Palestinian Medical and Pharmaceutical Journal

Targeting Drug-Resistant Bacteria: The Promise of Oxazole-Based Antibacterial Agents and their structure-activity relationships (SAR): *Review*

Nadine M.Qalalweh[1]*

Received: 13rd May. 2024, Accepted: 23rd Aug. 2024, Published: ××××

Accepted Manuscript, In press

ABSTRACT: The emergence of drug resistance has led to an unfulfilled medical demand for the creation of novel antibiotic classes. Developing novel antibacterial drugs with fresh modes of action is still a top priority everywhere. Oxazoles are heterocyclic scaffolds of five members, including oxygen and nitrogen atoms separated by one carbon. They can easily attach to different enzymes and receptors in biological systems through various non-covalent interactions and exhibit a variety of pharmacological properties, including antioxidants, antitubercular, antimalarial, anti-HIV, antibacterial, antifungal, anticancer, anti-inflammatory, and analgesic effects. The study of oxazole-based derivatives as therapeutic medicines has been a highly active area of research, resulting in multiple significant accomplishments. Many oxazole compounds have been extensively used as clinical medications or candidates for treating various medical conditions. These compounds have demonstrated significant development potential and wide-ranging therapeutic properties. Recently, the use of these heterocyclic nuclei as building blocks for creating new chemical compounds in medical and pharmaceutical chemistry has significantly increased globally. Internationally, ongoing research focuses on identifying Oxazole-based compounds that have the potential as highly effective therapeutic drugs. The current study centers on the recent advances in medicinal chemistry to identify different chemical structures that could be used as possible antimicrobial medicines. This review also covered the structure-activity relationships (SAR) investigations related to these structures and the design of these derivatives.

Keywords: Oxazole; Antibacterial; SAR; Heterocyclic.

INTRODUCTION

The rising resistance of many bacterial isolates to broad-spectrum antibiotics is making bacterial infections a global issue. The world lives in a post-antibiotic era where simple mishaps and bacterial diseases can be fatal [1]. Single-celled microorganisms known as bacteria are generally safe for humans to handle, with certain strains even having therapeutic properties. Numerous bacterial species are harmful and can potentially spread dangerous infectious illnesses [2]. For instance, the majority of hospital- and community-acquired infections are caused by Gram-positive bacteria like Staphylococcus aureus (S. aureus), Streptococcus pneumonia (S. pneumoniae), and Gram-negative species like Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa), and others [3]. Antimicrobial agents are traditionally classified into two primary groups based on their effect on bacteria in a laboratory setting: bactericidal and bacteriostatic [4]. The bacteriostatic agents comprised tigecycline, linezolid, macrolides, sulphonamides, tetracyclines, and streptogramins. The bactericidal agents comprised b-lactam antibiotics, glycopeptide antibiotics, fluoroquinolones, and aminoglycosides [5].

Fortunately, various natural and synthetic antibiotics have greatly improved human health since penicillin's discovery as a powerful antibacterial agent in the 1940s [6]. The growing number of microbial strains that are resistant to drugs and the emergence of illnesses that are becoming irreversible make treating bacterial inspection a persistent issue. Although many different antibacterial specialists and chemotherapeutics aren the market, the development of both new and ancient adversaries of bacterial resistance in previous decades has led to a liberal need for new classes of antibacterial agents [7]. The prevalence of antibiotic resistance and the absence of viable new treatments significantly worsen the health complications associated with microbial infections. Annually, around 400,000 individuals get multidrug-resistant tuberculosis (MDR-TB) [8-9]. Azoles are an extensive class of five-membered heterocycles containing one nitrogen atom and at least one non-carbon element (nitrogen, sulfur, or oxygen) within the ring structure [10]. Azoles or their compounds have antimicrobial properties [11]. Antifungal [12-13], anti-inflammatory [14- 15], antimalaria [16-17], anti-tuberculosis [18-19] antiviral [20-21], and anti-trypanosomal activities [22-23]. Typically, heterocycles with five members that have two or three heteroatoms (such as thiazole, benzothiazole, thiazolidinone, triazole, and others) play a vital role as structural components in different antibacterial compounds.[24-25]

Several heterocycle scaffolds, such as benzodioxole [26], benzoxazole, phenyl-isoxazole, and Isoxazole-carboxamide Derivatives, were discovered to have a significant impact on enhancing antibacterial activity [27-28]. The synthesis of 2-methyloxazole in 1876 marked the beginning of oxazole chemistry, and the parent oxazole was created in 1962. Since penicillin was believed to contain the oxazole ring structure, oxazole chemistry acquired prominence during World War II. The study of oxazole chemistry has advanced with the discovery of oxazoles as dienes in Diels-Alder processes and 1,3-dipolar cycloaddition reactions of mesoionic heterocycles [29]. The crucial heterocycle component oxazole has three loci for

1 Department of Pharmacy, Faculty of Pharmacy, Arab American University, P.O Box 240 Jenin, 13 Zababdeh, Jenin, Palestine.
*Corresponding author: nadine.qalalweh@aaup.edu

substitution and a potent medicinal impact. One carbon separates the oxygen and nitrogen atoms in the heterocyclic oxazole nucleus (Figure 1). Though not as aromatic as thiazoles, oxazoles are nonetheless aromatic compounds.

Since imidazole has a pKa of 7, oxyazole's conjugate acid has a pKa of 0.8, making it a weak base. A large class of heterocyclic aromatic organic compounds has oxazole as their parent component. Oxazole has been studied to develop new compounds that rely on different substitutions with promising medicinal properties [30-31]. The oxazole moiety's distinct structure allows its derivatives to exert a variety of weak interactions, including van der Waals force, hydrophobic effect, cation-π, π-π stacking, coordination bonds, ion-dipole, and hydrogen bonds. Consequently, oxazole-based molecules exhibit a wide range of possible uses [32]. In medicinal chemistry, oxazole compounds have a wide range of biological activity and can bind to several enzymes and receptors in biological systems [33]. Many scientists have recently focused on studying oxazole compounds as potential therapeutic agents to findnnovative chemical scaffolds with a wide range of applications, high bioactivity, low toxicity, and superior pharmacokinetic properties [34]. It has been shown in recent years that oxazole and its derivatives have antibacterial action against many pathogenic bacteria, including Candida albicans, Staphylococcus aureus, Bacillus subtilis, and Escherichia coli [35]. Numerous oxazoles have been identified and have demonstrated strong biological activity throughout a wide range. The diverse synthetic application and potent biological activity of these heterocycles will assist medicinal chemists in planning, coordinating, and performing innovative strategies for the discovery of new pharmaceuticals. In light of this, this study provides a thorough summary of recent advancements in oxazole-based derivatives as antibacterial agents by merging the authors' research with other works from the literature. The importance of this study lies in the lack of a recent scientific review so far, focusing on oxazole as an antibacterial agent.

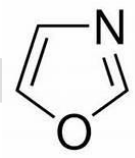


Figure (1): Oxazole ring.

The main topic of this study is the discussion of the many oxazole derivatives' antibacterial activity that have been documented in the literature from 2016-2024, along with their pharmacological targets. A particular emphasis is placed on the structure-activity relationship (SAR). Consequently, the current review does not address the production of oxazole derivatives. This review aims to inspire new ideas in the development of rational designs for oxazole medications that are more potent and less harmful.

Oxazole derivatives as potent antibacterial agents

There are several research studies in the literature on oxazole derivatives as antibacterial agents, and the following studies are listed in the timeline of the research.

N-(3,4,5-trimethoxybenzylidene)-4-substituted oxazol-2-amine

Bhupender and his colleagues investigated the effects of three methoxy groups on the antibacterial activity of produced compounds against Staphylococcus aureus, B. subtilis, P. aeruginosa, and E. coli, as well as the reaction with modified thiazole/oxazole nuclei. Compounds 1c, 1d, 1f, and 1g showed maximum inhibition against all four strains with a ZOI larger than 15 mm (Table 1); compound 1e showed moderate activity against all four strains. The structure-activity relationship (Figure 2) revealed that the compounds with hydroxyl, methoxy, and fluoro groups at para locations showed excellent antibacterial activity [36]. Thus, compound 1 displayed excellent antibacterial activity.

Table (1): Antibacterial activity of N-(3,4,5-trimethoxybenzylidene)-4-substituted oxazole-2-amine analogs.

Compounds	Inhibition Zone (mm)			
	Gram +ve Bacteria		Gram -ve Bacteria	
	S. aureus	B. subtilis	P. Aeruginosa	E. coli
a	6	9	11	8
b	9	11	13	9
c	16	17	17	16
d	17	18	18	16
e	14	13	11	14
f	16	18	17	18
g	17	16	16	17
Ampicillin	22	24	20	18

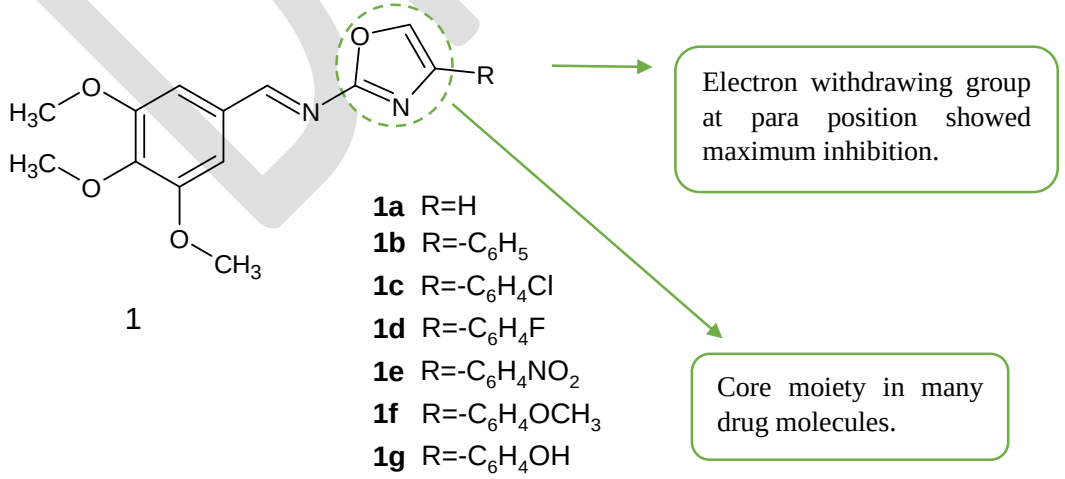


Figure (2): Structures and SAR of N-(3,4,5-trimethoxybenzylidene)-4-substituted oxazole-2-amine analogs.

2,3-Dihydrooxazole-spirooxindoles derivatives

Shailendra et al. efficiently produced and tested the antibacterial efficacy of two sets of novel 2,3-dihydrooxazole-spirooxindole derivatives against various harmful bacteria strains.

Oxazole-benzamide derivatives are a significant group of heterocyclic compounds. A recent study examined the synthesis, design, and structure-activity connection of several of these derivatives andheir potential antibacterial and pesticidal properties [37]. Spirooxindoles are a significant family of naturally occurring compounds known for their strong biological characteristics and serve as the fundamental structure for numerous synthesized medicines [38].

