CONVENTIONAL AND ULTRASOUND ASSISTED SYNTHESIS AND ANTIBACTERIAL EVALUATION OF SOME *N′*-(NITRO-SUBSTITUTED BENZYLIDENE)-2(3-OXO-2*H*-BENZO[B][1,4]OXAZIN-4(3*H*)-YL)ACETOHYDRAZIDE

Nawel CHETTIBI[1], Houria BENTOUMI[2], Messaoud LIACHA[3]*

An efficient and simple method for the synthesis of some novel benzoxazinonylacetohydrazide derivatives has been developed, using conventional heating and ultrasound (US) irradiation, by condensation of benzoxazinonylhydrazide intermediate with various 2,3,4-nitrosubstituted benzaldehydes. The yields as well as reaction times are compared. The structures of the synthesized acetohydrazide derivatives were elucidated and characterized on the basis of FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The synthesized compounds were screened for their antibacterial and antifungal activities in vitro. Derivative having nitro group on the 3-position in the aldehyde aromatic ring exhibited the strongest activity for all tested compounds.

Keywords: Benzoxazin-3-(4*H*)-ones, Hydrazides-Hydrazones, Antimicrobial, Green synthesis, Ultrasound irradiation.

1. Introduction

During the last decade, greener and eco-friendly approach as well as synthetic organic chemistry methods have received increasing attention and are often considered as an interesting alternative for conventional heating reactions requiring long term heating [1-3]. Effectively, a large number of organic reactions can be carried out under milder reaction conditions in higher yields, for the synthesis of bioactive heterocyclic compounds under non-conventional methods [4-10]. Recent improvements have been made to these methods, including the use of ultrasound irradiations [11-13].

Benzoxazine derivatives are very important compounds used in organic synthesis for the development of new heterocyclic systems. They have gained considerable attention due to their variety of applications including agricultural and diverse biological properties [14-22]. However, it is interesting to note that the 1,4-benzoxazin-3(4*H*)-one nucleus represents an ideal scaffold for the synthesis of potent antimicrobial agents. Flumioxazine and Thidiazimine are examples of compounds containing a 1.4-benzoxazinone pharmacophore used as

[1] BADJI Mokhtar-Annaba University, Annaba, Algeria, E-mail: Nawelchettibi23@yahoo.fr
[2] BADJI Mokhtar-Annaba University, Annaba, Algeria, E-mail: houriabentoumi@yahoo.fr
[3] BADJI Mokhtar-Annaba University, Annaba, Algeria,
Contact author, E-mail: m_liacha@yahoo.fr

effective herbicides. They are also known to exhibit diverse pharmacological activities in areas related particularly to antimicrobials, antioxidants, anti-inflammatory, plant resistance factors against microbial diseases and insects, antifungal agents, antihypertensive and potassium channel modulating properties [23-33].

Due to the increased interest to the environmentally friendly synthetic reactions, and in continuation of our earlier published data on the synthesis of heterocyclic biologically active compounds [54-58], an attempt was made to develop a more efficient method and novel protocol, for the synthesis of new compounds containing both hydrazide and 2H-1,4-benzoxazin-3-(4*H*)-one rings in the same structure. Furthermore, we have investigated the eventual role of the benzoxazinone pharmacophore as well as position of the nitro group in the acetohydrazide subunit, on the chemical and biological activities. Finally, the synthesized compounds were tested for their antibacterial and antifungal activities.

2. Materials and methods

2.1. General

Melting points have been determined in open capillary tubes on electrothermal 9100 melting point apparatus and were uncorrected. The structures of products were confirmed by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The NMR spectra were measured in solutions on a Bruker AC 300 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 ethylacetate/cyclohexane (8:2, 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 room temperature (25°C). Preliminary testing of the antimicrobial activity of newly synthesized compounds was performed by disc diffusion method using Mueller–Hinton agar medium under described standard conditions [59].

2.2. Methods and procedures

2.2.1. Synthesis of ethyl 2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3H)-yl)acetate (2)

Method A. A mixture of benzoxazin-3(4*H*)-one (2g, 13 mmol) and ethyl bromoacetate (3.34g, 20 mmol) in the presence of anhydrous K_2CO_3 (3.59g, 26 mmol) was dissolved in dry acetone and was stirred at 60°C for 2h. The progress

of the reaction was monitored by TLC. After the completions of the reaction, the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The residue obtained was recrystallized from ethanol to give the suitable compound as a white solid.

Method B. Compound **2** was synthesized in the similar manner by a mixture of benzoxazin-3(4*H*)-one (2g, 13 mmol), ethyl bromoacetate (2.67g, 16. mmol), K_2CO_3 (0.10g, 14.37 mmol) in DMF as solvent, and the reaction was stirred at 100°C for 2h. At the end of this period, the mixture was diluted with water. The separated solid formed was filtered, washed repeatedly with water and recrystallized from ethanol to give the desired compound, which is in any point identical to that found by method **A**. The benzoxazinonic ester was used in the next step without further purification.

Compounds **2** (method **A** and method **B**) was obtained as white solid. Yield: method **A** (84%) and method **B** (82%). Mp 81-82°C; ^{1}H-NMR (400 MHz, DMSO-d6): δ=1.26-1.29 (t, 3H, CH_2-$\underline{CH_3}$, CH_3), 4.21-4.27 (q, 2H, -$\underline{CH_2}$-CH_3, CH_2) 4.65-4.68 (d, 4H, $\underline{CH_2}$COOEt, -NCO-$\underline{CH_2}$O-, 2CH_2) 6.74-7.26 (m, 4H, Ar-H); ^{13}C-NMR (100MHz, $CDCl_3$): 167.91 (C=O), 165.04 (C=O), 145.2, 128.76, 124.37, 123.06, 117.33, 114.53 (aromatic carbons), 67.62 (CH_2), 62.00 (CH_2), 43.07 (CH_2), 14.27 (CH_3).

2.2.2. Synthesis of 2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetohydrazide (3)

A solution of the ethyl 2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetate ester (2.55g, 11 mmol) in absolute ethanol was refluxed with hydrazine hydrate (2.75g, 55 mol) for 3h, monitored by TLC until completion. Solid residue was filtered out and dried to isolate corresponding pure 2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetohydrazide. Compound **3** was obtained as white solid. Yield: 83%. Mp: 171-173°C. ^{1}H-NMR (400 MHz, DMSO-d6): δ=6.89-7.03 (m, 4H, Ar-H), 8.00 (s, H, NH), 4.66-4.69 (d, 4H, **$\underline{CH_2}$**CONHNH$_2$, -NCO-**$\underline{CH_2}$**O-, 2CH_2), 4.27-4.28 (d, 2H, NH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.9 (C=O), 164.12 (C=O), 144.43, 128.74, 123.41, 122.35, 116.23, 115.07 (aromatic carbons), 66.82 (CH_2), 42.28 (CH_2).

2.2.3. General procedure for the synthesis of N′-(Nitro-Substituted Benzylidene)-2(3-oxo-2H-Benzo[b][1,4]oxazin-4(3*H*)-yl)acetohydrazides (4a-d).

A typical procedure has been used for the preparation of the all acetohydrazide derivatives.

Conventional method (method A): Substituted aromatic aldehyde derivatives (1.0 equiv., 0.23 mmol) dissolved in pure ethanol was mixed with a boiling solution of acetohydrazide **3** (50 mg, 0.23 mmol) in the same solvent. The resulting mixture was stirred under reflux conditions for 35 min in the presence of acetic acid as catalyst. After the completion monitored by TLC, using ethylacetate/cyclohexane (8:2, v/v) as eluent, the formed product was filtered off, washed with cold ethanol and then dried. The product was in addition purified by recrystallyzation from the appropriate solvent.

Ultrasound method (method B): The procedure was similar to that described in conventional method, except that the mixture was placed in an open glass tube and exposed to ultrasound irradiation (40 kHz and nominal power 250 W) at room temperature, under catalyst-free condition for the appropriate time until completion of the reaction (monitored by TLC). The resulting solid was collected by filtration and purified by recrystallyzation from the appropriate solvent.

2.2.3.1. N'-(2-Nitrobenzylidene)-2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetohydrazide (4a)

Following the typical procedure 2.2.3., pure acetohydrazide **4a** was obtained as white powder by reaction of 2-nitrobenzaldehyde and benzoxazolinonylhydrazide **3**. Yield: method **A** (77%) and method **B** (80%). Mp: 226-227°C. IR (KBr, cm^{-1}): 3425.34 (ν_{O-H}), 3251.76 (ν_{N-H}), 2985.60 (ν_{CH2}), 1685.67 ($\nu_{C=Ooxazin}$), 1608.41 ($\nu_{C=N}$), 1566.09 ($\nu_{C=Caromatic}$), 1338.51 (ν_{NO2}). ^{1}H-NMR (300 MHz, DMSO-d6): δ=4.72 (s, 2H, $\underline{CH_2}$CONH-, CH_2), 5.08 (s, 2H, -NCO-$\underline{CH_2}$O-, CH_2), 8.06 (s, 1H, CO$\underline{NH}$-), 8.20 (s, 1H, N=$\underline{CH}$, azomethine), 7.05-7.96 (m, 8H, Ar-H). ^{13}C-NMR (100MHz, DMSO-d6): δ=168.28 (C=O), 165.06 (C=O), 163.72 (N=C), 153.82, 152.75, 147.78, 139.94, 129.45, 123.16, 117.11, 116.84, 115.92, 113.75, 110.12, 109.82 (aromatic carbons), 67.56 (CH_2), 55.94 (CH_2).

