrazol-3-one derivatives (2a, c, d). 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 1, 5-dimethyl-4-(1H-naphtho [1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one(3). This reaction begins with the introduction of $ZrClO_2$-K_2CO_3 catalyst system and proceeds through condensation and cyclization. The key objectives of the present combined approach are the utilization of a small-scale catalyst, the simplicity of the work-up technique, the elimination of waste in the generated section, and the promotion of environmental sustainability. All produced compounds were analyzed through IR, ^{1}H NMR, and ^{13}C NMR spectra data to illustrate each of these distinct structures. Using the twofold serial dilution approach 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. 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: 1, 3-naphthoxazine, one pot synthesis, Ultrasound irritation, zirconyl chloride

أمينو-4 لمشتقات للميكروبات المضاد والنشاط الطيفي والتوصيف التخليق :الصوتية فوق بالموجات التوسط نافثوكسازين-1،3 على القائمة الجديدة أنتيبيرين

الخلاصة:

تم تخليق سلسلة جديدة من مشتقات-4-(((2-hydroxynaphthalen-1-yl) (phenyl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1a-e)عن طريق تفاعل مباشر ، وعاء واحد ، ثلاثي المكونات بين الألدهيدات الاروماتيه، -2نافثول و -4أمينو أنتيبيرين باستخدام كلوريد الزركونيل كمحفز فعال تحت حالة التشعيع بالموجات فوق الصوتية ، هذه المشتقات مهمة لأنها قد تكون بمثابة الموادالاوليه لتخليق مشتقات من 1,5-dimethyl-2-phenyl-4-(1-phenyl-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)-1,2-dihydro-3H-pyrazol-3-one (2 a،c،d). أيضًا ، MCRs التي أدت إلى تكوين مركب حلقي غير متجانس -1،3 نافثوكسازين) من خلال تفاعل 4-aminoantipyrine ، و الفورمالديهايد ، و 2-naphthol بنسبة مول 1 :2 :1لتوليد-1, 5-dimethyl-4-(1H-naphtho [1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3). يبدأ هذا التفاعل بإدخال نظام محفز $ZrClO_2$-K_2CO_3ويستمر من خلال التكثيف وتكوين الحلقه .تتمثل الأهداف الرئيسية للنهج المشترك الحالي في استخدام محفز صغير الحجم ، وبساطة أسلوب العمل ، والقضاء على النفايات في القسم المتولد ، وتعزيز الاستدامة البيئية .تم استخدام بيانات أطياف IR و H^1 NMR و C^{13} NMR لتشخيص كل من هذه المركبات المجضرة .وباستخدام نهج التخفيف التسلسلي المزدوج وطريقة نشر القرص ، تم تقييم الأنشطة المضادة للبكتيريا والفطريات للمركبات مقابل إيجابية الجرام وسالبة الجرام مقارنة بالأدوية التقليدية .كان للمركبات المحضرة مجموعة واسعة من الإجراءات ، مع قيم MIC من ,600 200و 1000ميكروغرام /مل ضد البكتيريا التي تم فحصها ، كما هو محدد بواسطة التحليل الميكروبيولوجي.

الكلمات المفتاحية-3 ، 1 :نافثوكسازين ، تركيب وعاء واحد ، تشعيع الموجات فوق الصوتية، كلوريد الزركونيل.

Introduction

In order to build varied and complex organic compounds with excellent synthetic efficiency and great stereo selectivity[1], multicomponent reactions (MCR) have emerged as a crucial tool. They are preferable than two-component reactions in a number of aspects, including the simplicity of one-pot processes and the possibility for structural diversity[2]. The multiple tandem bond formation processes in MCR are what give rise to the synthetic competence. One-pot multicomponent reactions (MCR), which may yield target products in a single operation without separating the intermediates[3], have grown in significance, in recent years in organic synthesis because they reduce reaction duration and energy input, which saves time, energy, and raw materials. As a result, MCR is now a recognized method in organic chemistry for the quick and simple synthesis of a large variety of molecule[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 (1a-e).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 ZnClO4.8H2O at 25 °C and ultrasonic irradiation is described Scheme1.

In an effort to create a more efficient synthetic method, In the second part of this work, we present a technique for the synthesis of new 1, 5-dimethyl-2-phenyl-4-(1-phenyl-1H-naphtho [1, 2-e] [1, 3] oxazin-2(3H)-yl)-1,2-dihydro-3H-pyrazol-3-one derivatives (2a, c, d) derivatives through the one-pot reaction of 1(a, c, d) with formaldehyde employing K_2CO_3 as a base and zirconyl chloride as a catalyst in the presence of ultrasound Scheme 2.

Also included in the third section of this research report are various routes to substituted 1,3-naphthoxazine, primarily cyclic condensation of 4-aminoantipyrine with formaldehyde and 2-naphthol catalyzed by zirconium chloride and presenting potassium carbonate as a base under ultrasound irradiation with various mechanisms (scheme 3). For the manufacture of 1, 5-dimethyl-4-(1H-naphtho [1,2-e] [1,3] oxazin-2(3H)-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one, the primary goals of the current combination ($ZrOCl_2.8H_2O/K_2CO_3$) method has demonstrated to be an effective, environmentally friendly, conveniently available, and cost-effective catalyst system.

Experimental

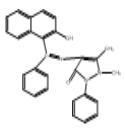
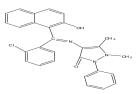
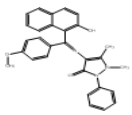
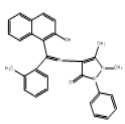
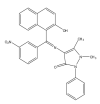
Chemicals and apparatus

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 (1a-e)

A combination of 4-aminoantipyrine (0.01mol), substituted aromatic aldehyde (0.01mol), and 2-hydroxy naphthol (0.01mol) was dissolved in (10 mL) of 95% ethanol in a one pot and irradiated at room temperature in the presence of zirconyl chloride (0.1 mmol) for (1-5 minutes), as shown in Table 1. As mobile phase, a combination of ethyl acetate and hexane 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.

Table1.Synthesis of (1a-e) catalyzed by $ZrOCl_2$ (0.1mmol)

Comp.	substituted aldehyde	Stucture	Chemical Formula	M.wt	Time min.	Timp.	M.P°C	Yield
1a	C_6H_5CHO		$C_{28}H_{23}O_2N_3$	433	2	25	180-181	95
1b	$2\text{-}ClC_6H_4CHO$		$C_{28}H_{22}O_2N_3Cl$	467,5	1.5	25	195-197	97
1c	$4\text{-}OCH_3C_6H_4CHO$		$C_{29}H_{25}O_3N_3$	463	5	30	174-175	88
1d	$2\text{-}CH_3C_6H_4CHO$		$C_{29}H_{25}O_2N_3$	447	3	25	177-179	90
1e	$3\text{-}NO_2C_6H_4CHO$		$C_{28}H_{22}O_4N_4$	462	1.5	25	221-222	98

4-(((2-hydroxynaphthalen-1-yl) (phenyl)methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1a); IR (KBr, cm^{-1}): 3460 (–OH), 3068,3053 (Ar–H), 2970 (–CH_3) 1651 (C=O),1595(C=N) .^{1}H NMR (Chloroform-*d,* 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, -CH_3). ^{13}CNMR ($CDCl_3$, ppm):118.58(C1),160.87(C2),118.50(C3),130.21(C4),122.9(C5),129(C6),124.63(C7),126.91(C8),127.8(C9),128.94 (C10),160.87(C11),134.79(C12),127.80(C13),128.55(C14),129.77(C15),128.54(C16),127.8(C17),160.86 (C18).134.51 (C19),152.11 (C20),10.16(C21),35.86C22),134.79(C23),124.38(C24, C28),129.21(C25, C27),126.91(C26).

4-(((2-chlorophenyl) (2-hydroxynaphthalen-1-yl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1b); IR (KBr, cm^{-1}): 3460 (–OH), 3068,3053 (Ar–H), 2975 (–CH3) 1680 (C=O), 1590 (C=N),720 (C–Cl). ^{1}H NMR(Chloroform-*d,* 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, CH_3). ^{13}CNMR ($CDCl_3$,ppm):124.49(C1),153.59(C2),118(C3),130.93(C4),126.66(C5),127.93(C6),124.49(C7),127.03(C8),127.03(C9),130.93(C10), 153.59(C11),129.9 (C12), 129.9 (C13),129.23 (C14),130.90 (C15),127.03 (C16),129.23 (C17),153.59 (C18).126.66(C19),139.93(C20),10.16(C21),35.72(C22),129.9(C23),124.49 (C24).129.23(C25),127.3(C26),129.23(C27),124.49(C28).

4-(((2-hydroxynaphthalen-1-yl) (4-methoxyphenyl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1c); IR (KBr, cm^{-1}): 3446 (–OH), 3060,3045 (Ar–H), 2985 (–CH_3), 1647 (C=O), 1593 (C=N). ^{1}HNMR (Chloroform-*d* , 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, CH_3), 3.89 (s,3H, -OCH_3), ^{13}CNMR ($CDCl_3$, ppm):118.85 (C1),161.4 (C2),114.33 (C3),132 (C4),129.44 (C5),122,8 (C6),124.23(C7),126.77 (C8),129.06(C9),161.04(C10), 161.47(C11),130.84 (C12), 129.16(C13),114 (C14),161.04 (C15),114 (C16),129.16 (C17),153.59 (C18).132 (C19),151.68(C20),10.19(C21),36(C22),134.9(C23),124.23 (C24, C28).129.16(C25, C27),126.77(C26).161.04(-OCH_3).

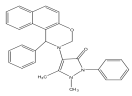
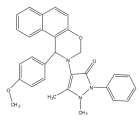
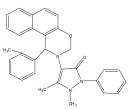
4-(((2-hydroxynaphthalen-1-yl) (o-tolyl) methylene) amino)-1, 5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1d); IR (KBr, cm^{-1}): 3566 (–OH), 3066 -3047(Ar–H), 2971 (–CH_3), 1687 (C=O), 1590 (C=N). ^{1}HNMR(Chloroform-*d*, ppm) δ 10.13(s,1H, –OH), 7.49–8.15 (m,6H, Ar), 7.43 -7.45 (m,4H, Ar), ,7.20-7.36 (m,5H, Ar) 2.48 (s,3H, –CH_3), 2.58 (s,3H, CH_3),3,19 (s,3H, -OCH_3), . ^{13}CNMR ($CDCl_3$, ppm):119 (C1),155.80 (C2),119 (C3),131.81 (C4),126.36 (C5),126 (C6),125.94(C7),126.97 (C8),125.94(C9),129.96(C10), 138.38(C11),133.70 (C12), 135.71(C13),129.25 (C14),126.97 (C15),125.94 (C16),124.45 (C17),160.9(C18).124.45(C19),138.38(C20),10.2(C21),35.83(C22),135.71(C23),124.45 (C24, C28).129.25(C25, C27),126.97(C26). 10.40 (C13--CH_3).

4-(((2-hydroxynaphthalen-1-yl) (3-nitrophenyl) methylene) amino)-1-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1e); IR (KBr, cm^{-1}): 3429 (–OH), 3069 -3050(Ar–H), 2975 (–CH_3), 1690 (C=O), 1590 (C=N), 1568(-NO_2). ^{1}HNMR (Chloroform-*d*, 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, CH_3),. ^{13}CNMR ($CDCl_3$, ppm):121.52 (C1),160.44(C2),117.67(C3),129.34(C4),124.80(C5),129.34(C6),124.80(C7),129.34(C8),124.80(C9),133.93(C10), 152.32(C11),133.93 (C12), 124.41(C13),148.74 (C14),124.21 (C15),129.49 (C16),133.93 (C17),153.60(C18).129.49(C19),153.60(C20),10.16(C21),35.53(C22)Chloroform*d*,ppm)δ,139.76(C23),124.8 (C24, C28).129.34(C25, C27),124.80(C26).

General procedure for synthesis of 1,3-naphthoxazine derivatives (2a, c, d)

Into a 100 ml round bottle flask dissolved (1mmol) of 4-(((2-hydroxynaphthalen-1-yl) (phenyl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one derivatives (1a, c, d) and formaldehyde (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 (0.01 mmol) and irradiated in an ultrasonic bath at 60 ^{o}C 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 Table 2.

Table2: some physical properties of 1,3-naphthoxazines 2(a, c, d)

Entry	R	Product	structure	Chemical formula	M.wt	Time min.	Yield %	M.P
1	H	2a		C29H27O2N2	433	55	86	190-192
2	4-OCH_3	2c		C30H27O3N2	463	60	90	201-203
3	2-CH_3	2d		C30H27O2N2	447	58	88	188-198

1,5-dimethyl-2-phenyl-4-(1-phenyl-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)-1,2-dihydro-3H-pyrazol-3-one (2a); IR (KBr, cm^{-1}): 3037 (Ar–H)), 3020 (CH_3), 2941 (CH_2), 2930 (CH), 1656 (C=O), 1298 (C-O-C),1246 (C-N-C). ^{1}HNMR (Chloroform-*d*, 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 (Chloroform-*d*, ppm) δ118.97 (C1),151.81 (C2),123.65 (C3),128.11 (C4),129.11 (C5),128.56 (C6),123.65 (C7),126.62 (C8),123.45 (C9),123.65 (C10), 80.73(C11),47.93 (C12), 131.14 (C13),126.62 (C14),128.98 (C15),128.56(C16),128.98(C17),126.62(C18).148.52(C19),126.31(C20),128.11(C21),10.64(C22),36.77(C23),135.0 3 (C24), 123.45 (C25, 29).129.11(C26, C28),126.32(C26).

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 (2c); IR (KBr, cm^{-1}): 3051 (Ar–H)), 2995 (–CH_3), 2958 (-CH_2), 2936 (-CH), 1645 (C=O), 1283 (C-O-C),1213 (C-N-C). ^{1}HNMR (Chloroform-*d*, 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 (Chloroform-*d*, ppm) δ 118.64 (C1),153.40 (C2),118.64 (C3),126.90 (C4),126.90 (C5),126.90 (C6),124.90 (C7),126.90 (C8),126.90 (C9),129.89 (C10), 81.73(C11),57.93 (C12), 134.64(C13),129.23(C14),118.64(C15),160.61(C16),118.64(C17),129.23(C18).160.61(C19),134.64(C20),135.02(C2 1),10.13(C22),35.70(C23),135. (C24), 124.50 (C25, 29).129.89(C26, C28),126.90(C26), 55.7(O-CH_3).

1,5-dimethyl-2-phenyl-4-(1-(o-tolyl)-1H-naphtho[1,2-e] [1,3] oxazin-2(3H)-yl)-1,2-dihydro-3H-pyrazol-3-one (2d); IR (KBr, cm^{-1}): 3045 (Ar–H)), 2994 (–CH_3), 2952 (-CH_2), 2930 (-CH), 1645 (C=O), 1290 (C-O-C),1250 (C-N-C). ^{1}HNMR (Chloroform-*d*, 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 (Chloroform-*d*, ppm) δ118.96 (C1),153.40 (C2),118.96 (C3),128.12 (C4),128.56 (C5),126.37 (C6),123.57 (C7),126.63 (C8),121.23 (C9),129.10 (C10), 80.73(C11), 47.73 (C12), 129.10 (C13),129.10 (C14),118.64(C15),129.10(C16),118.64(C17),129.23(C18).129.1(C19),134.64(C20),128.12(C21),10.63(C22),36.66 (C23),129.1 (C24), 123.57 (C25, 29).129.1 (C26, C28),126.63(C26),36.72(-CH_3).

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

In a 100 ml round bottle flask, 1,4-dioxane (15 ml), formaldehyde (0.02 mol), 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 (0.01 mol) and zirconyl chloride (0.1 mmol) were added. After adding 2-naphthol (0.01 mol), the mixture was irradiated in an ultrasonic bath at 40^0Cfor thirty minutes. TLC was used to monitor the progression of 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. (0.363 g, 97.8%), m.p (178-179 ^{o}C); 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 (chloroform *d*,

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). ^{13}CNMR (Chloroform-*d*, ppm) δ118.96 (C1),151.80 (C2),118.96 (C3),128.56 (C4),128.11 (C5),126.34 (C6),123.54 (C7),126.62 (C8),121.23 (C9),129.10 (C10), 80.73(C11), 47.93 (C12), 163.17 (C13),129.10 (C14),10.63 (C15),36.75 (C16),163.17 (C17),131.14 (C18).128.99 (C19,23),126.62(C20,22),135.01 (C21).

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 150 l of each chemical substance generated at three distinct concentrations (1000, 600, and 200 g/L) using a micropipette. Positive controls [Ciprofloxacin (5 g/L) 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 4.

Minimum Inhibitory Concentration (MIC)

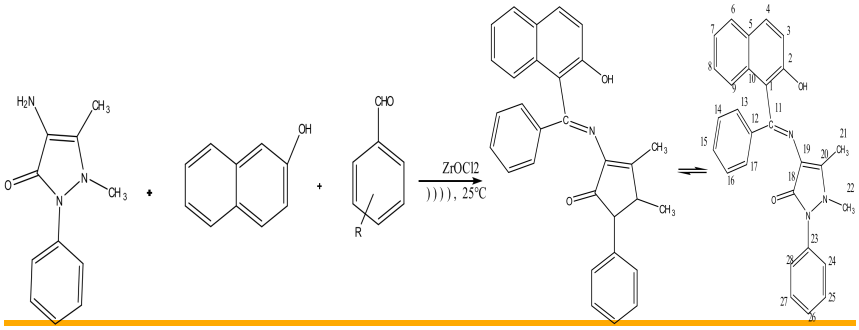
The Minimum Inhibitory Concentration (MIC) was measured using the broth micro dilution technique[23]. To assess the lowest concentration of antibacterial activity[24], cultures isolated for 18–24 hours were employed and their turbidity was compared to the 0.50 McFarland standards. The 96-well polystyrene 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 5.

Result and discussion

Chemistry

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 (1a-e) 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, ^{1}HNMR, and ^{13}CNMR spectra corroborate the hypothesized structures. In the case of naphthol, the infrared spectra of these compounds show an unique OH group stretch between 3429 and 3662 cm^{-1}, while the infrared spectra of pyrazolone show (C=O) stretching vibrations between 1647 and 1662 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.



1 (a-b)

1	A	B	C	D	E
R	H	2-Cl	4-OMe	2-Me	3-NO_2

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

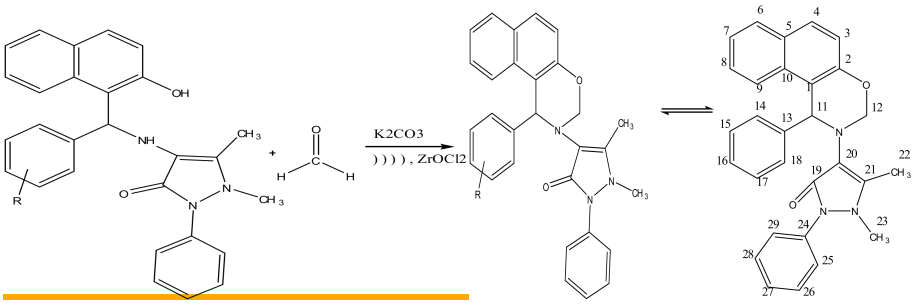
In our early experiments, we explored the optimization of reaction conditions for the ecologically benign synthesis of 4-(((2-hydroxynaphthalen-1-yl) (3- nitro phenyl) methyl) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1e). First, 3-nitrobenzaldehyde, 4-aminoantipyrine, and 2-naphthol 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 3, 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 3. 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 (1e)

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

In the second part of this approach novel compounds1,3-naphthoxazines 2(a, c, d) 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 1(a, c, d) 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.

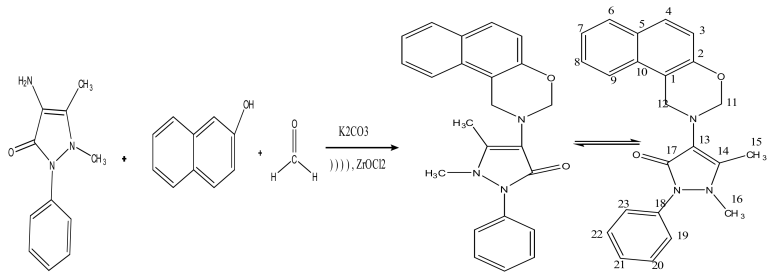


2(a,c, d)

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

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 (1e) and 4-(((2-chlorophenyl) (2-hydroxynaphthalen-1-yl) methylene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (1b) 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 an reactive towards this reaction. All structures 2(a, c, d) 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

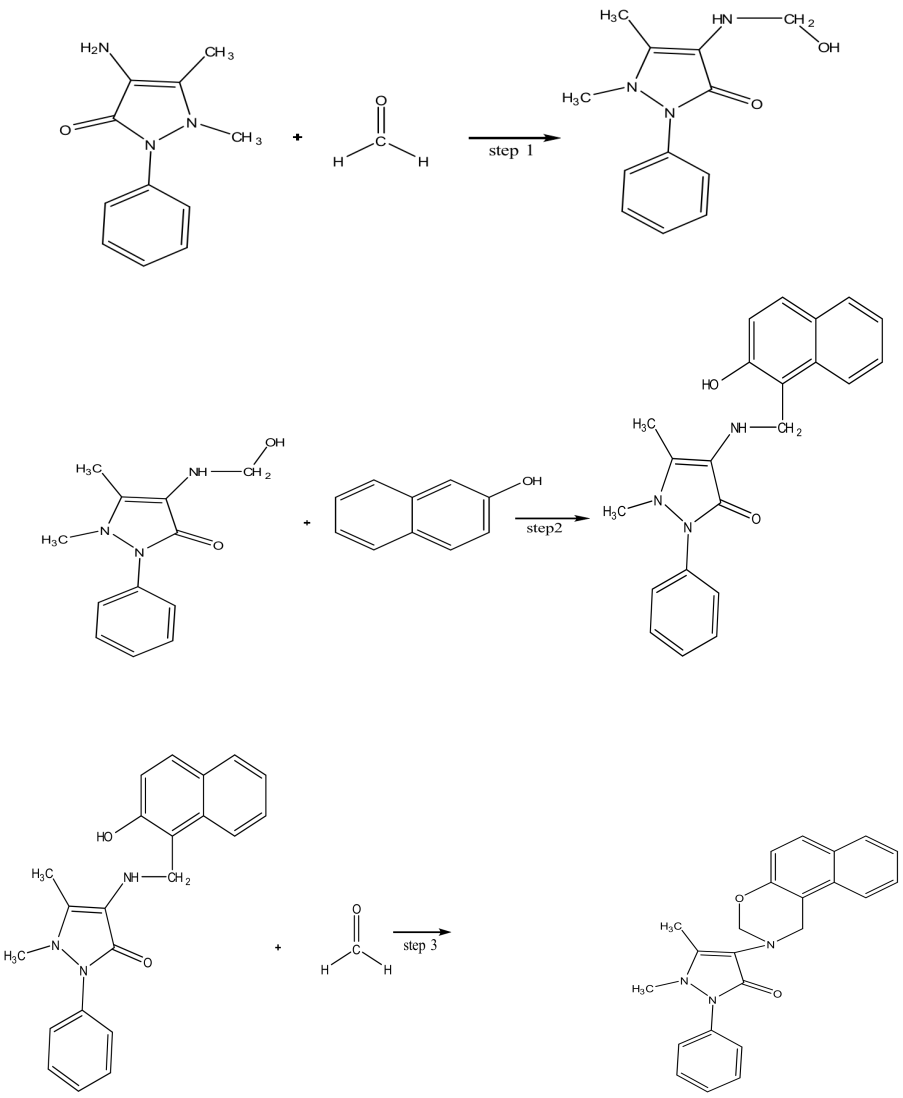
To expand the preparative usefulness and wide applicability of this multicomponent reaction, formaldehyde, 4-aminoantipyrine, and 2-naphthol were used in a molar ratio of 1:2:1. Good yields of the matching 1,3-naphthoxazine were achieved Scheme 3. A possible mechanism for this cyclic condensation resulted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



(3)

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 (3)

First, 4-aminoantipyrine reacts with formaldehyde to form formaldehyde-aminoantipyrine quickly (scheme4, step1), then formaldehyde-aminoantipyrine reacts with 2-naphthol to obtained 4-((hydroxymethyl)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (mannich base) slowiy (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 (3). 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.

Antimicrobial activity: The antibacterial activity of all produced compounds was evaluated using the disc diffusion technique. The preliminary screening findings for inhibitory zones are:

Compounds (1a and 1e) had the maximum activity against Staphylococcus aureus (G^+), while compounds (1b and 2c) exhibited less activity against this organism.

Compounds 1c and 1d are less active against E. coli (G^-) than compounds 1b and 1a. Although other compounds had only modest activity, compound (3) has no impact Table 4.

Compounds 1a and 3 had the greatest efficacy against C. albicans.

Table 4. Zion of inhibition screening for synthesized compounds

Compouns	E.coli	S.aureus	C.albicans
1a	++	+++	+++
1b	++	+	++
1c	+	-	-
1d	+	-	-
1e	++	+++	+
2a	++	++	++
2c	++	+	+
2d	++	++	+
3	-	++	+++

- = 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 5. Compounds with MIC values of 200,600, and 1000 µg/ml shown antibacterial action against S. aureus, E. coli, and C.albicans, respectively. Compounds 3 and 2c 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 1d, 1e, and 2d 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 1b 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 5. Antimicrobial activity of the synthesized compounds

Comp. no.	Minimum Inhibitory Concentration (Mic µg/ml)		
	Grame-Positive	Gram-Negative	Funqi
	E.coli	S.aureus	C.albicans
1a	1000	1000	1000
1b	600	600	600
1c	1000	1000	1000
1d	1000	600	1000
1e	1000	1000	600
2a	200	1000	200
2c	600	200	200
2d	1000	1000	600
3	200	200	600

Conclusion

1- An alternative synthesis for the aforementioned compounds was developed using a one-pot procedure, multi-component reaction under ultrasound irradiation in the presence of ZrClO2, 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.

2- The use of ultrasonic and MCR as a combined catalytic system (ZeClO2/K2CO3) 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.

3-The synthetic product (3) 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.

4-This study's findings will aid in understanding the synthesis of 1, 3-naphthoxazine and the design and creation of innovative naphthoxazine.

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