Developing novel bioprobes or therapeutic agents would benefit greatly from the structural motifs provided by hybrids of spiro-cyclic oxindoles fused with an oxazole-benzamide framework (Figure 3). Compounds 2b, 2e, 2f, 3a, and 3g (Table 2) exhibited moderate activity against the gram-positive bacteria B. subtilis. Compounds 2e, 2g, 3c, 3d, and 3g were effective against gram-negative enterobacter at 30-50 µg/ml concentrations. At 25 µg/ml, compound 3g was the only one to show action against K. pneumoniae. The current understanding of these compounds under investigation's that the antibacterial effect is lacking [39]. Generally, 2,3-Dihydrooxazole-spirooxindoles hybrids showed good antibacterial activity.

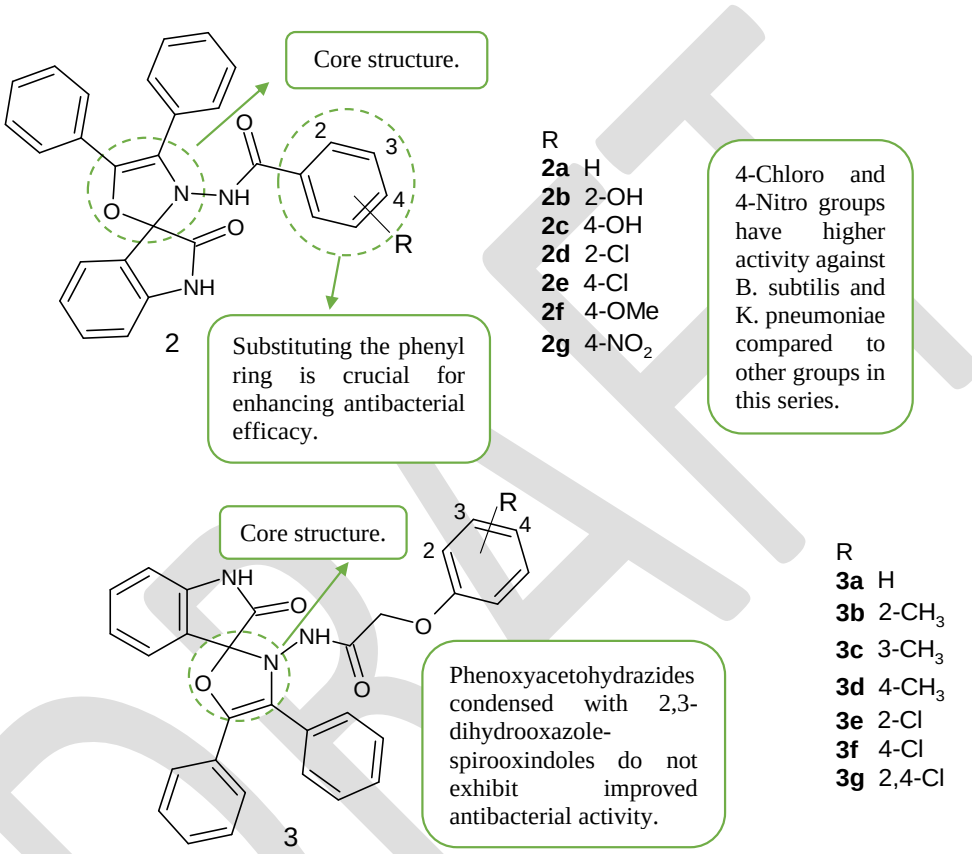


Figure (3): Structures and SAR of 2,3-Dihydrooxazole-spirooxindoles hybrids.

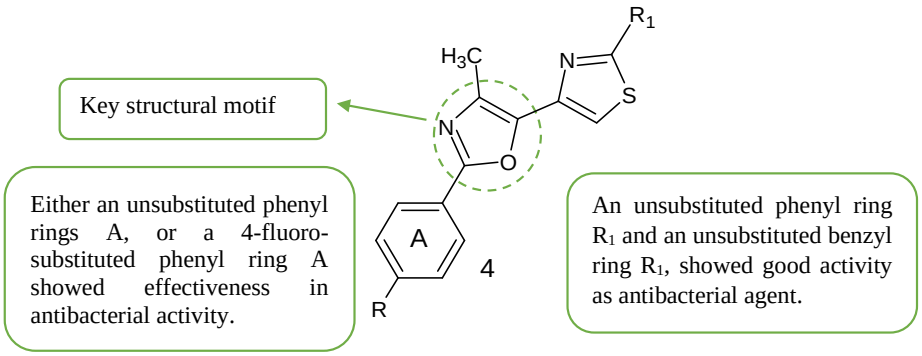
Table (2): Antibacterial activity of novel 2,3-dihydrooxazole-spirooxindole derivatives.

Compounds	B. subtilis		Enterobacter	
	MIC (µg/ml)	MBC (µg/ml)	MIC (µg/ml)	MBC (µg/ml)
2b	70	100	40	50
2e	50	100	30	50
2f	100	200	50	100
2g	30	50	30	50
3a	50	100	40	100
3b	N.A.	N.A.	30	50
3c	N.A.	N.A.	40	100
3d	N.A.	N.A.	50	100
3g	25	50	40	100
Ciprofloxacin	6.25	12.5	10.25	25

N.A. = No activity.

Thiazolyl-oxazole derivatives

The creation of structures including several heterocyclic rings has been a focus of interest in recent years [40]. Specialized scaffolding for the synthesis of target molecules in drug development are oxazole and thiazole rings. The biological significance and structural variety of thiazoles and oxazoles [41-42]. Yogita et al. produced and evaluated a series of 4-methyl-2-aryl-5-(2-aryl/benzyl thiazol-4-yl) oxazole compounds (Figure 4) for their antibacterial properties [43]. Synthesized compounds were tested for antibacterial activity against standard Gram-negative bacteria E. coli (NCIM 2576) and P. flurescence (NCIM 2059), as well as Gram-positive pathogens S. aureus (NCIM 2602) and B. subtilis (NCIM 2162). Ampicillin was used as a positive control to test antibacterial activity [43-44].



Compounds	R	R1	Compounds	R	R1	Compounds	R	R1
4a	H	C_6H_5	**4i**	H	3-$ClC_6H_4CH_2$	**4q**	4-F	4-FC_6H_4
4b	H	4-Br-C_6H_4	**4j**	H	4-$ClC_6H_4CH_2$	**4r**	4-F	4-CH_3
4c	H	3-Cl-C_6H_4	**4k**	H	4-$FC_6H_4CH_2$	**4s**	4-F	$C_6H_5CH_2$
4d	H	4-Cl-C_6H_4	**4l**	4-F	C_6H_5	**4t**	4-F	3-$ClC_6H_4CH_2$
4e	H	3-Cl,4FC_6H_3	**4m**	4-F	4-BrC_6H_4	**4u**	4-F	4-$ClC_6H_4CH_2$
4f	H	4-FC_6H_4	**4n**	4-F	3-ClC_6H_4	**4v**	4-F	4-$FC_6H_4CH_2$
4g	H	4-$CH_3C_6H_4$	**4o**	4-F	4-ClC_6H_4			
4h	H	$C_6H_5CH_2$	**4p**	4-F	3-Cl,4FC_6H_3			

Figure (4): Structures and SAR of thiazolyl-oxazole derivatives.

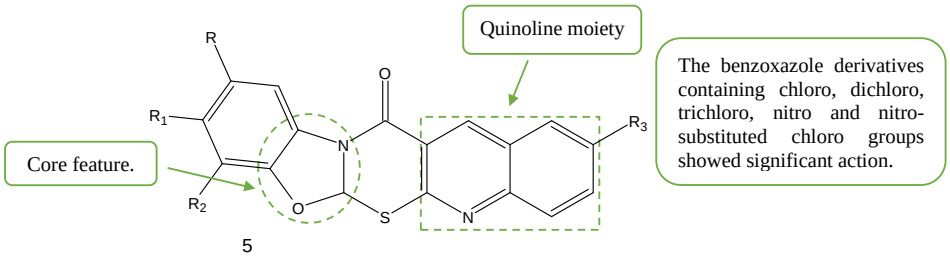
With MIC values of 2.4, 4.4, and 2.52 µg/mL, respectively, compound 4a—which contains unsubstituted phenyl rings R, R1=H exhibited outstanding efficacy against E. coli, P. flurescence, and B. Subtilis. With a MIC of 12.5 µg/mL, it demonstrated strong action against S. Aureus as well (Table 3). Against every strain, compounds 4i and 4j had good activity. With a 4-F substituted phenyl ring A and a substituted phenyl ring R1, the majority of these compounds; 4l-r showed modest activity. On the other hand, the activity rose when the benzyl ring in R1 was exchanged for the phenyl ring. Compound 4s had excellent activity against all strains, but compound 4t and 4v demonstrated good activity against all strains. The results showed that oxazole connected with thiazole can be regarded as a primary structure for future investigation [43] because these thiazolyl-oxazole derivatives showed potential antibacterial activities.

Table (3): Antibacterial activities of the active derivatives, MIC in µg /mL.

Compounds	E. coli	P. flurescence	S. aureus	B. subtilis
4a	2.4	4.4	12.5	2.52
4i	15.4	20.9	25.6	21.7
4j	18.3	18	22.7	27.6
4s	7.2	6.7	2.4	2.1
4t	26.8	22.1	21.4	20.7
4v	22.2	20.2	23.1	14.4
Ampicillin	1.46	4.36	1	10.32

Benzoxazole fused quinoline derivatives

Shreedhara S H and co-workers synthesized new heterocyclic compounds with a novel structure, 6aH,13H-benz[4,5]oxazole [2,3,2,3] [1,3] Thiazino [6,5-b] quinolin-13-one derivatives (Figure 5) and were tested for their antibacterial properties [45]. Benzoxazoles are a highly esteemed group of chemical compounds that hold great medicinal value due to their well-established biological chemotherapeutic properties [46-47]. The quinoline moiety is highly significant to both chemists and biologists due to its presence in a wide range of naturally occurring compounds and chemically valuable molecules with various biological functions. Several compounds containing quinoline have demonstrated a broad range of pharmacological effects, including antibacterial, antimalarial, antiplasmodial, and anticancer properties [48]. The fused cyclic quinoline with benzoxazole derivatives was produced. The recently synthesized compounds underwent testing to determine their antibacterial activities against bacterial strains, Escherichia coli (ATTC-8739), Staphylococcus aureus (ATTC-6538), Pseudomonas aeruginosa (ATTC-9027), Bacillus subtilis (ATTC-6633), Bacillus cereus (ATTC-11778), Staphylococcus epidermidis (ATTC-12228) and Salmonella typhimurium (ATTC-23564) by agar well diffusion methodology (Table 4). A few numbers of compounds have demonstrated a strong zone of inhibition. The synthesized compounds b, c, e, f, h, j, and l exhibited a significant zone of inhibition against bacteria, whereas compounds a, d, g, i, and k showed the least activity compared to the conventional antibiotic Chloramphenicol [21]. As a result; these benzoxazole fused quinoline derivatives (a-l) considered potent antibacterial activity.



5

Compounds	R	R_1	R_2	R_3
5a	H	H	H	H
5b	Cl	H	H	H
5c	NO_2	Cl	H	H
5d	CH_3	H	H	H
5e	H	NO_2	H	H
5f	Cl	H	Cl	H
5g	H	H	H	Cl
5h	Cl	H	H	Cl
5i	NO_2	Cl	H	Cl
5j	CH_3	H	H	Cl
5k	H	NO_2	H	Cl
5l	Cl	H	Cl	Cl

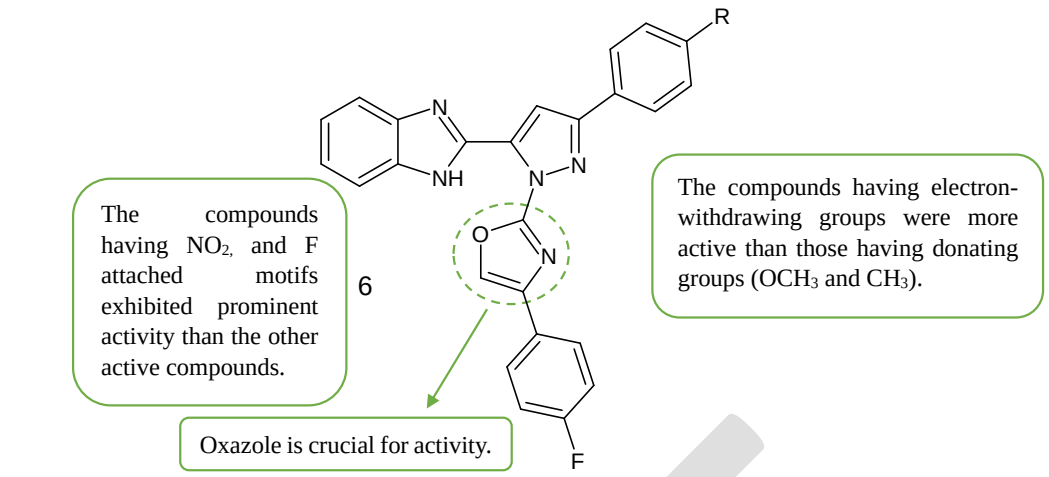
Figure (5): Structures and SAR benzoxazole fused quinoline derivatives.

Table (4): Antibacterial activity of compounds 5a-5l.

Compounds	Zone of inhibition in mm						
	S. aureus	S. epidermis	S. typhi	E. coli	B. subtilis	B. cereus	P. aeruginosa
5a	17	14	16	18	17	16	14
5b	21	20	22	19	21	19	18
5c	20	22	20	19	19	20	20
5d	18	17	15	17	19	18	16
5e	20	19	21	19	20	19	19
5f	18	20	19	21	19	20	21
5g	19	18	16	21	18	17	17
5h	22	19	21	19	20	19	18
5i	18	20	19	18	16	21	18
5j	20	17	22	19	21	19	22
5k	20	15	19	17	18	21	19
5l	18	21	17	20	19	21	18
Chloramphenicol	25	24	26	25	25	24	25

Benzimidazole-containing pyrazolyl oxazoles derivatives

Benzimidazoles are versatile structures commonly utilized in the molecular design of antibacterial, antivirals, fungicides, and antimutagens[49]. Pyrazole is recognized as a significant structural element found in many medications. One example is celecoxib, which is widely used as a safe anti-inflammatory and analgesic treatment [50]. The oxazole nucleus is commonly found in natural compounds, including pyrronazol [51]. diazonamides [52]. The oxazole rings found in multiple medications, are highly effective and possess diverse bioactivities, including hypoglycemic properties [53]. N. Bakthavatchala and his research group created benzimidazole-containing pyrazolyl oxazoles derivatives. The increasing popularity of heterocyclic applications is evident due to their tendency to demonstrate exceptional biological and pharmacological activity. The antibacterial activity of the derivatives was evaluated against Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, and Klebsiella pneumoniae bacterial strains. Four different concentrations (12.5, 25, 50, and 100 µg/mL) were tested. Chloramphenicol was used as the standard drug (Table 5). The studied chemicals (Figure 6) showed greater susceptibility towards Gram-negative bacteria compared to Gram-positive bacteria. Compounds 6d and 6e demonstrated more pronounced action compared to the other active compounds. The compound 6d exhibited superior activity compared to all the compounds that were examined. Furthermore, 6d has superior antibacterial efficacy against Pseudomonas aeruginosa in comparison to the conventional antibiotic chloramphenicol [54].



Compounds	a	b	c	d	e	f	G
R	H	Me	OMe	NO_2	F	Cl	Br

Figure (6): Structures and SAR of benzimidazole containing pyrazolyl oxazole derivatives.

Table (5): Antibacterial activities of benzimidazole containing pyrazolyl oxazole (6d, 6e) derivatives.

Compounds	MIC µg/mL					
	S. aureus	B. subtilis	P. aeruginosa	K. pneumoniae	A. niger	P. chrysogenum
d	25	25	6.25	12.5	12.5	25
e	50	50	25	25	50	25
Chloramphenicol	6.25	6.25	6.25	12.5	-	-

Benzoxazole derivatives

A series of benzoxazole derivatives was synthesized and the antibacterial potential of the examined substances was investigated against specific bacterial organisms, including Gram-positive bacteria such as S. aureus and B. subtilis, as well as Gram-negative bacteria such as E. coli, K. pneumoniae, and S. typhi by Saloni et al. A structure-activity relationship investigation of the synthesized compounds (Figure 7) revealed that the compounds containing an electron-withdrawing group at various positions of the substituted portion exhibited significant antibacterial properties. Compound 7e shown substantial activity against B. Subtilis and S. typhi, with minimum inhibitory concentrations (MIC) of 6.2 µg/ml and 12.5 µg/mL, respectively (Table 6). This activity was observed specifically against Gram positive bacteria. On the other hand, compound 7d exhibited significant action against S. aureus and E. coli, with minimum inhibitory concentrations (MIC) of 12.5 µg/mL and 6.2 µg/ml, respectively. Compound 7g, with a minimum inhibitory concentration (MIC) of 12.5 µg/ml, showed significant efficacy against K. pneumoniae. Compound 7d, which is part of this series, exhibits a significant antibacterial potential compared to the other produced compounds. Therefore, it can be considered a promising candidate for the synthesis of a new antimicrobial agent [55].

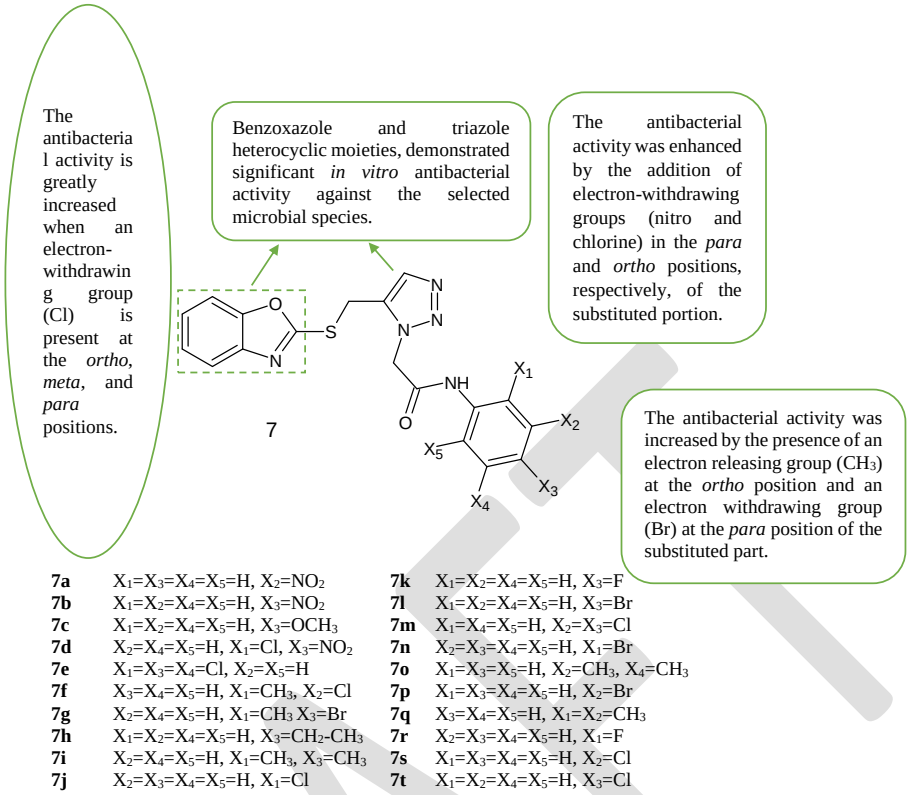


Figure (7): Structures and SAR of benzoxazole with triazole derivatives.

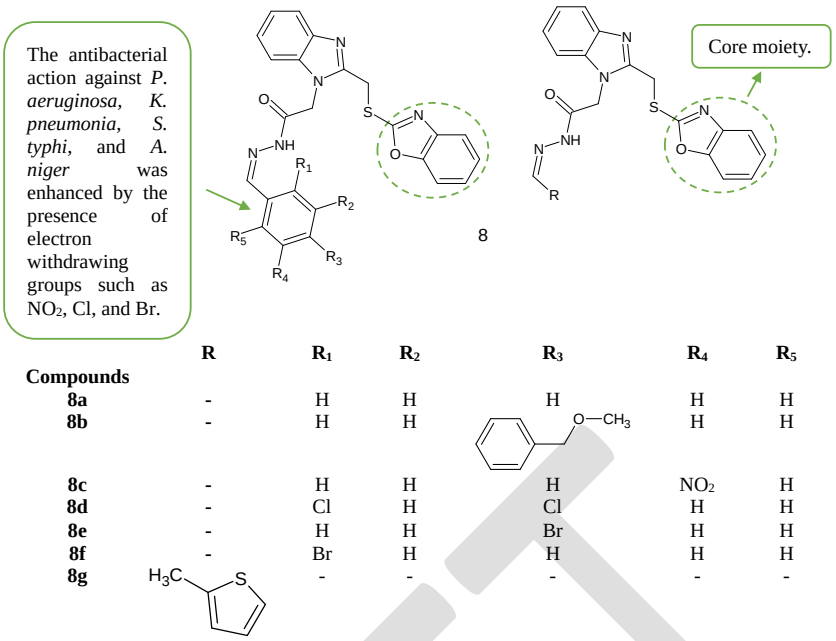
Table (6): Antibacterial activities of the most active benzoxazole derivatives.

Compounds	(MIC= µg/ml)				
	Bacillus subtilis	Staphylococcus aureus	Escherichia coli	Salmonella typhi	Klebsiella pneumoniae
7d	12.5	12.5	6.2	12.5	25
7e	6.2	25	50	12.5	25
7g	12.5	25	25	25	12.5
Ofloxacin	6.3	12.5	12.5	12.5	12.5

In continuing efforts to discover new potent antibacterial, Saloni and his co-workers developed a novel set of twenty-six benzoxazole analogs and evaluated their antibacterial properties in laboratory tests. The tested microbes include one Gram-positive bacterium, Bacillus subtilis, and four Gram-negative bacteria: Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Salmonella typhi [56]. The tube dilution method was used to evaluate the generated compounds' antibacterial activity [57]. The investigation demonstrated that the produced compounds exhibited a range of antibacterial activity, ranging from moderate to good, against the different microbial strains employed. Specifically, compounds 8a, 8b, 8c, 8d, 8e, 8f, and 8g (Fig. 8) have exhibited superior antibacterial activity compared to the conventional drug ofloxacin. Compound 8b (MIC = 0.624×10−3 µg/ml) had the highest efficacy against B. subtilis (Table. 7). Compound 8g exhibited activity against E. coli with a minimum inhibitory concentration (MIC) of 0.626×10−3 µg/ml. Compound 8c showed activity against P. aeruginosa with a MIC of 1.25×10−3 µg/ml. Compounds 8e and 8f were active against S. typhi with a MIC of 1.24×10−3 µg/ml. Compound 8d showed activity against K. pneumonia with a MIC of 0.622×10−3 µg/ml. The other compounds exhibited average to poor antibacterial efficacy against all seven species. Using (methoxymethyl)benzene (compound 8b) enhanced the antibacterial activity against B. subtilis, according to the structure-activity relationship of the benzoxazole derivatives with their antibacterial activity results. By substituting benzoxazole derivatives with thiophene (compound 8g), a five-member cyclic, the antibacterial activity against E. coli was increased [56].

Table (7): Antibacterial activities of selected active benzoxazole derivatives.

Compounds	(MIC= ×10−3 µg/ml)				
	Bacillus subtilis	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Klebsiella pneumoniae
8a	1.249	1.249	1.249	1.249	1.249
8b	0.624	2.5	1.248	2.5	2.5
8c	1.25	1.25	2.5	2.5	0.622
8d	0.622	2.5	1.25	2.5	0.622
8e	1.248	2.49	2.49	1.248	2.49
8f	1.248	2.49	1.248	2.49	2.49
8g	1.248	2.5	0.626	1.248	1.248
Ofoxacin	0.625	1.25	1.25	0.625	1.25



Compounds	R	R_1	R_2	R_3	R_4	R_5
8a	-	H	H	H	H	H
8b	-	H	H		H	H
8c	-	H	H	H	NO_2	H
8d	-	Cl	H	Cl	H	H
8e	-	H	H	Br	H	H
8f	-	Br	H	H	H	H
8g		-	-	-	-	-

Figure (8): Structures and SAR of benzoxazole with benzimidazole derivatives.

3-(2-Aminooxazol-5-yl)-2H-chromen-2-one derivatives

A new set of oxazole derivatives was synthesized (Figure 9), and their chemical structures were confirmed using spectrum data, considering the wide range of biological activities exhibited by oxazole. Coumarin, commonly referred to as benzopyran-2-one, has demonstrated several biological activities, including anti-inflammatory [58-59], antioxidant [60], anti-HIV [61], antitubercular [62], and antimicrobial [63]. Due to the significant role of oxazole and coumarins as distinct pharmacophores in antibacterial drugs, the intention was to combine and create a hybrid compound by synthesizing an oxazole benzopyran-2-one. The antibacterial properties of the produced oxazole derivatives were evaluated by Saloni et al. Compound 9c showed moderate potency against S. aureus, with a minimum inhibitory concentration (MIC) value of 6.2604 µg/mL (Table 8). Compound 9h exhibited moderate activity against B. subtilis, with a MIC value of 6.28 µg/mL. Compound 9c, with a minimum inhibitory concentration (MIC) of 6.26 µg/mL, showed efficacy against E. coli. Compound 9l, with a minimum inhibitory concentration (MIC) of 6.28 µg/mL, showed significant activity against P. aeruginosa. Similarly, compound 9f, with a MIC of 6.25 µg/mL, had promising action against S. enterica. The antibacterial screening results are equivalent to those of the standard medication (cefadroxil). These compounds can serve as a starting point to identify new antibacterial agents [64].

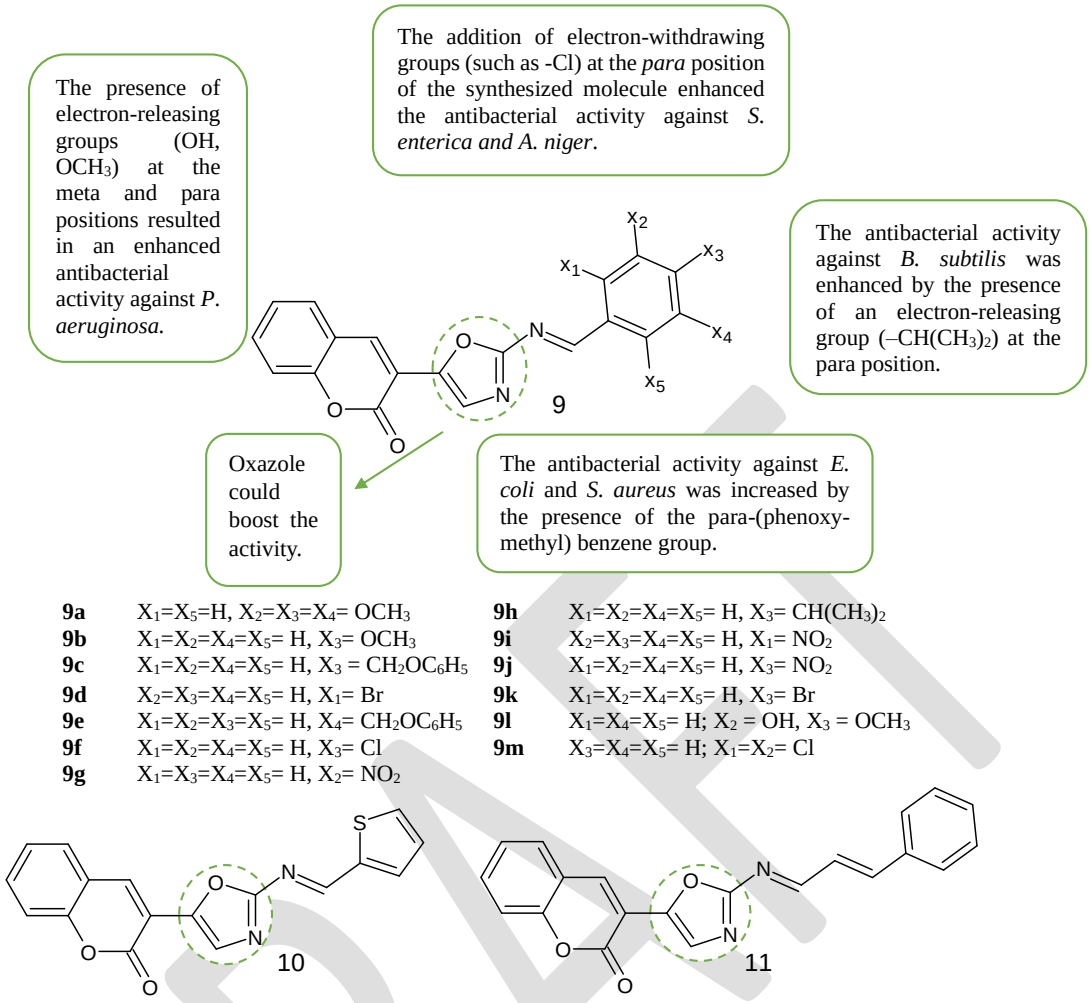


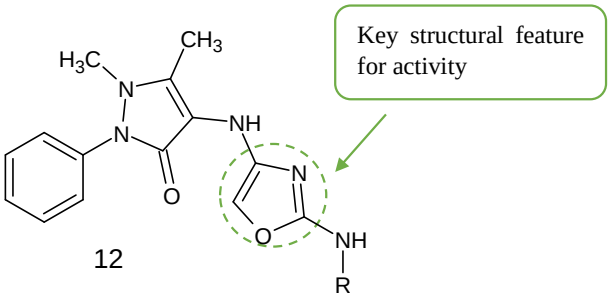
Figure (9): Structures and SAR of 3-(2-aminooxazol-5-yl)-2H-chromen-2-one derivatives.

Table (8): *In vitro* antimicrobial activity of the most potent synthesized compounds.

Compounds	(MIC= µg/mL)				
	Staphylococcus aureus	**Escherichia coli**	**Bacillus subtilis**	**Pseudomonas aeruginosa**	**Salmonella enterica**
9c	6.26	6.26	25.04	25.04	25.04
9f	25.03	25.03	25.03	12.49	6.25
9h	12.53	12.53	6.28	25.06	25.06
9l	25.08	25.08	25.08	6.28	25.08
Cefadroxil	6.25	6.25	6.25	6.25	6.25

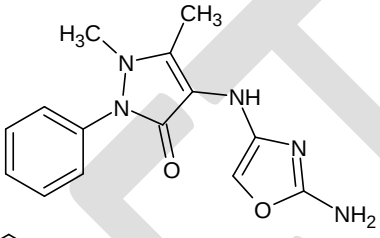
Antipyrine and oxazole moieties

Cyclic imides have been thoroughly investigated due to their diverse spectrum of biological actions [65-66]. They exhibit their significance as synthetic intermediates. Currently, there is a strong emphasis on this significant group of substances due to their potential for novel uses, particularly in the field of medicinal chemistry [67]. Combining cyclic imides with azoles in a single molecule appears to be a valuable effort since it has the potential to display diverse biological actions [68]. Eleven compounds of novel cyclic imides containing two unique azole rings, namely antipyrine and oxazole moieties (Figure 10) were successfully synthesized. The cup plate method was employed to investigate the antibacterial efficacy of the synthesized cyclic imides against various bacterial strains, with gentamicin serving as the control molecule. The investigation included four species of bacteria: Staphylococcus aureus, Staphylococcus epidermidis, Eshreshia coli, and Pseudomonas. The results demonstrated that compounds 12a, 12b, 12c, and 12d had significant efficacy against both Staphylococcus aureus and Staphylococcus epidermidis (Table 9). Compound 12d exhibits significant activity against Eshreshia coli, Pseudomonas, and Candida albicans. Other compounds exhibited a moderate level of effectiveness against the microorganisms and Candida albicans that were tested [69]. However, cyclic imides bearing different heterocycles derivatives which were based on the key compound [9a] showed excellent antibacterial activity.

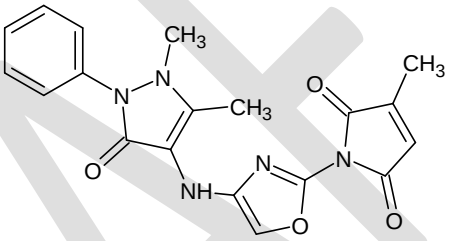


Compounds **Structure**

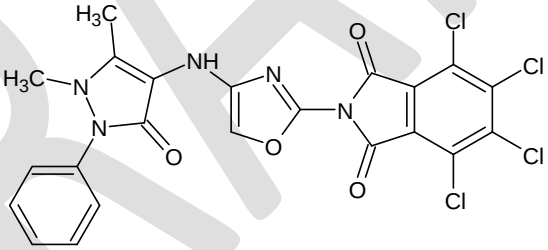
12a



12b



12c



12d

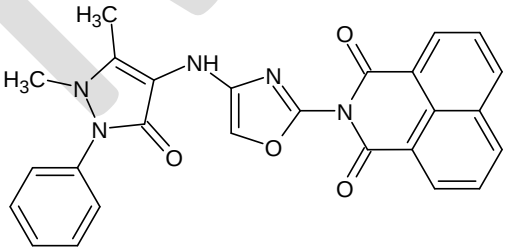


Figure (10): Antipyrine and oxazole moieties.

Table (9): Inhibition zones of antimicrobial activity of cyclicimides.

Compounds	Zone Inhibition in mm			
	Staphylococcus aureus	Staphylococcus epidermidis	E. coli	Pseudomonas
12a	> 11	> 11	8-11	8-11
12b	> 11	> 11	> 11	> 11
12c	> 11	> 11	8-11	8-11
12d	> 11	> 11	> 11	> 11
Gentamicin	> 11	> 11	> 11	> 11

Natural compounds containing oxazole

Prior research has shown the extraction of numerous biologically potent substituted oxazole-containing natural compounds, primarily from marine invertebrates and microorganisms [70-71]. One example is hennoxazole A (Figure 11), which was obtained from a sea sponge called Polyfibrospongia sp. It has been found to have antiviral properties [72-73].

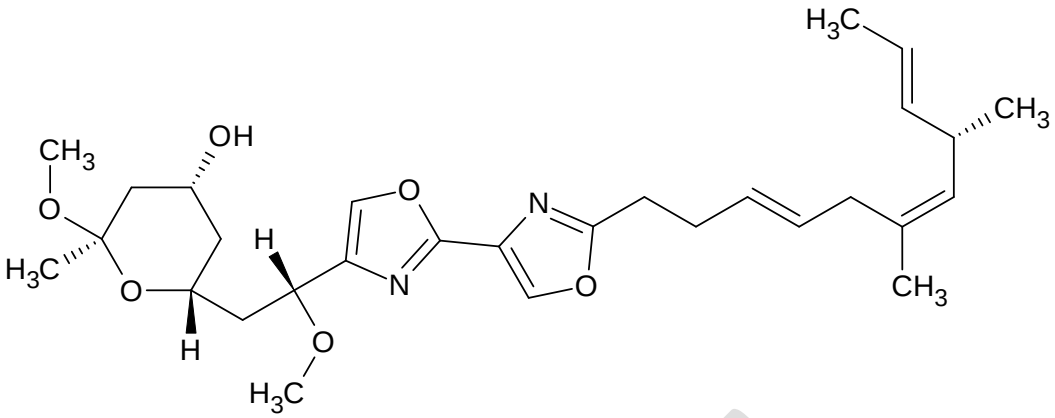


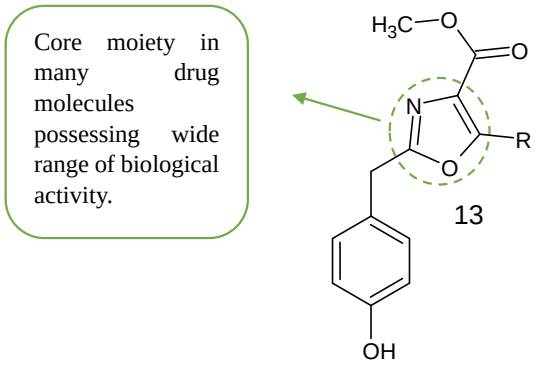
Figure (11): Hennoxazole A

Likewise, in vitro experiments have demonstrated the selective efficacy of phthoxazolins derived from Streptomyces sp. against the oomycete Phytophthora parasitica [74]. Previous research has demonstrated the capacity to create phytotoxic metabolites known as macrocidins from the liquid culture of the fermentation extract from the plant pathogenic fungus Phoma macrostoma, which was originally isolated from its host, the dangerous weed Cirsium arvense. It has been discovered that applying these macrocidins to the leaves of several dicotyledonous species results in bleaching [75-76]. Four newly discovered oxazole-4-carboxylic acid derivatives (13a–13d) were found (Figure 12), in the liquid culture of Phoma macrostoma by Blondelle et al. The structures of the isolates were determined using high resolution electro-spray ionization mass spectrometry (HR-ESIMS) data and 1D and 2D nuclear magnetic resonance (NMR) spectroscopy data. The antibacterial and cytotoxic properties of all compounds were examined. With the use of a variety of test microorganisms, serial dilution tests were used to determine the Minimum Inhibitory Concentrations (MIC) of the four compounds. For Gram-positive bacteria, these microbes included Mycobacterium smegmatis, Bacillus subtilis, Staphylococcus aureus, and Micrococcus luteus. For Gram-negative bacteria, the microorganisms used were Chromobacterium violaceum, Escherichia coli, and Pseudomonas aeruginosa. Only the newly discovered metabolite 13c exhibited activity against the tested species. The remaining compounds showed no activity. compound 13c demonstrated moderate activity against Bacillus subtilis at 66.7 µg/mL. Compounds 13b and 13c demonstrated moderate to mild suppression of both biofilm production and preformed biofilm of the bacterium. All the compounds (13a–13d) were tested as pure compounds, compound 4 was not tested because it was isolated as a mixture. Thus, these compounds were assessed for their efficacy in suppressing the formation of biofilm by Staphylococcus aureus. Compounds 10b and 10c exhibited moderate-to-weak effectiveness in inhibiting biofilm formation, with inhibition percentages of 65% and 75% respectively, at a maximum dosage of 250 µg/mL (Table 9), whereas none of the isolates showed antibacterial activity against S. aureus [77]. Therefore, these secondary metabolites isolated from Phoma macrostoma showed moderate antibacterial activity.

Table (10): Inhibition of biofilm in Staphylococcus aureus by compounds 13a, 13b and 13c.

Compounds	Inhibition of Biofilm Formation (%)
13a	N. A.
13b	65 (250 µg/mL)
13c	75 (250 µg/mL)

N.A = No activity



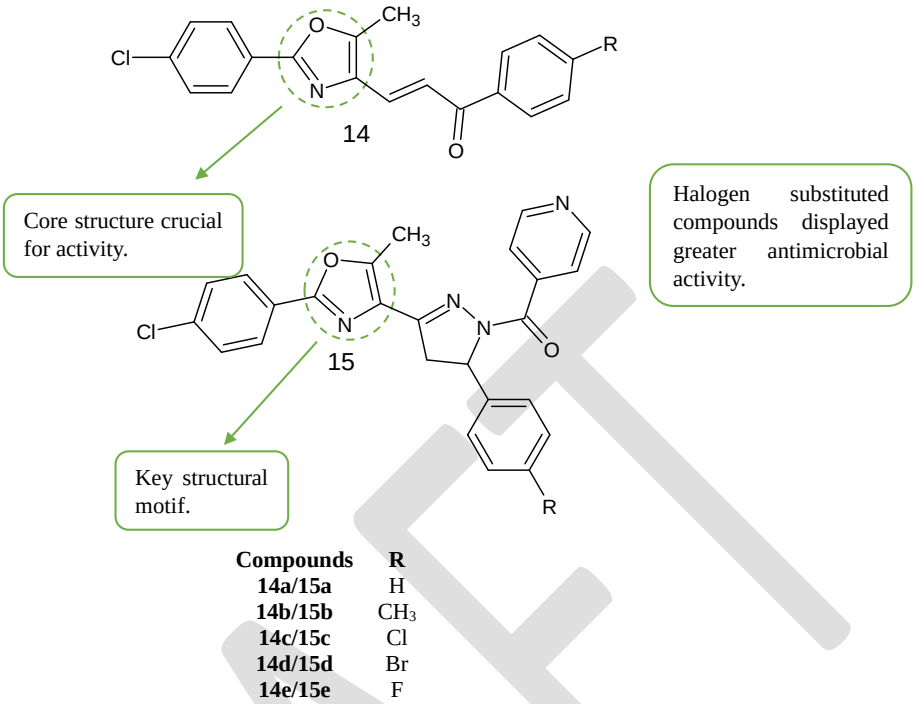
Compounds	R
13a	H_2C OH
13b	HO CH OH
13c	HC═CH_2
13d	HC, O

Figure (12): Oxazole-4-carboxylic acid derivatives.

Oxazolyl chalcones and 1,3-oxazoles attached to pyridyl-pyrazoline moieties

Kanubhai D and his research group synthesized new and powerful heterocyclic compounds by combining biologically active heterocyclic components, specifically oxazole, pyrazoline, and pyridine. The compounds (Figure 13) were examined for their antibacterial activity in a laboratory setting against several pathogenic strains (S. aureus (MTCC 96) and B. subtilis (MTCC 619) as Gram positive bacteria and E. coli (MTCC 739) and P. aeruginosa (MTCC 741) as Gram negative bacteria [78]. The researchers found pyrazoline to be intriguing. Pyrazoline-containing chemicals are commonly found in nature as alkaloids, vitamins, pigments, and components of animal and plant cells. Various synthetic compounds containing the pyrazoline moiety have been extensively documented, showing an expansive range of biological activity [79-80-81]. In addition, pyridine, a six-membered nitrogen heterocycle, is a significant heterocycle present in numerous naturally occurring chemicals. Pyridine derivatives are widely employed as industrial, medicinal, and agricultural chemicals. Furthermore, numerous studies have been conducted on compounds that include a pyridine scaffold and exhibit a wide range of biological functions (82–84]. Chalcone, also known as 1,3-diphenyl-2-propenone, serves as a precursor in the natural production of flavonoids and isoflavonoids. It is an intermediary compound in the synthesis of flavone, namely in the open-chain form, [85-86]. The chalcone scaffold has garnered significant interest from chemists due to its straightforward synthesis, the potential for diverse substituents, and its wide range of biological functions, making it valuable to biologists as well [87–91]. Out of all the synthesized compounds, a few demonstrated strong antimicrobial properties. From 3-(2-(4-chlorophenyl)−1-aryl-propenones 14(a-e), Specifically, compounds 14b and 14d displayed significant inhibitory effects against the S. aureus bacterial strain, with minimum inhibitory concentrations (MIC) of 12.5 µg/ml and 25 µg/ml, respectively (Table 11). Additionally, these compounds showed effective inhibition against B. subtilis, with a MIC of 12.5 µg/ml. Compound 14b and compound 14e exhibited inhibition against P. aeruginosa at 12.5 µg/ml. 14b exhibited excellent inhibitory activity (MIC = 6.25 µg/ml) against E. coli. Among the (oxazolyl-pyrazolyl)-pyridinyl)-methanones 15(a-e), only compound 15(b) exhibited higher inhibition with a minimum inhibitory concentration (MIC) of 6.25 µg/ml against S. aureus compared to the parent chalcone 14b. Compound 15e also demonstrated good inhibition with a MIC of 12.5 µg/ml against the same strain of bacteria, S. aureus. The compound 15d exhibited the greatest inhibition, with a minimum inhibitory concentration (MIC) of 6.25 µg/ml against B. subtilis. Compound 15b exhibited good inhibition with a minimum inhibitory concentration (MIC) of 12.5 µg/ml against the identical bacterial strain, which is consistent with the parent chalcone 14b. Compounds 15b, 15c, and 15d showed significant inhibition against E. coli, a Gram-negative bacterium. The minimum inhibitory concentration (MIC) for these compounds was found to be 12.5 µg/ml, which is greater than that of the original chalcones. This indicates that pyridyl-pyrazoline 15d is more potent than 14d. Compounds 15c and 15e exhibited inhibition against P. aeruginosa at a concentration of 12.5 µg/ml, which is similar to the inhibition shown by the oxazolyl chalcones 14c and

14e. The antibacterial activity results indicate that pyridyl-pyrazolines 15(a-e) exhibit higher potency against bacterial strains compared to the parent oxazolyl-propenones 14(a-e). Therefore, the new 1,3-oxazoles attached to pyridyl-pyrazoline moieties displayed good to excellent activity.



Compounds	R
14a/15a	H
14b/15b	CH_3
14c/15c	Cl
14d/15d	Br
14e/15e	F

Figure (13): Structures and SAR of oxazolyl chalcones and 1,3-oxazoles attached to pyridyl-pyrazoline moieties.

Table (11): Antimicrobial activity results of the synthesized compounds 14(a-e) and 15(a-e).

Compounds	(MIC in µg/mL)			
	S. aureus	B. subtilis	E. coli	P. aeruginosa
14a	125	100	50	25
14b	12.5	12.5	6.25	12.5
14c	100	50	25	25
14d	25	12.5	125	50
14e	100	125	25	12.5
15a	100	50	100	125
15b	6.25	12.5	12.5	25
15c	12.5	25	12.5	12.5
15d	25	6.25	12.5	25
15e	12.5	25	50	12.5
Ciprofloxacin	<3.12	<3.12	<3.12	<3.12

2-(4-Substituted benzyl)-5-substituted benzoxazole derivatives

Muhammed and his research group synthesized 2-(4-substituted benzyl)-5-substituted benzoxazole derivatives (Figure 14) and tested their antibacterial effects on standard strains and clinical isolates of E. coli, P. aeruginosa, S. aureus, E. faecalis, and C. albicans [92]. The benzoxazole molecule bears resemblance to the adenine and guanine bases. As a result, it is considered a crucial heterocyclic structure employed in the process of medication design. The benzoxazole scaffold can engage in several energetically favorable interactions with receptors. The structure of the compound contains oxygen and nitrogen atoms that can function as hydrogen bond acceptors (HBAs). The aromatic planar structure of the compound allows for π-π and π-cation interactions. Hydrophobic interactions can occur with receptors because of its lipophilic nature [93]. 2-Substituted benzoxazole derivatives have undergone comprehensive investigation, resulting in significant data regarding their structural properties and activities [94]. Regarding this matter, it has been noted that 2-substituted benzoxazole derivatives possess a wide range of pharmacological activities, such as antibacterial properties [56], anti-inflammatory[95], and analgesic [96]. There are medications with benzoxazole structures that have substitutions at the 2-position, which are now available on the market. Flunoxaprofen and benoxaprofen, which are nonsteroidal anti-inflammatory medicines (NSAIDs), along with calcimycin and boxazomycin A-B, which are antibiotics, and chloroxazone, a muscle relaxant, are examples of pharmaceuticals that include a 2-substituted benzoxazole nucleus [56].

The synthesized compounds exhibited activity only at significantly higher concentrations compared to the standard drugs. The conducted antimicrobial activity experiments showed that the synthesized compounds exhibited activity against both Gram-positive and Gram-negative bacteria at concentrations ranging from 128-512 µg/mL. These concentrations were quite high when compared to the concentrations of the standard medications utilized. The active benzoxazoles exert their antibacterial activity through the inhibition of DNA gyrase.

The antibacterial activity of the synthesized compounds was compared to that of their benzoxazole derivative analogs lacking the methylene bridge connecting the oxazole and phenyl ring (compound 17). There was a notable disparity in the activity levels of the two groups. Non-methylene-bridged benzoxazole derivatives exhibited higher activity compared to their methylene-bridged counterparts. Previous studies have shown that certain derivatives exhibit strong antibacterial action against comparable bacterial species, even at doses as low as 6.25 µg/mL [92] (Table 12). The antibacterial activity of benzoxazole derivatives, which were substituted with 5-methylsulfonyl with and without a methylene bridge, was examined in a prior work. Two compounds without the methylene bridge had the highest level of activity against B. subtilis at a dose of 7.8125 µg/ml [97]. During another study on the antibacterial activity of 5-substituted-2-(4-tertbutylphenyl) benzoxazole derivatives, it was discovered that one of the derivatives lacking the methylene bridge had greater activity than the standard medications against E. coli at a concentration of 8 µg/mL [98].

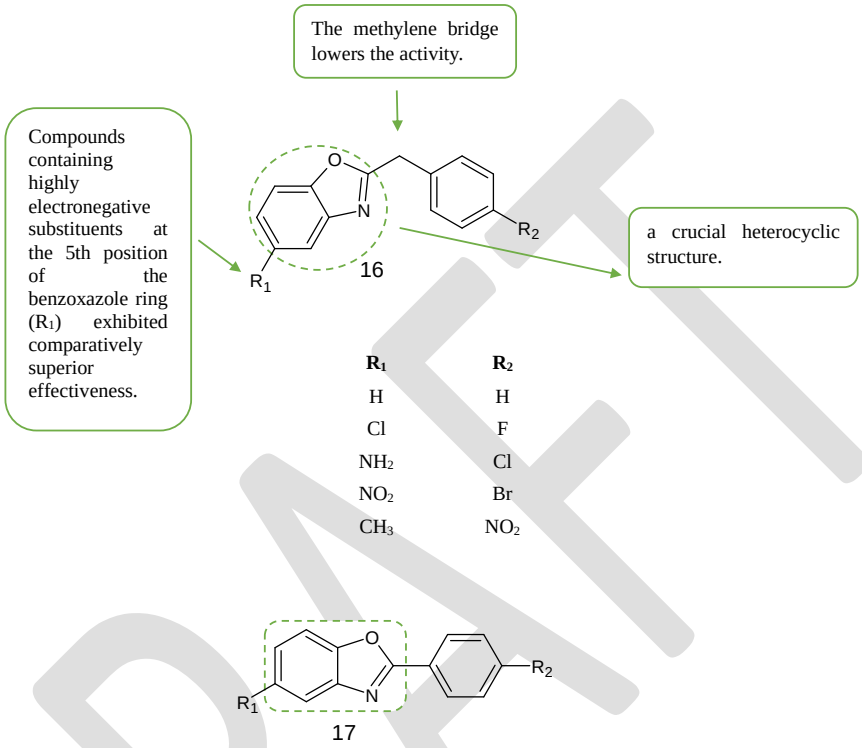


Figure (14): Structures and SAR benzoxazole derivatives with and without the methylene bridge.

Table (12): Antimicrobial activity of two benzoxazole derivatives with and without the methylene bridge (MIC in µg/mL) against S.aureus.

R1	R2	Without the methylene bridge	With the methylene bridge
NO2	Br	6.25	256
NO2	H	12.5	256
Ampicillin		0.39	0.5

1,3-Oxazole-quinoxaline amine hybrids

Ali and colleagues have reported a series of 1,3-oxazole-quinoxaline amine hybrids (Figure 15) and screened for antibacterial properties [99]. 2-Aryl oxazoles are highly useful heterocycles because of their wide range of biological and physical features [100]. Quinoxaline derivatives are crucial heterocyclic compounds due to their advantageous role as intermediates in chemical synthesis. The quinoxaline moiety is essential as a fundamental framework for developing new heterocyclic compounds with a wide range of biological features. This structure holds significant importance in the field of medicine [101–103] and technology [104-105]. The produced compounds were tested for their antibacterial properties against two bacterial strains, Micrococcus luteus (Gram-positive) and Pseudomonas aeruginosa (Gram-negative), using the dilution method. Compounds 18a, 18b, 18c, 18g, and 18j exhibit the lowest minimum inhibitory concentration (MIC) value of 62.5 µg/mL against M. luteus (Table. 13). Similarly, compounds 18b, 18c, 18e, 18g, 18h, 18i, 18j, and 18k demonstrate the lowest MIC value of 31.25 µg/mL against P. aeruginosa. Compounds 18b, 18c, 18e, 18g, 18i, 18j, and 18k exhibit superior antibacterial activity in comparison to the remaining compounds. Furthermore, the antibacterial properties of compounds 18b, 18c, 18g, and 18j were found to be similar to tetracycline, exhibiting potent inhibition with a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of 62.5 µg/mL [99].

Table (13): *In vitro* antimicrobial activities of all products expressed as MIC (µg/mL).

Compounds	M. luteus	P. aeruginosa
21a	62.5	125
21b	62.5	31.25
21c	62.5	31.25
21d	125	125
21e	125	31.25
21f	250	125
21g	62.5	31.25
21h	250	31.25
21i	125	31.25
21j	62.5	31.25
21k	125	31.25
21l	125	125
Tetracycline	62.5	31.25

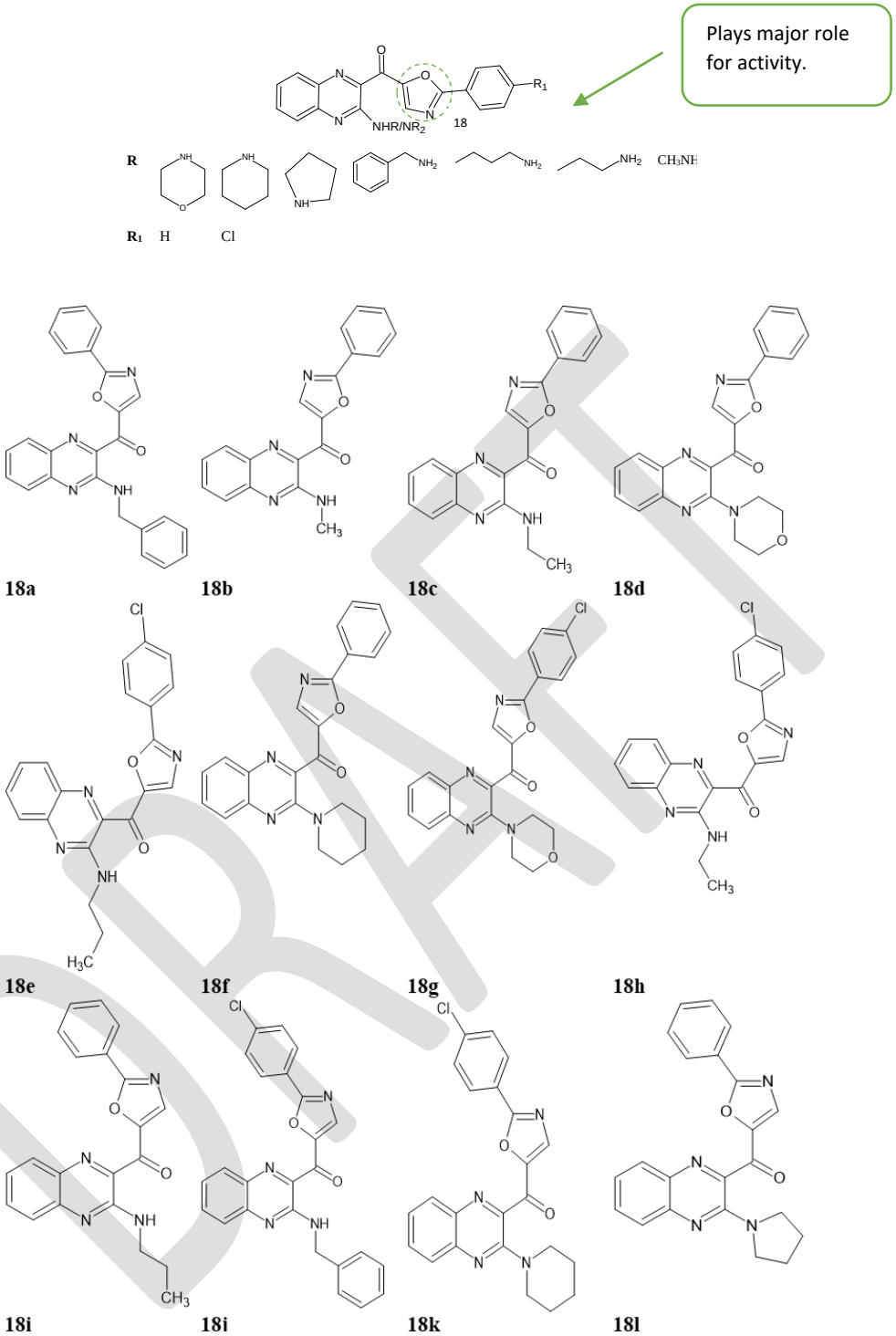


Figure (15): 1,3-Oxazole-quinoxaline amine hybrids.

Benzoxazole derivatives containing 2-phenyl and 2-N-phenyl groups

Two sets of new benzoxazole derivatives (Figure 16), one with 2-phenyl groups and the other with 2-N-phenyl groups were synthesized using the principles of green chemistry by Gajanan S et al. The newly synthesized compounds underwent screening against gram-positive bacteria (Streptococcus pyogenes, Staphylococcus aureus), and gram-negative bacteria (Pseudomonas aeruginosa, Escherichia coli), and their antibacterial activity was found to be associated with the inhibition of DNA gyrase [106].

The 2-substituted benzoxazole, a type of benzoxazole derivative, has consistently gained significant interest from researchers due to its wide range of applications in the field of medicinal chemistry [107]. Scaffold hopping has been a prevalent strategy in medicinal chemistry for discovering potent inhibitors, such as those targeting DNA gyrase. By employing this method, it is possible to synthesize bicyclic ring structures such as benzimidazole and benzothiazole [108- 109] and benzoxazole[110] The antibacterial properties of these compounds were associated with their ability to inhibit DNA topoisomerase II, as evidenced by their significant IC50 values [111]. DNA gyrase is a vital enzyme that is a component of

topoisomerase and is important for catalyzing alterations in DNA topology. The presence of DNA gyrase in bacteria and its absence in higher eukaryotes makes it a promising target for antibacterial research [112-113].

Compounds derived from the 2-amino phenyl benzoxazole series exhibited greater antibacterial efficacy compared to the 2-phenyl benzoxazole framework. All the benzoxazole derivatives that were synthesized showed significant antibacterial activity against Staphylococcus aureus, Streptococcus Pyogenes, P. Aeruginosa, and E. coli at a concentration of 25 µg/mL. Cefixime was used as a positive control standard in antibacterial research.

Compound-20a exhibited superior antibacterial efficacy against Staphylococcus aureus, with an inhibition rate of 81% at a concentration of 25 µg/mL (Table 14). Both compound-20a and compound-20b exhibited strong efficacy against Streptococcus pyogenes (82% inhibition) and staphylococcus aureus (85% inhibition). Specifically, compound-20b had the most potent antibacterial action against Escherichia coli, inhibiting 90% of its growth. The observed inhibition of compound 20b against pseudomonas aeruginosa is 72%. The chemical 19a from the aryl benzoxazole series exhibited a moderate level of efficacy against E. coli. Researchers believed that benzoxazole derivatives derived from 2-amino phenyl benzoxazole scaffolds had the potential to serve as effective inhibitors of DNA gyrase. These compounds might potentially be developed into new and powerful classes of antibiotic medicines [106].

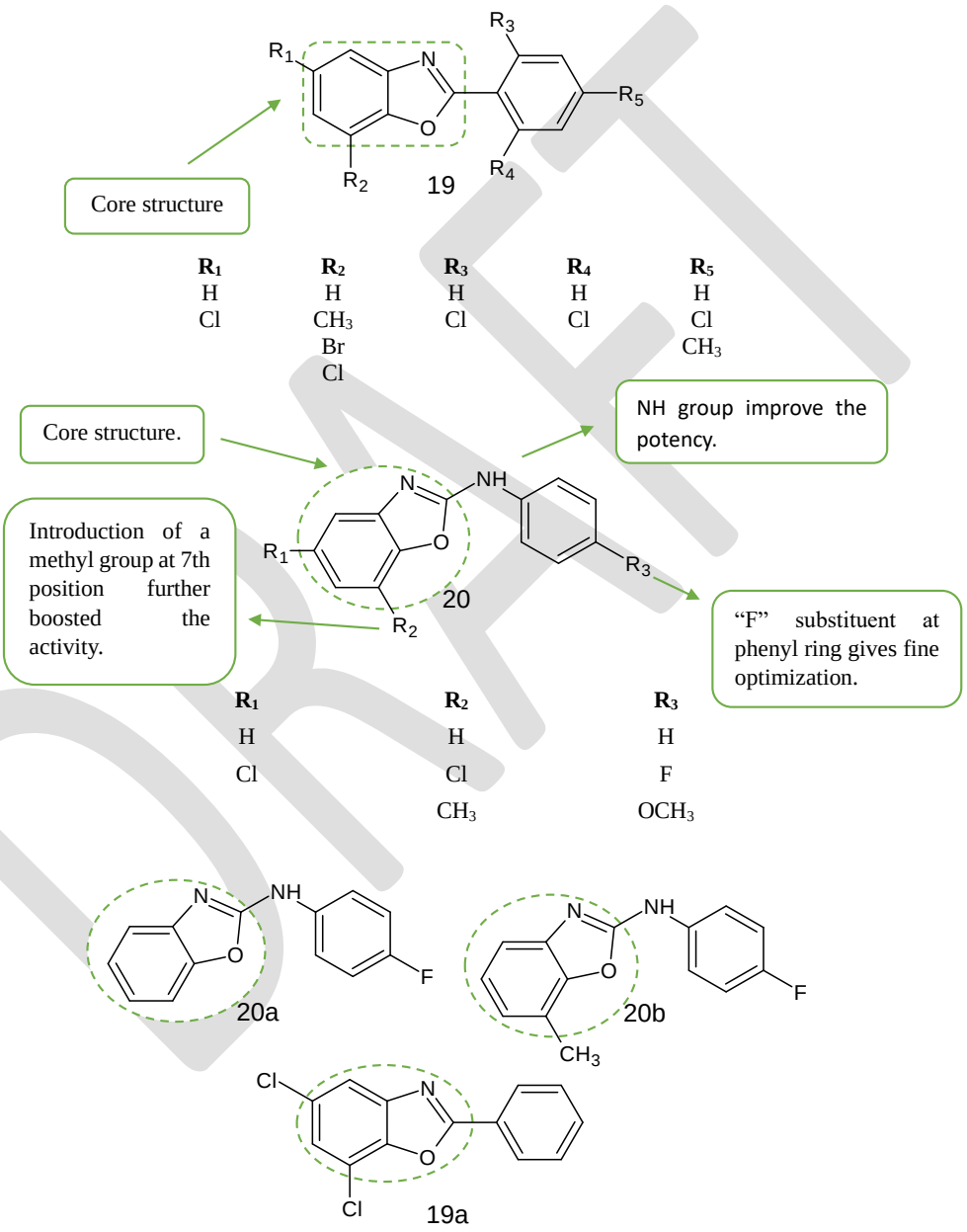


Figure (16): Structures and SAR of benzoxazole derivatives containing 2-phenyl and 2-N-phenyl groups.

Table (14): Antibacterial activities of benzoxazole derivatives containing 2-phenyl and 2-N-phenyl groups.

Compounds		20a	20b	Cefixime
MIC50 (µg/mL)	S. aureus	15.3 ±04	15.2±03	0.9 ±0.05
	S. pyogenes	16.1±02	14.8±05	0.8 ±0.06
	E. coli	16.5±07	13.2±01	1 ±0.03
	P. aeruginosa	6.6±04	18.7±05	0.9 ±0.04

Benzoxazole/carboximidamide and benzoxazole/1,2,4-oxadiazole hybrids

Many research groups have continued to focus their attention on the design of novel benzoxazoles. Carboximidamide and its corresponding five-membered heterocyclic 1,2,4-oxadizole scaffold have been extensively used as a central component in various bioactive compounds for the past forty years. These compounds exhibit a wide range of biological activities, including anti-inflammatory, anticonvulsant, anticancer, anxiolytic, antidepressant, analgesic, antiparasitic, antifungal, and antimicrobial properties [114–122]. The carboximidamide and 1,2,4-oxadiazole moieties have been found to be bioisosteric equivalents of amide and ester functional groups. This is because they can form particular interactions, such as hydrogen bonding. Furthermore, these compounds retain their effectiveness even in situations when the stability of those groups is compromised, such as under hydrolytic circumstances [123]. Abdulrahman A. Alsimaree and his research group prepared two series of 1,3-benzoxazole/carboximidamides 21(a-i) and 1,3-benzoxazole/3-aryl-1,2,4-oxadiazoles 22(a-I) derivatives (Figure 17) and tested their antibacterial activities against a panel of microorganisms (Table 15), which included Gram-positive bacteria (Bacillus subtilis, ATCC 6633, and Staphylococcus aureus, ATCC 6538) and Gram-negative bacteria (Escherichia coli, ATCC 8739, and Klebsiella pneumonia, ATCC 13,883) [124].

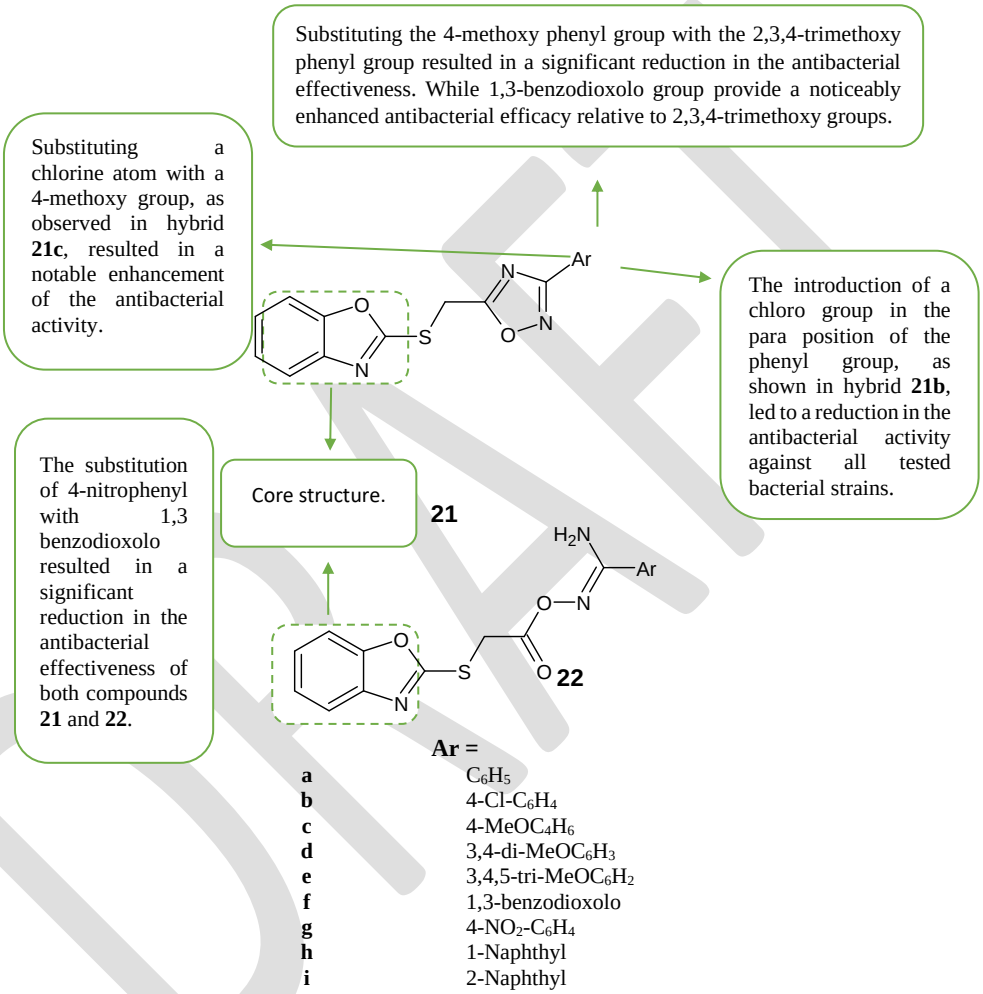


Figure (17): Structures, SAR, and antibacterial activities of benzoxazole/carboximidamide and benzoxazole/1,2,4-oxadiazole hybrids.

Table (15): Antibacterial activities of benzoxazole/carboximidamide and benzoxazole/1,2,4-oxadiazole hybrids.

Compounds	Diameter of zone inhibition in mm			
	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis	S. aureus	E. coli	K. pneumoniae
21a	34	36	15	32
21b	26	29	8	30
21c	31	30	8	33
21e	26	25	N	27
21f	31	35	N	33
21g	N	13	N	15
21i	28	28	N	31
22a	27	29	N	30
22b	31	34	12	35
22c	31	34	10	33
22e	32	36	11	34
22g	30	29	9	28
Gentamicin	25	15	17	22

N: No inhibition.

Table (16): Minimal Inhibitory Concentration (MIC) of (21a, 22b, and 22e) derivatives.

Compounds	Minimal Inhibitory Concentration (MIC) in µg/mL			
	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis	S. aureus	E. coli	K. pneumoniae
21a	0.61	0.3	77.34	1.21
22b	2.83	1.41	180.9	1.41
22e	1.63	0.4	417.44	0.81
Gentamicin	3.73	29.85	29.85	7.46

The hybrid 21a, which contains an unsubstituted phenyl group, exhibited remarkable efficacy against Gram-positive bacteria B. subtilis and S. aureus, resulting in 34 mm and 36 mm inhibitory zones, respectively. In addition, hybrid 21a demonstrated significant antibacterial activity against the Gram-negative bacteria K. pneumoniae, resulting in an inhibition zone measuring 32 mm. However, hybrid 21a exhibited a modest activity level against Gram-negative E. coli, leading to a 15 mm zone of inhibition. Regarding the antibacterial outcomes of benzoxazole/1,2,4-oxadiazole hybrids, it was found that the majority of the examined 1,2,4-oxadiazoles exhibited more potency compared to their corresponding carboximidamide derivatives, except for 21a. Additionally, these oxadiazoles show a wide range of antibacterial activity. Notably, most of the test compounds had more favorable antibacterial activity compared to the reference medication gentamicin. The three most powerful hybrids, 21a, 22b, and 22e, were selected to determine their minimum inhibitory concentration (MIC) values (Table 16). Hybrids 21a, 22b, and 22c have the potential to serve as a promising framework for the development and advancement of future derivatives through the incorporation of additional elements because these hybrids had the highest level of effectiveness against B. subtilis, S. aureus, and K. pneumoniae, respectively. Their minimum inhibitory concentration (MIC) values were also greater than the reference medication gentamicin [124].

As we have seen in the above various studies, each chemical structure has given different results on bacteria, but there have been some common points; for example, adding a benzene ring to the compound and substituting it with an electron-withdrawing or electron-releasing group enhances the antibacterial activity of the compounds on a particular type of bacteria as compounds 14, 16, 17, 19 and 20. Adding an electron-withdrawing or releasing group on the oxazole ring itself changes and optimizes the activity, as observed in compounds 1 and 13. Adding adjacent benzene and heterocyclic rings to the oxazole ring is good for its bacterial activity in general or a particular type of bacteria, such as compounds 2, 3, 4, and the rest of the compounds. The size and configuration of the heterocycle can impact its interaction with target bacterial enzymes, resulting in varying levels of effectiveness against specific bacteria. Specific functional groups on the heterocycle can also influence its capacity to permeate bacterial cell membranes, altering its range of effectiveness.

CONCLUSION

With the increasing gap between the effectiveness of antibacterial agents and their ability to combat various harmful bacteria, primarily caused by widespread and careless usage, there is an urgent requirement to identify new compounds that have demonstrated antimicrobial activity, particularly those with a heterocyclic structure. Oxazole-based analogs have diverse pharmacological properties and play a significant role in creating numerous medications. Significant focus has been directed toward developing novel heterocyclic-based medication candidates for their potential use as antibacterial agents in the current decade. Considering this, numerous Oxazole-hybrids with diverse structures were created, produced, and tested for their effectiveness in laboratory and animal studies. This review, a collection of studies from 2016 to 2024, will help researchers develop new, improved drugs that work as good antibacterial agents. Adding electron-donating or electron-withdrawing substituents to certain aryl/heteroaryl groups attached to the main oxazole structure was essential in augmenting or reducing the antibacterial effectiveness. The text conveys the urgency of the drug resistance situation and highlights oxazoles as prospective possibilities, given their broad pharmacological features and recent advancements in their chemical development.

Competing interest

The author declares no competing interests.

Funding

None.

Acknowledgments

The author would like to acknowledge the AAUP Research Foundation's support in publishing this work. Additionally, the author would like to thank Prof Hatem Hijaz for his continuous support and supervision of the current work.

REFERENCES

1] Verma R, Verma SK, Rakesh KP, Girish YR, Ashrafizadeh M, Sharath Kumar KS, et al. Pyrazole-based analogs as potential antibacterial agents against methicillin-resistance staphylococcus aureus (MRSA) and its SAR elucidation. Eur J Med Chem. 2021 Feb 15;212:113134.

2] Cabeen MT, Jacobs-Wagner C. Bacterial cell shape. Vol. 3, Nature Reviews Microbiology. 2005; 3(8):601-610

3] Zhang B. Comprehensive review on the antibacterial activity of 1,2,3-triazole hybrids. Eur J Med Chem. 2019 Apr 15;168:357–72.

4] Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. Clinical Infectious Diseases. 2004;38(6):864-870.

5] Nemeth J, Oesch G, Kuster SP. Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: Systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy. 2015;70(2).

6] Palumbi SR. Humans as the World' s Greatest Evolutionary Force the Pace of Human-Induced Evolution. Science (1979). 2001(September);293.

7] Kumar Verma S, Verma R, Xue F, Kumar Thakur P, Girish YR, Rakesh KP. Antibacterial activities of sulfonyl or sulfonamide containing heterocyclic derivatives and its structure-activity relationships (SAR) studies: A critical review. Bioorg Chem. 2020 Dec 1;105: 104400.

8] Jaradat N, Khasati A, Abu-Shanab BA, Al-Lahham S, Naser Zaid A, Abualhasan MN, et al. Bactericidal, fungicidal, helminthicidal, antioxidant, and chemical properties of chrozophora obliqua extract. Phytotherapie. 2020;18(5).

9] Jaradat N, Khasati A, Hawi M, Qadi M, Amer J, Hawash M. In vitro Antitumor, Antibacterial, and Antifungal Activities of Phenylthio-Ethyl Benzoate Derivatives. Arab J Sci Eng. 2021;46(6).

10] Devasia J, Nizam A, Vasantha VL. Azole-Based Antibacterial Agents: A Review on Multistep Synthesis Strategies and Biology. Polycycl Aromat Compd. 2021;42(8):5474-5495

11] Ebrahimi HP, Hadi JS, Almayah AA, Bolandnazar Z, Swadi AG, Ebrahimi A. Metal-based biologically active azoles and β-lactams derived from sulfa drugs. Bioorg Med Chem. 2016;24(5).

12] Allen D, Wilson D, Drew R, Perfect J. Azole antifungals: 35 years of invasive fungal infection management. Expert Review of Anti-Infective Therapy. 2015;13(6):787-798.

13] Mast N, Zheng W, Stout CD, Pikuleva IA. Antifungal azoles: Structural insights into undesired tight binding to cholesterol-metabolizing cyp46a1s. Mol Pharmacol. 2013;84(1).

14] Sowmya D V., Basha SS, Devi PUM, Lavanyalatha Y, Padmaja A, Padmavathi V. Synthesis, antimicrobial, and anti-inflammatory activities of acetamido pyrrolyl azoles. Medicinal Chemistry Research. 2017;26(5).

15] Toma A, Mogoşan C, Vlase L, Leonte D, Zaharia V. Heterocycles 39. Synthesis, characterization and evaluation of the anti-inflammatory activity of thiazolo[3,2-b] [1,2,4] triazole derivatives bearing pyridin-3/4-yl moiety. Medicinal Chemistry Research. 2017;26(10).

16] Bekhit AA, Saudi MN, Hassan AMM, Fahmy SM, Ibrahim TM, Ghareeb D, et al. Synthesis, in silico experiments and biological evaluation of 1,3,4-trisubstituted pyrazole derivatives as antimalarial agents. Eur J Med Chem. 2019;163.

17] Gao C, Chang L, Xu Z, Yan XF, Ding C, Zhao F, et al. Recent advances of tetrazole derivatives as potential antitubercular and antimalarial agents. European Journal of Medicinal Chemistry. 2019; 163, 404-412

18] Desai NC, Trivedi A, Somani H, Jadeja KA, Vaja D, Nawale L, et al. Synthesis, biological evaluation, and molecular docking study of pyridine clubbed 1,3,4-oxadiazoles as potential antituberculars. Synth Commun. 2018;48(5).

19] Gholap S, Tambe M, Nawale L, Sarkar D, Sangshetti J, Damale M. Design, synthesis, and pharmacological evaluation of fluorinated azoles as antitubercular agents. Arch Pharm (Weinheim). 2018;351(2).

20] Dawood KM, Eldebss TMA, El-Zahabi HSA, Yousef MH. Synthesis and antiviral activity of some new bis-1,3-thiazole derivatives. Eur J Med Chem. 2015;102.

21] Rhoden E, Nix WA, Weldon WC, Selvarangan R. Antifungal azoles itraconazole and posaconazole exhibit potent in vitro antiviral activity against clinical isolates of parechovirus A3 (Picornaviridae). Antiviral Res. 2018;149.

22] Decker M. Design of Hybrid Molecules for Drug Development. Design of Hybrid Molecules for Drug Development. 2017.

23] Fandiño OE, Reviglio L, Linck YG, Monti GA, Marcos Valdez MM, Faudone SN, et al. