SONOCHEMICAL SYNTHESIS OF SOME NOVEL 6-IMINOBENZOXAZOLINONES WITH POTENTIAL ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

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*An environmentally benign protocol for the synthesis of a novel series of imine derivatives containing 2-oxo-3H-benzoxazole scaffold was successfully developed. Thus benzoxazolinone-6-carbaldehyde (**3**) was carried out by the formylation of 3-methyl-2-oxo-3H-benzoxazole (**1**) using hexamethylenetetramine (HMTA) in polyphosphoric acid (PPA). The designed compounds were prepared by the treatment of compound (**3**) with primary amines in the presence of methanol as solvent, by using ultrasonic-assisted method under catalyst-free conditions and conventional heat in methanol at reflux in presence of catalytic amount of acetic acid, to afforded the pure desired 6-imino-2-oxo-3H-benzoxazoles (**4a-4f**) in appreciable yields; their purity was confirmed by melting point as well as thin layer chromatography (TLC). The chemical structures of the new synthesized compounds were elucidated on the basis of the FT-IR, ^{1}H and ^{13}C-NMR spectroscopic techniques.*

Keywords: 2-Oxo-3H-benzoxazole, Imines, Ultrasound irradiations, Conventional heat.

1. Introduction

2-oxo-3*H*-benzoxazole ring represents one of the important and preferred scaffolds for a bioisosteric replacement in the field of medicinal chemistry, to develop new molecules with interesting potential biological activities [1]. 2-oxo-3*H*-benzoxazole derivatives have been described as allochemical compounds, which play an important role in the resistance of plant to insect pests and plant pathogenic fungi; these compounds are therefore also relevant as potential substitutes for pesticides in plant protection [2-3]. 2-oxo-3*H*-benzoxazole is also a cyclic isostere of coumarin whose antimicrobial activities have been extensively investigated and performed [4-5]. They have been incorporated into a wide variety of pharmaceutically interesting drug candidates and have also been used as lead

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structure in the design of novel antiviral compounds, particularly directed against Human immunodeficiency Virus (HIV) and cytomegalovirus (CMV) species [6]. In the literature, several works on the bioactive substances based on the benzoxazolinonic nucleus have led to the discovery of a number of derivatives endowed with various types of biological activities, such as antibacterial and antifungal [7], insecticide [8], anti-HIV [9], analgesic and anti-inflammatory [10-12] as well as cytotoxicity against various cancer cell lines [13-15].

Imines derivatives possessing an azomethine group –N=CH–, on the other hand, are an important class of compounds that have a wide variety of applications in many fields [16-18]. The considerable number of publications, and the various applications concerning this type of compounds in organic synthesis, especially for the synthesis of nitrogen-containing heterocyclic compounds, implicates that these derivatives are one of the most widely studied organic compounds. So much interest in imines can be explained by the fact that the presence of the carbon-nitrogen (C=N) bond in imines, makes them one of the most important functional groups in organic chemistry, chemical catalysis and medicinal chemistry. They have also received much interest in the field of biochemistry and medicinal chemistry due to the wide range of their potential pharmacological properties, including antimicrobial [19-21], antibacterial [22], antifungal [23], antitumor [24], anticancer [25], antiviral [26] and antioxidant [27] activities. The development of efficient methods to construct new imine derivatives has attracted the interest of researchers and has been the subject of considerable synthetic effort for organic reactions [28]. Therefore, several strategies have been developed for the formation of the nitrogen–carbon double bond; this can be realized by the reaction of carbonyl compounds with primary amines under a variety of conditions [29-31]. Thus, the benzoxazolone containing heterocyclic imine appears to be an ideal pharmacophore for design and development of various pharmacologically active lead compounds.

In addition, in view of the restricted applications of protocols using conventional heat with strong acidic conditions, requiring prolonged reaction time, toxic organic solvents, expensive and toxic catalysts as well as higher temperatures; recent several studies directed towards the development of eco-friendly approaches have been reported in the literature [32-36]. Consequently, intensive research efforts based on the use of methodologies employing green approaches have been reported to promote the synthesis of highly functionalized Schiff base compounds [37-41].

In this regard, the ultrasound irradiation has been used over the last few years as a versatile tool in a large variety of applications [42-45]. Ultrasound-assisted chemical reactions can be considered environmentally benign methods. They possess several advantages such as improved yields and selectivity, easy

purification, significant decreases of reaction time, lower costs, and are more energy efficient [46-47].

Motivated by these interesting results and in continuation of our efforts toward development of useful green synthetic methodology [48–50], we report a successful and convenient procedure for the preparation of some novel heterocyclic imines as potential antimicrobial agents. The benzoxazole nucleus was used as precursors from reaction of 3-methyl-2-oxo-3*H*-benzoxazole-6-carbaldehyde with different primary amines (Fig. 1), under ultrasound irradiations as well as conventional heat.

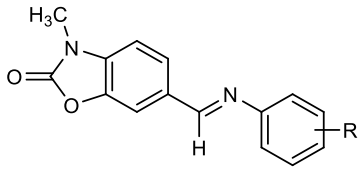


Fig. 1: General structure of the synthesized Schiff base ligands (**4a-4f**).

2. Materials and methods

2.1. General

Melting points were determined using a Köfler apparatus and are uncorrected. The structures of the newly synthesized compounds were elucidated by IR and nuclear magnetic resonance (NMR) spectroscopy. The Fourier Transform Infrared (FT-IR) spectra were measured by the KBr disc method using Shimadzu FT-IR 8300S infrared spectrophotometer. FT-IR spectra were recorded in the transmittance mode over the range of 500–4000 cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were measured in solutions on a Bruker AC 400 spectrometer using dimethylsulfoxide-d_6 and chloroform $CDCl_3$ as solvents with TMS as internal standard, with chemical shifts reported as (*ppm*). Analytical thin layer chromatography was performed with commercial silica gel plates 60 F254 (Merck) and visualized with UV light, using ethyl acetate/cyclohexane (6:4, v/v) solvent system as eluent. Ultrasound assisted reactions were carried out using a FUNGILAB ultrasonic bath with a frequency of 40 kHz and a nominal power of 250 W. The reactions were carried out in an open glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 mL) at 80°C. The purity and chemical structures were detected by sharp melting point, IR and ^{1}H-NMR as well as ^{13}C-NMR spectra.

2.2. Methods and procedures

2.2.1. Synthesis of 2-oxo-3*H*-benzoxazole (1)

A mixture of 2-aminophenol (10.91 g, 0.1 mol) and urea (18.01 g, 0.3 mol, 3 equiv.) was placed in a flask equipped with a reflux condenser, and a few drops of concentrated hydrochloric acid were added under magnetic agitation. The reaction mixture was stirred and heated at 160-165°C for 3 hours. After cooling, the mixture was diluted with water under stirring. The precipitate formed was filtered using a Buchner funnel, and washed repeatedly with water to produce 2-oxo-3*H*-benzoxazole (**1)**. Compound **1** was obtained as beige solid. Yield 10.45 g (97%). Mp: 136–138°C (Ref. [51]; 137–138°C).

2.2.2. Synthesis of 3-methyl-2-oxo-3*H*-benzoxazole (2)

To a solution of the sodium hydroxide (1.77 g, 0.044 mol) in 20 mL of ice water, was added the 2-oxo-3*H*-benzoxazole (5g, 0.037 mol) and then dimethyl sulfate (5.54 g, 0.044 mol) was added slowly under magnetic agitation for 3 hours at room temperature. The progress of reaction was monitored by thin layer chromatography (**TLC**). After completion of reaction, the residue formed was filtered, dried and recrystallized from cyclohexane to isolate pure 3-methyl-2-oxo-3*H*-benzoxazole **(2)**. Compound **2** was obtained as light green solid. Yield: 72%; Mp: 83–84°C. The melting point as well as spectroscopic data of the obtained compound is in accordance with published data [52].

2.2.3. Synthesis of 2,3-dihydro-3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde (3)

into a flask equipped with a reflux condenser containing 3-methyl-2-oxo-3*H*-benzoxazole (2 g, 0.013 mol) in 34.05 g of polyphosphoric acid (PPA), was added hexamethylenetetramine (HMTA) (0.02 mol, 3.08 g), and the mixture was heated at 150°C for 10 minutes. The resultant mixture was poured into ice water (50 mL) with vigorous stirring for 1h, and extracted with chloroform (3x20 mL). The combined organic layers were washed with water (2x40 mL) and dried over calcium chloride. After removal of the solvent *in vacuo*, the formylated derivative was purified by recrystallization from ethanol to give pure desired product. Compound **3** was obtained as light yellow solid. Yield: 77%; Mp: 145–146°C ((Lit. [53]; 145–146°C).

2.2.4. General procedure for the preparation of 3-methyl-6-((E)-(arylimino)methyl)benzo[d]oxazol-2(3*H*)-ones (4a-4g)

The following procedures illustrate the two general methods used to convert the parent 3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde (**3**) into substituted 6-iminobenzoxazolone derivatives.

***Conventional method (Method 1)*:** To a solution of amine derivatives (1.0 equiv., 2.8 mmol) dissolved in pure methanol, was added a solution of 6-carbaldehyde **3** (50 mg, 2.8 mmol) in the same solvent. The resulting mixture was stirred under reflux conditions for 1-5h in the presence of acetic acid as catalyst, until completion of the reaction (monitored by TLC) using ethyl acetate/cyclohexane (6:4, v/v) as eluent. The resulting solid was collected by simple filtration, washed with cold methanol, dried and purified to afford the suitable pure products in satisfactory yields.

***Ultrasound method (Method 2)*:** The procedure was similar to that described in method **1**, except that the mixture was placed in an open glass tube and exposed to ultrasound irradiations (40 kHz and nominal power 250 W) at 80°C, under catalyst-free conditions for the appropriate time, until completion of the reaction (monitored by TLC).

2.2.4.1. 3-methyl-6-((E)-(phenylimino)methyl)benzo[d]oxazol-2(3*H*)-one (4a)

Following the typical procedure 2.2.4 (method **1** and method **2**), pure 3-methyl-6-((E)-(phenylimino)methyl)benzo[d]oxazol-2(3*H*)-one **4a** was obtained as Light brown powder by the reaction of aniline and 3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde **3**. Yield: method **1** (28%) and method **2** (52%). Mp: 188–190°C. IR (KBr, cm^{-1}): 2954 (CH_3), 1774 (C=O, oxazole), 1623 (C=N in imine), 1602-1585 (aromatic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3. 48 (s, 3H, $\underline{CH_3}$-N), 7.05-7.89 (m, 8H, Ar-$\underline{H}$), 8.46 (s, 1H, $\underline{C}$H=N, azomethine). ^{13}C-NMR (100MHz, $CDCl_3$): δ 28.38 (CH_3-N), 120.82-143.09 (Aromatic carbons), 158.95 (C=O), 151.61 (N=C).

2.2.4.3. 6-((E)-(2-mercaptophenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one (4b)

Following the typical procedure 2.2.4 (method **1** and method **2**), pure 6-((E)-(2-mercaptophenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one **4b** was obtained as white powder by the reaction of 2-mercaptoaniline and 3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde **3**. Yield: method **1** (64%) and method **2** (91%). Mp: 252–254°C. IR (KBr, cm^{-1}): 2943-2981 (CH_3), 1774 (C=O, oxazole), 1612 (C=N in imine), 1557 (aromatic C=C). ^{1}H-NMR (400 MHz, CDCl3): δ = 3.48 (s, 3H, $\underline{CH_3}$-N), 7.05-7.89 (m, 7H, Ar-$\underline{H}$), 8.46 (s, 1H, $\underline{C}$H=N, azomethine). ^{13}C-NMR (100MHz, $CDCl_3$): δ 28.38 (CH_3-N), 108.20-154.07 (Aromatic carbons), 166.95 (C=O), 154.61 (N=C).

2.2.4.4. 6-((E)-(4-methoxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one (4c)

Following the typical procedure 2.2.3 (method **1** and method **2**), pure 6-((E)-(4-methoxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one **4c** was obtained as white powder by the reaction of 4-methoxyaniline and 3-methyl-2-

oxobenzo[d]oxazole-6-carbaldehyde **3**. Yield: method **1** (75%) and method **2** (88%). Mp: 202–204°C. IR (KBr, cm^{-1}): 2889-2954 (CH_3), 1762 (C=O, oxazole), 1604 (C=N in imine), 1578 (aromatic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.48 (s, 3H, $\underline{CH_3}$-N), 3.87 (s, 3H, -O-$\underline{CH_3}$), 6.95-7.88 (m, 7H, Ar-$\underline{H}$), 8.49 (s, 1H, $\underline{C}$H=N, azomethine). ^{13}C-NMR (100MHz, $CDCl_3$): δ 28.36 (CH_3-N), 55.54 (CH_3-O), (CH_3-Ar), 107.88-143.08 (Aromatic carbons), 162.00 (C=O), 156.93 (N=C).

2.2.4.5. 6-((E)-(4-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one (4d)

Following the typical procedure 2.2.4 (method **1** and method **2**), pure 6-((E)-(4-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3H)-one **4d** was obtained as white powder by the reaction of 4-hydroxyaniline and 3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde **3**. Yield: method **1** (72%) and method **2** (83%). Mp: 270–272°C. IR (KBr, cm^{-1}): 3421 (OH), 2916-2947 (CH_3), 1760 (C=O, oxazole), 1605 (C=N in imine), 1581 (aromatic C=C). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 3.38 (s, 3H, $\underline{CH_3}$-N), 3.33 (s, 1H, OH), 6.79-7.82 (m, 7H, Ar-$\underline{H}$), 8.61 (s, 1H, $\underline{C}$H=N, azomethine). ^{13}C-NMR (100MHz, $CDCl_3$): δ 28.76 ($\underline{C}H_3$-N), 108.27-154.57 (aromatic carbons), 156.67 (N=C), 156.92 (C=O).

2.2.4.6. 6-((E)-(2-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one (4e)

Following the typical procedure 2.2.4 (method **1** and method **2**), pure 6-((E)-(2-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one **4e** was obtained as yellow powder by the reaction of 2-hydroxyaniline and 3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde 3. Yield: method 1 (48%) and method 2 (72%). Mp: 250–252°C. IR (KBr, cm^{-1}): 3421 (OH), 2920 (CH_3), 1775 (C=O, oxazole), 1620 (C=N in imine), 1585 (aromatic C=C). ^{1}H-NMR (400 MHz, DMSO-d6): δ = 3.39 (s, 3H, $\underline{CH_3}$-N), 6.82-8.16 (m, 7H, Ar-$\underline{H}$), 8.74 (s, 1H, $\underline{C}$H=N, azomethine), 8.95 (s, 1H, OH). ^{13}C-NMR (100MHz, $CDCl_3$): δ 28.78 ($\underline{C}H_3$-N), 108.75-152.02 (Aromatic carbons), 154.62 (N=C), 158.50 (C=O).

2.2.4.7. 6-((E)-(5-chloro-2-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one (4f)

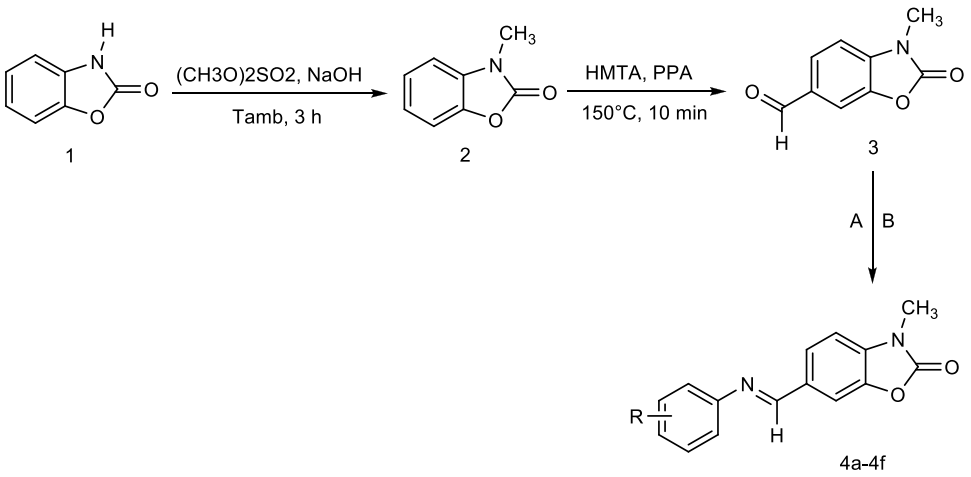
Following the typical procedure 2.2.4 (method **1** and method **2**), pure 6-((E)-(5-chloro-2-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3*H*)-one **4f** was obtained as yellow powder by the reaction of 5-chloro-2-hydroxyaniline and 3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde **3**. Yield: method **1** (53%) and method **2** (79%). Mp: 276–278°C. IR (KBr, cm^{-1}): 3390 (aromatic O-H), 2696 (CH_3), 1766 (C=O, oxazole), 1627 (C=N in imine), 1605-1589 (aromatic C=C), 748 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.33 (s, 3H, $C\underline{H_3}$-N), 6.89-8.13 (m, 6H, Ar-$\underline{H}$), 8.76 (s, 1H, $C\underline{H}$=N, azomethine). ^{13}C-

NMR (100MHz, $CDCl_3$): δ 28.78 (CH_3-N), 108.75-152.02 (Aromatic carbons), 154.59 (N=C), 160.24 (C=O)

3. Results and discussions

3.1. Chemistry

The synthesis pathway illustrating our strategy for the preparation of the title compounds is given in Scheme 1. 2-oxo-3*H*-benzoxazole, starting material (**1**), was synthesized according to the literature method using 2-aminophenol and urea [51]. The 2-aminophenol was treated with urea under acidic conditions to obtain 2-oxo-3*H*-benzoxazole (**1**), which was further reacted with dimethyl sulfate in basic medium NaOH to afford the N-methylated compound 3-methyl-2-oxo-3*H*-benzoxazole (**2**) [52]. The 3-methyl-2-oxo-3*H*-benzoxazole-6-carbaldehyde (**3**) was prepared *via* formylation reaction of the 3-methyl-2-oxo-3*H*-benzoxazole (**2**) with hexamethylenetetramine (HMTA) in polyphosphoric acid (PPA) at 150°C, which produced a 77% yield. For formylation; as both the **3**-nitrogen and **1**-oxygen atoms are electron-donating, both **5-** and **6**-position are activated, but the reaction is regioselective and only the **6-**formyl derivative is formed [53]. This carbaldehyde derivative was then reacted with various primary amines, using two different methods (conventional synthesis and reaction under ultrasound conditions); resulting in imine compounds (**4a**–**4f**) with an azomethine group at the 6-position of the benzoxazole ring. The yields were moderate when the imines were synthesized by conventional method in methanol at reflux in presence of catalytic amount of acetic acid. The use of ultrasound irradiations under catalyst-free condition, on the other hand, has resulted in the formation of the desired imine derivatives in shorter reaction times (2–15 minutes), higher yields (52–91%) and purity of the final products. The proposed structures of the synthesized products, yields and reaction times for the condensation of various primary amines 3-methyl-2-oxo-3*H*-benzoxazole-6-carbaldehyde, using conventional heat synthesis (Method **1**) and reaction under ultrasound conditions (Method **2**) are listed in Table 1. The spectroscopic data related to these new products were in complete accord with the proposed structures.

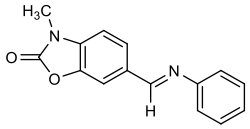
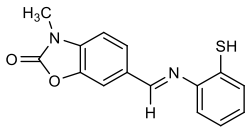
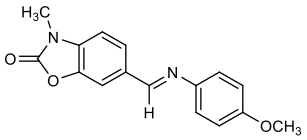
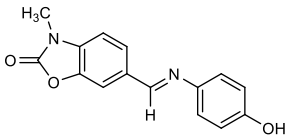
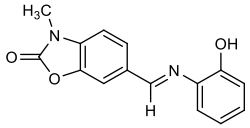
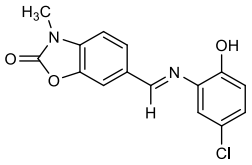


Scheme 1: Synthesis of the target imines. **A**: Method **1** (Conventional heat: Methanol, Reflux, Glacial acetic acid, 28–75%, 2.30–5h); **B:** Method **2 (**Ultrasound irradiations: Catalyst-free conditions, 80°C, Methanol, 52–91%, 2–15min).

The structure of the synthesized compounds were elucidated by IR, ^{1}H-NMR and ^{13}C-NMR spectra. The spectral data of the isolated products were completely compatible with their proposed structures. For example, the infrared spectra of the prepared compounds reveals the absence of the band at about 1700 cm^{-1} for the carbonyl group (C=O) of starting aldehyde, and the presence of a band in the region 1600−1627 cm^{-1} attributed to the azomethine (−N=C−H) bond, thereby confirming the formation of the imine in all cases. Furthermore, the formation of the imine group was confirmed by appearance of a singlet at δ 8.46 to 8.76 for the methine protons characteristic of the azomethine proton, −N=C(H) in the ^{1}H-NMR spectra. The aromatic protons in the imine derivatives appeared in the range at δ 6.79–8.16. The signals due to benzoxazolone methylene protons present in all the prepared compounds appeared at 3.33–3.48 ppm, as singlets. The ^{13}C-NMR spectra gave more information on the formation of the imine products. A signal at 165.4 ppm in compounds **4a**–**4f** was assigned to the carbonyl carbon C=O of the benzoxazole moiety. The azomethine carbon is observed at 151.61–156.93 ppm in the spectrum of all compounds. Also, signals due to aromatic carbon atoms are resonating at a chemical shift between 107.88–154.07 ppm. Aliphatic methyl carbon was assigned to a signal between 28.38–28.78 ppm. All other aliphatic and aromatic protons, which were observed at the predictable regions, support the proposed structures.

Table 1

Newly synthesized 6-Iminobenzoxazole derivatives (4a-4f)

Compound	[a]Structure	Method **1** Time (h)	[b]Yield (%)	Method **2** Time (min)	[b]Yield (%)	Mp(°C)	Mol. Formula
4a		5	28	3	52	188–190	$C_{15}H_{12}O_2N_2$
4b		4	64	15	91	252–254	$C_{15}H_{12}O_2N_2S$
4c		2.30	75	3	88	202–204	$C_{16}H_{14}O_3N_2$
4d		3	72	2	83	270–272	$C_{15}H_{12}O_3N_2$
4e		5	48	5	72	250–252	$C_{15}H_{12}O_3N_2$
4f		3	53	7	79	276–278	$C_{15}H_{11}O_2N_2Cl$

[a]All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, and IR spectroscopy.
[b]Isolated and optimized yields.

4. Conclusions

In this study, an environmentally benign synthesis approach has been successfully applied for preparing new substituted five-membered heterocycle derivatives containing 2-oxo-3H-benzoxazole using ultrasound irradiation and conventional heating methodologies. The ultrasound-assisted synthesis has been compared with the conventional method and the results obtained from this comparative study showed that the ultrasound technique is superior. Additionally, high yields of the products, shorter reaction times and high purity of the final isolated compounds make it an attractive and advantageous method in organic synthesis. Thus, this protocol can be applied and extended to the preparation of various other heterocyclic substrates structurally comparable having important pharmaceutical interest. Furthermore, this research study was essential to accelerate the drug discovery and development process, and can be used to discover biologically active compounds that may serve as leads for the development of new and more potent synthetic compounds. However, we hope that these results could make an additional contribution and a solid platform for future studies in the development of novel antimicrobial drugs bioactive compounds.

REFERENCES

[1]. *J. Poupaert, P. Carato, E. Colacino, S. Yous*, "2(3H)-Benzoxazolone and Bioisosters as "Privileged Scaffold" in the Design of Pharmacological Probes**"**, Current Medicinal Chemistry, **vol. 12,** no. 7, 2005, pp. 877–885

[2]. *D.R. Batish, H.P. Singhb, N. Setia, S. Kaur, R.K. Kohli*, "2-Benzoxazolinone (BOA) induced oxidative stress, lipid peroxidation and changes in some antioxidant enzyme activities in mung bean (Phaseolus aureus)", Plant Physiology and Biochemistry, **vol. 44**, no. 11-12, 2006, pp. 819–827

[3]. *E. Eljarrat, D. Barcelo*, "Sample handling and analysis of allelochemicalcompounds in plants", Trends in analytical chemistry**, vol. 20**, no. 10, 2001, pp. 584–590

[4]. *G. Tataringa, C. Tuchilus, A. Jitareanu, A.M. Zbancioc*, "antimicrobial prospection of some coumarin derivatives", Farmacia, **vol. 66**, no. 2, 2018, pp. 323–330

[5]. *P. López-Rojas, M. Janeczko, K. Kubiński, Á. Amesty, M. Masłyk, A. Estévez-Braun*, "Synthesis and Antimicrobial Activity of 4-Substituted 1,2,3-Triazole-Coumarin Derivatives", Molecules, **vol. 23**, no. 1, 2018, pp. 199(1-18)

[6]. *H.X. Wang, T.B. Ng*, Comparative Biochemistry and Physiology, Part C/ Toxicology & Pharmacology, **vol. 132C**, no. 2, 2002, pp. 261–268

[7]. *D.D. Erol, M.D. Aytemir, N. Yuluğ N*, "Synthesis and antibacterial and antifungal properties of thiazolinoethyl-2(3H)-benzoxazolone derivatives", European Journal of Medicinal Chemistry, **vol. 31**, no. 9, 1996, pp. 731–734

[8]. *A. Friebe*, "Role of benzoxazinones in cereals", Journal of Crop Production, **vol. 4**, no. 2, 2001, pp. 379–400

[9]. *B.-L. Deng, M.D. Cullen, Z. Zhou, T.L. Hartman, R.W. Buckheit, C. Pannecouque, E.D. Clercq, P.E. Fanwick, M. Cushman*, "Synthesis and anti-HIV activity of new alkenyldiarylmethane (ADAM) non-nucleoside reverse transcriptase inhibitors (NNRTIs) incorporating benzoxazolone and benzisoxazole rings", Bioorganic Medicinal Chemistry, **vol. 14**, no. 7, 2006, pp. 2366–2374

[10]. *Y. Mulazim, C. Berber, H. Erdogan, M. Hacer Ozkan, B. Kesanli*, "Synthesis and analgesic activities of some new 5-chloro-2(3H)-benzoxazolone derivatives, The EuroBiotech Journal, **vol. 1**, no. 3, 2017, pp. 1–6

[11]. *N. Gökhan, H. Erdoğan, B.Tel, R. Demirdamar*, "Analgesic and antiinflammatory activity screening of 6-acyl-3-piperazinomethyl-2-benzoxazolinone derivatives", European Journal of Medicinal Chemistry, **vol. 31**, no. 7-8, 1996, pp. 625–628

[12]. *N. Gökhan, H. Erdoğan, N.T. Durlu, R. Demirdamar, M. Ozalp*, "Synthesis and evaluation of analgesic, antiinflammatory and antimicrobial activities of 6-acyl-3-piperazinomethyl-2-benzoxazolinones", Arzneimittel-Forschung/Drug Research, **vol. 53**, no. 2, 2003, pp. 114–120

[13]. *Y. Ivanova, G. Momekov, O. Petrov, M. Karaivanova, V. Kalcheva*, "Cytotoxic mannich bases of 6-(3-aryl-2-propenoyl)-2(3H)-benzoxazolones", European Journal of Medicinal Chemistry, **vol. 42**, no. 11-12, 2007, pp. 1382–1387

[14]. *O. Petrov, Y. Ivanova, G. Momekov, V. Kalcheva*, "New synthetic chalcones: cytotoxic Mannich bases of 6-(4-chlorocinnamoyl)-2(3H)-benzoxazolone", Letters in Drug Design & Discovery, **vol. 5**, no. 6, 2008, pp. 358–361

[15]. *Y.B. Ivanova, G.T. Momekov, O.I. Petrov*, "New heterocyclic chalcones. Part 6. Synthesis and cytotoxic activities of 5- or 6-(3-aryl-2-propenoyl)-2(3H)-benzoxazolones", Heterocyclic Communications, **vol. 19**, no. 1, 2013, pp. 23–28

[16]. *D.N. Dhar, C.L. Taploo*, "Schiff bases and their applications", Journal of scientific and industrial research, **vol. 41**, no. 8, 1982, pp. 501–506

[17]. *A. Mohindru, J.M. Fisher, M. Rabinovitz*, "Bathocuproine sulphonate: A tissue culture-compatible indicator of copper-mediated toxicity", Nature, **vol. 41**, no. 5912, 1983, pp. 64−65

[18]. *K. Małgorzata Brodowska, E. Lodyga-Chruscinska*, "Schiff bases–interesting range of applications in various fields of science", *Chemik*, **vol. 68**, no. 2, 2014, pp. 129−134

[19]. *L. Shi, H.M. Ge, S.H. Tan, H.Q. Li, Y.C. Song, H.L. Zhu, R.X. Tan*, "Synthesis and antimicrobial activities of schiff bases derived from 5-chloro-salicylaldehyde", European Journal of Medicinal Chemistry, **vol. 42**, no. 4, 2007, pp. 558–564

[20] *B. Soni, M.S. Ranawat, R. Sharma, A. Bhandari, S. Sharma*, "Synthesis and evaluation of some new benzothiazole derivatives as potential antimicrobial agents", European Journal of Medicinal Chemistry, **vol. 45**, no. 7, 2010, pp. 2938−2942

[21]. *M. Salihović, M. Pazalja, I. Mahmutović-Dizdarević, A. Jerković-Mujkić, J. Suljagić, S. Špirtović-Halilović, A. Šapčanin*, "Synthesis, DFT Study and Antimicrobial activity of schiff bases derived from benzaldehydes and amino acids", Rasayan Journal of Medicinal Chemistry, **vol. 11**, no. 3, 2018, pp. 1074−1083

[22]. *B.B. Sokmen, N. Gumrukcuoglu, S. Ugras, H. Sahin, Y. Sagkal, H.I. Ugras*, "Synthesis, Antibacterial, Antiurease, and Antioxidant Activities of Some New 1,2,4-Triazole Schiff Base and Amine Derivatives", Applied Biochemistry and Biotechnology, **vol. 175**, no. 2, 2015, pp. 705–714

[23]. *I. Karakaya, S. Karabuga, Z. Ulukanli, S. Ulukanli*, "Synthesis and antifungal evaluation of imines derived from 3-Amino-2-isopropyl-3H-quinazolin-4-one", Organic Communication, **vol. 6**, no. 4, 2013, pp. 139−147

[24]. *Sarah A. Mahdi*, "A study on Antitumor Effect of 1, 2, 4-Thiadiazole Derivatives in Liver and Breast Cancer Cell Lines Hep G2 by Using (HCS) Technique", Journal of Al-Nahrain University, **vol. 20**, no. 4, 2017, pp. 27−31

[25]. *J.A. Makawana, C.B. Sangani, L. Lin, H.L. Zhu*, "Schiff's base derivatives bearing nitroimidazole and quinoline nuclei: New class of anticancer agents and potential EGFR tyrosine kinase inhibitors", Bioorganic Medicinal Chemistry Letters, **vol. 24**, no. 7, 2014, pp. 1734–1736

[26]. *D. Sriram, P. Yogeeswari, N.S. Myneedu, V. Saraswat*, "Abacavir prodrugs: microwave-assisted synthesis and their evaluation of Anti-HIV activities", Bioorganic&Medicinal Chemistry Letters, **vol. 16**, no. 8, 2006, pp. 2127−2129

[27] *H. Chabane, M. Messarah, M. Liacha*, "Comparative study for the synthesis of new generation of 2(3H)-benzothiazolones as antioxidant agents", *Der Pharma Chemica*, **vol. 8**, no. 15, 2016, pp. 20−26

[28]. *W. Qin, S. Long, M. Panunzio, S. Biondi*, "Schiff Bases: A Short Survey on an Evergreen Chemistry Tool", *Molecules*, **vol. 18**, no. 10, 2017, pp. 12264−12289

[29]. *M. C. Mandewale, B. Thorat, U. Patil, R. Yamgar*, "Review: Synthesis and Applications of Schiff Bases", International Journal of chemical and pharmaceutical sciences, **vol. 3**, no. 8, 2015, pp. 1438−1447

[30]. *J. Kumar, A. Rai, V. Raj*, "A Comprehensive Review on the Pharmacological Activity of Schiff Base Containing Derivatives", Organic and Medicinal Chemistry International Journal, **vol. 1**, no. 3, 2017, pp. 1−14

[31]. *S.U. Cicekli, T. Onkol, S. Ozgen, M. F. Sahin*, "Schiff bases of 3-[(4-amino-5-thioxo-1,2,4-triazole-3-yl)methyl]-2(3H)benzoxazolonederivatives:synthesis and biological activity", Revue Roumaine de Chimie, **vol. 57**, no. 3, 2012, pp. 187−195

[32]. *A. V. Chate, U. B. Rathod, J. S. Kshirsagar, P. A. Gaikwad, K. D. Mane, P. S. Mahajan, M. D. Nikam, C. H. Gill*, "Ultrasound assisted multicomponent reactions: A green method for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines using β-cyclodextrin as a supramolecular reusable catalyst in water", Chinese Journal of Catalysis **vol. 37**, no. 1, 2016, pp. 146–152

[33]. *A. Sharma, P. Appukkuttan, E. Van der. Eycken*, "Microwave-assisted synthesis of medium-sized heterocycles", Chemical Communications, **vol. 48**, no. 11, 2012, pp. 1623–1637

[34]. *M.A. bakht*, "Lemon Juice catalyzed Ultrasound assisted synthesis of Schiff's base: A Total Green approach", Bulletin of Environment, Pharmacology and Life Sciences, **vol. 4**, no. 10, 2015, pp. 79−85

[35]. *V. Vahabi, F. Hatamjafari*, "Microwave assisted convenient one-pot synthesis of coumarin derivatives via Pechmann condensation catalyzed by FeF3 under solvent-free conditions and antimicrobial activities of the products", Molecules, **vol. 19**, no. 9, 2014, pp. 13093−13103

[36]. *R. patil, D. Kumbhar, S. Jadhav, S. More, P. Choudhari, M. Bhatia, M. Deshmukh*, "An Ecofriendly Synthesis, Molecular Docking and Antimicrobial Evaluation of 5-Arylidyne 2-Thiobarbituric Acid Derivatives", International Journal of Pharmaceutical Sciences Review and Research, **vol. 31**, no. 2, 2015, pp. 1−4

[37]. *H. Chabane, Y. Adjeroud, M. Liacha*, "Microwave-assisted and conventional synthesis of new nitrobenzaldehyde-Schiff base ligands derived from benzothiazolone with potential catalytic properties: A comparative study", PhytoChem&BioSub Journal, **vol. 10**, no. 2, 2016, pp. 73−78

[38]. *A. Shinde, S. Zangade, S. Chavan, Y. Vibhute*, "Microwave induced synthesis of bis-Schiff bases from propane-1, 3-diamine as promising antimicrobial analogs", Organic. Communications, **vol. 7**, no. 2, 2014, pp. 60−67

[39]. *L. Ravishankar, S.A. Patwe, N. Gosarani, A. Roy*, "Cerium(III)-Catalyzed Synthesis of Schiff Bases: A Green Approach", Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, **vol. 40**, no. 21, 2010, pp. 3177−3180

[40]. *M. Chakraborty, Sanjay Baweja, S. Bhagat, T.S. Chundawat*, "Microwave Assisted Synthesis of Schiff Bases: A Green Approach", International Journal of Chemical Reactor Engineering, **vol. 10**, no. A53, 2012, pp. 1–12

[41]. *V.K. Rao, S.S. Reddy, B.S. Krishna, K.R.M. Naidu, C.N. Raju, S.K. Ghosh*, "Synthesis of Schiff's bases in aqueous medium: a green alternative approach with effective mass yield and high reaction rates", Green Chemistry Letters and Reviews, **vol. 3**, no. 3, 2010, pp. 217−223

[42]. *S. Tangestaninejad, M. Moghadam, V. Mirkhani, H. Kargar*, "Efficient and selective hydrocarbon oxidation with sodium periodate under ultrasonic irradiation catalyzed by polystyrene-bound Mn (TPyP)", Ultrasonics Sonochemistry, **vol. 13**, no. 1, 2006, pp. 32–36

[43]. *G. Cravotto, M. Beggiato, A. Penoni, G. Palmisano, S. Tollari, J.M. Leveque, W. Bonrath*, "High-intensity ultrasound and microwave, alone or combined, *promote Pd*/*C-catalyzed aryl–aryl couplings*", Tetrahedron Letters, **vol. 46**, no. 13, 2005, pp. 2267–2271

[44]. *G. Cravotto, G. Palmisano, S. Tollari, G.M. Nano, A. Penoni*, "The Suzuki homocoupling reaction under high-intensity ultrasound", Ultrasonics Sonochemistry, **vol. 12**, no. 1-2, 2005, pp. 91–94

[45]. *D.E. Crawford*, "Solvent-free sonochemistry: Sonochemical organic synthesis in the absence of a liquid medium", Beilstein Journal of Organic Chemistry, **vol. 13**, no. 1, 2017, 1850–1856

[46]. *K.M. Khan, W. Jamil, N. Ambreen, M. Taha, S. Perveen, G.A. Morales*, "An expeditious synthetic approach towards the synthesis of Bis-Schiff bases (aldazines) using ultrasound", Ultrasonics Sonochemistry, **vol. 21**, no. 3, 2014, pp. 1200–1205

[47]. *B.S. Singh, H.R. Lobo, D.V. Pinjari, K.J. Jarag, A.B. Pandit, G.S. Shankarling*, "Comparative material study and synthesis of 4-(4-nitrophenyl)oxazol-2-amine via sonochemical and thermal method", Ultrasonics Sonochemistry, **vol. 20**, no. 2, 2013, pp. 633–639

[48]. *K. Seddiki, W. Yahia, M. Liacha, A. Defant, D. Sighel, I. Mancini*, "Microwave-assisted synthesis of new imide- and formamide-derivatives of 2(3*H*)-benzoxazolinones and 2(3*H*)-benzothiazolinones", ARKIVOC, **vol. part iv**, 2017, pp. 315–329

[49]. *Y. Adjeroud, H. Chabane, M. Liacha*, "comparative study of conventional and microwave-assisted synthesis of novel 6-(arylideneamino)benzo[d]oxazol-2(3*H*)-ones with potential antibacterial activity", Revue Roumaine de Chimie, **vol. 61**, no. 2, 2016, pp. 111–117

[50]. *H. Chabane, Y. Adjeroud, M. Liacha*, "Convenient synthesis and characterization of some novel benzothiazolone-based Schiff bases as potential pharmaceutically active agents", Organic Communications, **vol. 10**, no. 1, 2017, pp. 24–31

[51]. *G. Eren, S. Unlu, M.T. Nunez, L. Labeaga, F. Ledo, A. Entrena, E. Banoglu, G. Costantino, M.F. Sahin*, "Synthesis, biological evaluation, and docking studies of novel heterocyclic

diaryl compounds as selective COX-2 inhibitors", Bioorganic Medicinal Chemistry, **vol. 18**, no. 17, 2010, pp. 6367–6376

[52]. *P. Renard, D. Lesieur, C. Lespagnol, M. Cazin, C. Brunet, J.C. Cazin*, "Acyl-6 benzoxazolinones et acides (acyl-6-oxo-2-benzoxazolinyl-3)alcanoiqines", European Journal of Medicinal Chemistry, **vol. 15**, no. 5, 1980, 453-456

[53]. *J.P. Bonte, D. Lesieur, C. Lespagnol, M. Plat, M. Cazin*, "6-Acyl-benzoxazolinones", European Journal of Medicinal Chemistry, **vol. 9**, no. 5, 1974, pp. 491–496