2.2.3.2. N'-(3-nitrobenzylidene)-2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetohydrazide (4b)

Following the typical procedure 2.2.3., pure acetohydrazide **4b** was obtained as white powder by reaction of 3-nitrobenzaldehyde and benzoxazolinonylhydrazide **3**. Yield: method **A** (75%) and method **B** (79%). Mp: 281-282°C. IR (KBr, cm^{-1}): 3436.91 (ν_{O-H}), 3082.04 (ν_{N-H}), 2947.03 (ν_{CH2}), 1662.52 ($\nu_{C=Ooxazin}$), 1608.52 ($\nu_{C=N}$), 1566.09 ($\nu_{C=Caromatic}$), 1353.94 (ν_{NO2}). ^{1}H-NMR (300 MHz, DMSO-d6): δ=4.82 (s, 2H, $\underline{CH_2}$CONH, CH_2), 5.06 (s, 2H, -NCO-$\underline{CH_2}$O-, CH_2), 8.51 (s, 1H, NH, CO$\underline{NH}$-N), 8.78 (s, 1H, N=$\underline{C}$H, azomethine), 6.71-7.34 (m, 8H, Ar-H). ^{13}C-NMR (100MHz, DMSO-d6): δ=168.29 (C=O), 165.14 (C=O), 163.75 (N=C), 153.84, 152.78, 147.74, 139.94,

129.56, 123.26, 117.11, 116.84, 115.94, 113.75, 110.06, 109.82 (aromatic carbons), 67.66 (CH_2), 55.95 (CH_2).

2.2.3.3. N'-(4-nitrobenzylidene)-2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetohydrazide (4c)

Following the typical procedure 2.2.3., pure acetohydrazide **4c** was obtained as white powder by reaction of 4-nitrobenzaldehyde and benzoxazolinonylhydrazide **3**. Yield: method **A** (72%) and method **B** (83%). Mp: 237-238°C. IR (KBr, cm^{-1}): 3190.04 (ν_{N-H}), 3074.32 ($\nu_{C=\underline{C-H}}$), 2947.03 (ν_{CH2}), 1662.52 ($\nu_{C=Ooxazin}$), 1608.52 ($\nu_{C=N}$), 1593.09 ($\nu_{C=Caromatic}$), 1353.94 (ν_{NO2}). ^{1}H-NMR (300 MHz, DMSO-d6): δ=4.72 (s, 2H, $\underline{CH_2}$CONH-, CH_2), 5.09 (s, 2H, -N-CO-$\underline{CH_2}$-O-, CH_2), 8.40 (s, 1H, NH, CO$\underline{NH}$-N), 8.69 (s, 1H, N=$\underline{CH}$, azomethine), 7.02-7.80 (m, 8H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d6): δ=168.20 (C=O), 165.00 (C=O), 163.71 (N=C), 153.81, 152.74, 147.72, 139.94, 129.44, 123.17, 117.04, 116.82, 115.92, 113.78, 110.12, 109.88 (aromatic carbons), 65.56 (CH_2), 57.95 (CH_2).

2.2.3.4.N'-(4-hydroxy-3-nitrobenzylidene)-2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*) yl)acetohydrazide (4d)

Following the typical procedure 2.2.3., pure acetohydrazide **4d** was obtained as yellow powder by reaction of 4-hydroxy-3-nitrobenzaldehyde and benzoxazolinonylhydrazide **3**. Yield: method **A** (72%) and method **B** (78%). Mp: 302-303°C. IR (KBr, cm^{-1}): 3433.06 (ν_{O-H}), 3240.19 (ν_{N-H}), 3101.32 ($\nu_{C=\underline{C-H}}$), 2954.74 (ν_{CH2}), 1677.95 ($\nu_{C=Ooxazin}$), 1623.95 ($\nu_{C=N}$), 1535.23 ($\nu_{C=Caromatic}$), 1322.40 (ν_{NO2}). ^{1}H-NMR (300 MHz, DMSO-d6): δ=4.72 (s, 2H, $\underline{CH_2}$CONH-, CH_2), 5.06 (s, 2H, N-CO-$\underline{CH_2}$-O-, CH_2), 8.11 (s, 1H, NH, CO$\underline{NH}$-N), 9.53 (s, 1H, N=$\underline{CH}$, azomethine), 6.02-7.93 (m, 7H, Ar-H), 11.56 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d6): δ=168.48 (C=O), 165.07 (C=O), 163.70 (N=C), 153.73, 152.62, 147.78, 142.53, 139.94, 137.73, 129.56, 123.16, 116.72, 115.94, 114.83, 113.76, 110.12, 109.84 (aromatic carbons), 67.45 (CH_2), 55.95 (CH_2).

2.3. Biological studies

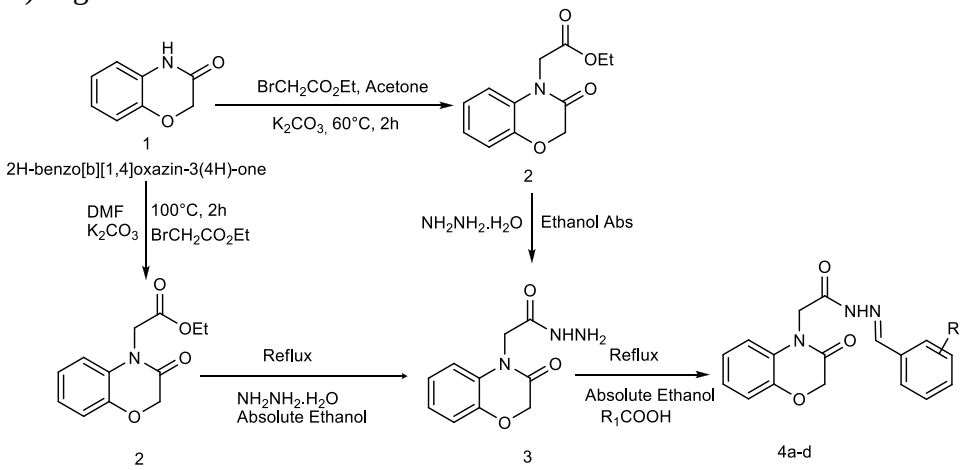
The investigated compounds (**4a-d**) were tested for their *in vitro* antibacterial and antifungal activities, against two pathogenic Gram-positive bacteria (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) as well as one gram negative bacteria (*Escherichia Coli*), and one fungal strain (*Candida Albicans*). The minimum inhibitory concentration (MIC) of compounds (**4a-d**) against all bacterial and fungal species was determined by serial dilution method. Stock solutions of tested compounds with 500, 200, 100 and 50 $\mu g.mL^{-1}$ concentrations were prepared with DMSO solvent. The solutions of standard drugs, Ampicillin and Penicilin were prepared in concentration of 10 $\mu g.mL^{-1}$ and

6 μg.mL^{-1} respectively. The minimum inhibitory concentration was defined as the highest dilution showing complete inhibition of the tested strains. The comparison of the MICs (in μg.mL^{-1}) of potent compounds and standard drugs against tested strains are summarized and classified as sensitive, intermediate or resistant. The zone of inhibition was measured and recorded in millimeters for 24h at 37°C**.**

3. Results and discussions

3.1. Chemistry

The general synthetic strategy leading to the synthesis of target compounds (**4a-d**) is given in Scheme 1.



Scheme 1: Synthesis of the target hydrazide-hydrazones. Reagents and conditions: **A**: method **A**, reflux, absolute ethanol, glacial acetic acid, 35 min; **B:** method **B**, absolute ethanol, 6-7 min.

The starting material, 2H-1,4-benzoxazin-3-(4H)-one (**1**) was prepared according to the reported procedures using 2-aminophenol and chloroacetylchloride. Treatment of 2H-1,4-benzoxazin-3(4*H*)-one with ethyl bromoacetate under strongly alkaline conditions in K_2CO_3/Acetone, gave the corresponding N(4)-substituted product ethyl 2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetate (**2**) as a white solid; spectral data are consistent with the assigned structure but the melting point 81°C was surprisingly very different from that described previously, and was not within the acceptable limits. Ravi Teja B and coworkers [23] reported the melting point of this material to be 176°C, which is 95° higher than the melting point of the product we obtained by an alternate methods. Although we have verified it several times, we obtained same value. Although we have verified it several times, we obtained same value. The acid hydrazide (**3**) was prepared by the reaction of ethyl 2-(3-oxo-2H-benzo[b][1,4]oxazin-4(3*H*)-yl)acetate and hydrazine hydrate in ethanol, which produced a 83% yield. The benzoxazinonylhydrazide (**3**) was condensed with the

appropriate nitrobenzaldehyde isomers in ethanol as solvent to give the corresponding benzoxazinonylacetohydrazide derivatives (**4a-d**), with yields ranging from 72 to 77%, when synthesized by conventional method in absolute ethanol at reflux in presence of catalytic amount of acetic acid. On the other hand, the use of ultrasound irradiation under catalyst-free condition has resulted in the formation of these acetohydrazide derivatives in very short times (6-7 minutes) and good yields (78-83%). The comparative study for ultrasound and conventional heating as well as physicochemical data of the synthesized compounds are presented in Table 1.

Table 1

Comparative study in terms of yield and reaction period for ultrasound and conventional heating and physicochemical data of the synthesized benzoxazinonylacetohydrazide compounds (4a-d).

Product	R	[a]Mp (°C)	CH		US		[d]Mol. F.
			Time (min)	[b]Yield (%)	Time (min)	[c]Yield (%)	
4a	2-NO_2	226-227	35	77	6	80	$C_{17}H_{14}N_4O_5$
4b	3-NO_2	281-282	35	75	6	79	$C_{17}H_{14}N_4O_5$
4c	4-NO_2	237-238	35	72	7	83	$C_{17}H_{14}N_4O_5$
4d	4-OH,3-NO_2	302-303	35	72	6	78	$C_{15}H_{14}N_4O_6$

[a]Melting point; [b,c]Isolated yield; CH: Conventional heat; US: Ultrasound irradiation; [d]Molecular formula.

For the preparation of acetohydrazide derivatives (**4a-d**), reaction time and yields are much better by using ultrasound irradiation compared to conventional heating, and results were compared and presented in Table 1. Therefore, acetic acid was preferred as solvent for all further conventional heating. Thin layer chromatography (TLC) was used for the purity characterization of the desired synthesized products, and their structures were identified and confirmed on the basis of FT-IR and proton as well as carbon-13 nuclear magnetic resonance.

The spectra of the obtained compounds gave satisfactory results and confirmed the proposed structure for the obtained products. In the ^{1}H-NMR spectra of compounds (**4a-d**), two singlet signals for -CONH and N=CH groups appeared at δ 8.06-8.51 ppm and δ 8.20-9.53 ppm, respectively.

As for the ^{13}C-NMR spectra, signals for N=CH group were found in the range of δ 165.00-168.48 ppm. Signals for methylene group carbons in these compounds were appeared at 55.95-67.66 ppm.

3.2. Antimicrobial activities

The results of the screening tests of benzoxazinoylhydrazones (**4a**–**d)** were reported in Table 2, which showed the minimum inhibitory concentrations (MICs) of the studied compounds, against one Gram-positive bacteria (*S. aureus*) and two Gram negative bacteria (*E. coli*, *P. aeruginosa*). The dimethylsulfoxide solvent has no antibacterial effect at the used concentration up to 500 µg.mL^{-1}.

Table 2

Antimicrobial activity *in vitro* of compounds 4a-d: Inhibition zone diameter in millimeter.

Bacterial and fungal species	Concentration (µg.mL^{-1})	Compounds **IZD** (mm)				Standards		
		4a	**4b**	**4c**	**4d**	**A (**10µg.mL^{-1})	**P** 6µg.mL^{-1}	**A**-B 20µg.mL^{-1}
S. aureus	500	–	**13**	10	–	24	22	–
	200	–	11	8	–			
	100	–	08	7	–			
	50	–	06	5	–			
E. coli	500	–	12	–	11	16	–	–
	200	–	09	–	9			
	100	–	08	–	7			
	50	–	07	–	5			
P.aeruginosa	500	–	–	–	–	–	–	–
	200	–	–	–	–			
	100	–	–	–	–			
	50	–	–	–	–			
C.albicans	500	12	**14**	10	12	–	–	13
	200	08	11	07	09			
	100	06	07	06	05			
	50	03	–	04	03			

A: Ampicillin, **P**: Pénicillin, **A-B**: Amphotericin-B; **–**: No sensitivity; **IZD**: Inhibition zone diameter (mm).

The *in vitro* studies results showed that all the synthesized compounds showed moderate to good antimicrobial activity against fungi. The compounds **4b** showed the highest antifungal activity against fungi *Candida albicans* among all the tested acetohydrazides. Compared the compounds with different NO_2-substituted position on the benzene ring, their activity order was 3-NO_2>2-NO_2>4-NO_2. It was observed that Gram-negative bacteria *Pseudomonas aeruginosa* has developed resistance against all the synthesized derivatives. Among the screened samples, compound 3-NO_2 substituted derivative **4b** has emerged as most active against both tested Gram negative *Escherichia coli* and Gram positive bacteria *Staphylococcus aureus* compared to the standard drug. The present results suggest that some of the title compounds are potential for the development of novel potential benzoxazinone antimicrobial agents.

4. Conclusions

In this present study, the effects of ultrasonic irradiations on the formation of benzoxazinonylacetohydrazide derivatives with potential biological activities have been explored. Thus, a significant procedure to prepare some novel 2,3,4-nitrosubstituted acetohydrazides under ultrasound irradiations and conventional heating methods without catalyst was reported, these Nitrobenzoxazinone analogues were evaluated for their *in vitro* antimicrobial activities. The results obtained, showed that the ultrasound irradiations procedure confirmed notable superiority compared to conventional synthetic protocol, and affords excellent yield of the isolated product, shorter reaction time and mild condition reactions. The antimicrobial screening results revealed that the prepared compounds showed moderate to good antimicrobial activity. Compounds **4b** showed the highest antifungal activity against fungi *Candida albicans*. Gram-negative bacteria *Pseudomonas aeruginosa* has developed resistance against all the synthesized derivatives. Among the screened samples, compound **3-NO_2** substituted derivative **4b** has emerged as most active against both tested Gram negative *Escherichia coli* and Gram positive bacteria *Staphylococcus aureus*. The present results suggest that some of the title compounds are potential for the development of novel potential benzoxazinone antimicrobial agents.

R E F E R E N C E S

[1]. *G. V. Ambulgekar, S. D. Samant, A. B. Pandit*, "Oxidation of alkylarenes using aqueous potassium permanganate under cavitation: comparison of acoustic and hydrodynamic techniques", Ultrasonics Sonochemistry, **vol. 12,** no. 1-2, 2005, pp. 85–90

[2]. *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

[3]. *F. Alonso, I. P. Beletskaya, M. Yus*, "Non-conventional methodologies for transition-metal catalysed carbon–carbon coupling: a critical overview, Part 1: The Heck reaction", Tetrahedron, **vol. 61**, no. 50, 2005, pp. 11771–11835

[4]. *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

[5]. *M. M. Mojtahedi, M. S. Abaee*, "Ultrasound applications in synthetic organic chemistry, in: D. Chen, S. K. Sharma, A. Mudhoo (Eds.), Handbook on Applications of Ultrasound Sonochemistry for Sustainability", CRC Press, New York, 2012, pp. 281–322

[6]. *G. Cravotto, P. Cintas*, "Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications", Chemical Society Review, Chem. Soc. Rev. **vol. 35**, no. 2, 2006, pp. 180–196

[7]. *T. J. Mason*, "Ultrasound in synthetic organic chemistry", Chemical Society Reviews, **vol. 26**, no. 6, 1997, pp. 443–451

[8]. *M. Nüchter, B. Ondruschka, A. Jungnickel, U. Müller*, "Organic processes initiated by non-classical energy sources", J. Phys. Org. Chem. **vol. 13**, no. 10, 2000, pp. 579–586

[9]. *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

[10]. *S. Puri, B. Kaur, A. Parmar, H. Kumar*, Applications of Ultrasound in Organic Synthesis-A Green Approach, Current Organic Chemistry, **Vol. 17,** no. 16, 2013, pp. 1790–1828

[11]. *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

[12]. *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

[13]. *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

[14. *M. Śmist, H. Kwiecień, M. Krawczyk*, "Synthesis and antifungal activity of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives", Journal of environmental science and health B., **vol. 51**, no. 6, 2016, pp. 393–401

[15]. *N. Matzanke, W. Lowe, S. Perachon, P. Sokoloff, J. C. Schwartz, H. Stark*, "Heterocyclic congeners of PD 128,907 with a partially hydrogenated benzomorpholine moiety as potencial dopamine D3-receptor ligands", European Journal of Medicinal Chemistry, **vol. 34**, no. 10, 1999, pp. 791–798

[16]. *S. Sebille, P. de Tullio, S. Boverie, M. H. Antoine, P. Lebrun, B. Pirotte*, "Recent developments in the chemistry of potassium channel activators: the cromakalim analogs", Current Medicinal Chemistry, **vol. 11**, no. 9, 2004, pp. 1213–1222

[17]. *B. C. Das, A. V. Madhukumar, J. Anguiano, S. Mani*, "Design, synthesis and biological evaluation of 2H-benzo[*b*][1,4] oxazine derivatives as hypoxia targeted compounds for cancer therapeutics", Bioorganic and Medicinal Chemistry Letters, **vol. 19**, no. 15, 2009, pp. 4204–4206

[18]. *M. Śmist, M. Krawczyk, H. Kwiecien*, "Synthesis and antifungal activity of 2 H -1,4-benzoxazin-3(4 H)-one derivatives", Journal of Environmental Science and Health, Part B: Pesticides, Food Contaminants, and Agricultural Wastes, **vol. 51**, no. 6, 2016, pp. 393–401

[19]. *M. Z. Huang, F. X. Luo, H. B. Mo, Y. G. Ren, X. G. Wang, X. M. Ou, M. X. Lei, A. P. Liu, L. Huang, M. C. Xu*, "Synthesis and herbicidal activity of isoindoline-1,3-dione substituted benzoxazinone derivatives containing a carboxylic ester group", Journal of Agricultural and Food Chemistry, **vol. 57**, no. 20, 2009, pp. 9585–9592

[20]. *H. B. Borate, S. R. Maujan, S. P. Sawargave, M. A. Chandavarkar, S. R. Vaiude, V. A. Joshi, R. D. Wakharkar, R. Iyer, R. G. Kelkar, S. P. Chavan, S. S. Kunte*, "Fluconazole analogues containing 2H-1,4-benzothiazin-3(4H)-one or 2H-1,4-benzoxazin-3(4H)-one moieties, a novel class of anti-Candida agents", Bioorganic and Medicinal Chemistry Letters, **vol. 20**, no. 2, 2010, pp. 722–725

[21]. *R. Fringuelli, D. Pietrella, F. Schiaffella, A. Guarraci, S. Perito, F. Bistoni, A. Vecchiarilli*, "Anti-candida albicans properties of novel benzoxazine analogues", Bioorganic and Medicinal Chemistry, **vol. 10**, no. 6, 2002, pp. 1681–1686

[22]. *G. Caliendo, P. Grieco, E. Perissutti, V. Santagada, A. Santini, S. Albrizio, C. Fattorusso, A. Pinto, R. Sorrentino*, "Synthesis, biological activity and conformational study of 1,4-benzoxazine derivatives as potassium channel modulators", European Journal of Medicinal Chemistry, **vol. 33**, no. 12, 1998, pp. 957–967

[23]. *T. B. Ravi, N. Lingaiah, B. Rajeeva*, "Synthesis and antimicrobial activity of novel series of pyrazoline derivatives bearing 1,4-benzoxazinone", International Research Journal of Pharmacy, **vol. 8**, no. 3, 2017, pp. 23–28

[24]. *G. Sonia, K. K. Thachil, M. K. Parameswaran, R. T. Kochupappy*, "Synthesis of some benzoxazinyl pyrazolone arylidenes as potent antimicrobials and antioxidants", Medecinal Chemistry Research, **vol. 23**, no. 3, 2014, pp. 1320–1326

[25]. *Y. Matsumoto, W. Uchida, H. Nakahara, I. Yanagisawa, T. Shibanuma, H. Nohira*, "Novel Potassium Channel Activators. III. Synthesis and Pharmacological Evaluation of 3,4-Dihydro-2*H*-1,4-benzoxazine Derivatives: Modification at the 2 Position, Chemical and Pharmaceutical Bulletin, **vol. 48**, no. 3, 2000, pp. 428–432

[26]. *S. Alper-Hayta, E. Aki-Sener, B. Tekiner-Gulbas, I. Yildiz, O. Temiz-Arpaci, I. Yalcin, N. E. Altanlar*, "Synthesis, antimicrobial activity and QSARs of new benzoxazine-3-ones", European Journal of Medicinal Chemistry, **vol. 41**, no. 12, 2006, pp. 1398-1404

[27]. *V. T. kumar, S. K. Rao, L. V. Narayana, P. K. Dube, V. Aparna*, "Synthesis of 6-(5-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-2H-1,4- benzoxazin-3(4H)-one as potential non-steroidal anti-inflammatory agents (NSAIDS)", Heterocyclic Communications, **vol. 9**, no. 1, pp. 51–56

[28]. *M. Largeron, B. Lockhart, B. Pfeiffer, M. B. Fleury*, "Synthesis and in vitro evaluation of new 8-amino-1,4-benzoxazine derivatives as References neuroprotective antioxidants", Journal of Medicinal Chemistry, **vol. 42**, no. 24, 1999, pp. 5043–5052

[29]. *S. Wahidulla, J. J. Bhattacharjee*, "Benzoxazinoids from Acanthus ilicifolius", Journal of the Indian Institute of Sciences, **vol. 81**, no. 4, 2001, pp. 485–489

[30] *H. M. Niemeyer*, "Hydroxamic acids (4-hydroxy-1,4-benzoxazin-3-ones) defence chemicals in Graminae", Phytochemistry, **vol. 27**, no. 11, 1988, pp. 3349–3358

[31]. *G. Thuillier, J. Laforest, P. Bessin, J. Bonnet, J. Thuillier*, "Synthèse et activité pharmacologique de dihydro-2,3 benzoxazine-1,4-ones-3-substituées en position 4", European Journal of Medicinal Chemistry, **vol. 10**, no. 1, 1975, pp. 37–42

[32]. *M. Kajino, k. Mizuno, H. T*awada, *Y. Shibouta, K. Nishikawa, K. Meguro*, "Synthesis and biological activities of new 1,4-benzothiazine derivatives", Chemical and Pharmaceutical Bulletin, **vol. 39**, no. 11, 1991, pp. 2888–2895

[33]. *G. Caliendo, P. Grieco, E. Perissutti, V. Santagada, A. Santini, S. Albrizio, C. Fattorusso, A. Pinto, R. Sorrentino*, "Synthesis, biological activity and conformational study of 1,4-benzoxazine derivatives as potassium channel modulators", European journal of medicinal chemistry, **vol. 33**, no. 12, 1998, pp. 957–967

[34]. *S. Rollas, Ş. G. Kűçűkgűzel*, "Biological activities of hydrazone derivatives", Molecules, **vol. 12**, no. 8, 2007, pp. 1910–1939

[35]. *S. Bala, G. Uppal, A. Kajal, S. Kamboj, V. Sharma*, "Hydrazones as promising lead with diversity in bioactivity-therapeutic potential in present scenario", International Journal of Pharmaceutical Sciences Review and Research, **vol. 18**, no. 1, 2013, pp. 65–74

[36]. *A. Gursoy, N. Terzioglu, G. Otuk*, "Synthesis of some new hydrazide-hydrazones, thiosemicarbazides and thiazolidinones as possible antimicrobials", European journal of medicinal chemistry, 1997, **vol. 32**, no. 9, 753–757

[37]. *W. W. Wardakhan, N. N. El-sayed, R. M. Mohareb*, "Synthesis and anti-tumor evaluation of novel hydrazide-hydrazone derivatives", Acta Pharmaceutica, **vol. 63**, no. 1, 2013, pp. 45–57

[38]. *P. Çıkla-Süzgün, D. Özsavcı, Ö. Bingöl-Özakpınar, A. Şener, Ö. Çevik, S. Özbaş-Turan, J. Akbuğa, F. Şahin, Ş.G. Küçükgüzel*, "Synthesis**,** cytotoxicity, and pro-apoptosis activity of etodolac hydrazide derivatives as anticancer agents", Archiv der Pharmazie-Chemistry in Life Sciences, **vol. 346**, no. 5, 2013, pp. 367–379

[39]. *Ş. G. Küçükgüzel, D. Koç, P. Çıkla, D. Özsavcı, Ö. Bingöl-Özakpınar, P. Mega-Tiber, O. Orun, P. Erzincan, S. S. Erdem, F. Şahin*, "Synthesis of Tolmetin Hydrazide-Hydrazones and Discovery of a Potent Apoptosis Inducer in Colon Cancer Cells", Archiv der Pharmazie-Chemistry in Life Sciences, **vol. 348**, no. 10, 2015, pp. 730–742

[40]. *K. B. Kaymakçıoğlu, E. E. Oruç, S. Unsalan, F. Kandemirli, N. Shvets, S. Rollas, D. Anatholy*, "Synthesis and characterization of novel hydrazidehydrazones and the study of their structure - antituberculosis activity", European journal of medicinal chemistry, 2006, **vol. 41**, no. 11, 1253–1261

[41]. *D. D. Mukherjee, N. M. Kumar, M. P. Tantak, A. Das, A Ganguli, S. Datta, D. Kumar, G. Chakrabarti*, "Development of novel bis(indolyl)-hydrazide-hydrazone derivatives as potent microtubule-targeting cytotoxic agents against A549 lung cancer cells", Biochemistry, **vol. 55**, no. 21, 2016, pp. 3020–3035

[42]. *C. M. Moldovan, O. Oniga, A. Pârvu, B. Tiperciuc, P. Verite, A. Pîrnău, O. Crişan, M. Bojiţă, R. Pop*, "Synthesis and anti-inflammatory evaluation of some new acyl-hydrazones bearing 2-aryl-thiazole", European journal of medicinal chemistry, **vol. 46**, no. 2, 2011, pp. 526–534

[43]. *R. M. Mohareb, K. A. El-Sharkawy, M. M. Hussein, H. M. El-Sehrawi*, "Synthesis of hydrazide-hydrazone derivatives and their evaluation of antidepressant, sedative and analgesic agents", Journal of Pharmaceutical Sciences and Research, **vol. 2**, no. 4, 2010, pp. 185–196

[44]. *Ł. Popiołek, U. Kosikowska, M. Wujec, A. Malm*, "Synthesis and antimicrobial evaluation of new Schiff base hydrazones bearing 1,2,4-triazole moiety", Phosphorus, Sulfur, and Silicon and the Related Elements, **vol. 189**, no. 11, 2014, pp. 1611–1623

[45]. *Ł. Popiołek, A. Biernasiuk*, "synthesis and in vitro antimicrobial activity of hydrazide-hydrazones of 2-substituted acetic acid", Chemical Biology and Drug Design, **vol. 88**, no. 11, 2016, pp. 873–883

[46]. *Ł. Popiołek, A. Biernasiuk*, "synthesis and in vitro antimicrobial activity of hydrazide-hydrazones of 2-substituted acetic acid", Saudi Pharmaceutical Journal, **vol. 25**, no. 11, 2017, pp. 1097–1102

[47]. *Ş. G. Küçükgüzel, E. E. Oruç, S. Rollas, F. Şahin, A. Ozbek*, "Synthesis, characterisation and biological activity of novel 4-thiazolidinones, 1,3,4- oxadiazoles and some related compounds", European journal of medicinal chemistry, **vol. 37**, no. 3, 2002, pp. 197–206

[48]. *L. C. Tavares, J. J. Chiste, M. G. Santos, T.C. Penna*, "Synthesis and biological activity of nifuroxazide and analogs. II.", Bollettino chimico farmaceutico, **vol. 138**, no. 8, 1999, pp. 432–436.

[49]. *A. Masunari, L. C. Tavares*, "A new class of nifuroxazide analogues: Synthesis of 5-nitrophenederivatives with antimicrobial activity against multidrug-resistant *Staphylococcus aureus*", Bioorganic & medicinal chemistry, **vol. 15**, no. 12, 2007, pp. 4229–4236

[50]. *M. R. Shiradkar, K. K. Murahari, H. R. Gangadasu, T. Suresh; C. A. Kalyan; D. Panchal; R. Kaur; P. Burange; J. Ghogare; V. Mokale; M. Raut*, "Synthesis of new S-derivatives of clubbedtriazolyl thiazole as anti-*Mycobacterium tuberculosis* agents", Bioorganic & medicinal chemistry, **vol. 15**, no. 12, 2007, pp. 3997–4008

[51]. *K. A Metwally, L. M. Abdel-Aziz, E. S. M. Lashine, M. I. Husseiny, R. H. Badawy*, "Hydrazones of 2-aryl-quinoline-4-carboxylic acid hydrazides: synthesis and preliminary evaluation as antimicrobial agents", Bioorganic & medicinal chemistry, **vol. 14**, no. 24, pp. 8675–8682

[52]. *S. Rollas, N. Gulerman, H. Erdeniz*, "Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3- acetyl-2, 5-disubstituted-1, 3, 4-oxadiazolines", Il Farmaco, **vol. 57**, no. 2, 2002, pp. 171–174

[53]. *S. Ersan, S. Nacak, R. Berkem*, "Synthesis and antimicrobial activity of N-[(α-methyl)benzylidene]-(3-substituted-1,2,4-triazol-5-yl-thio)acetohydrazides", Il Farmaco, **vol. 53**, no. 12, 1998, pp. 773–776

[54]. *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

[55]. *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

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

[57]. *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

[58]. *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

[59]. *A. H. Collins*, BT Microbiological Methods, 2nd ed., Butterworth, London 1976, pp. 235–237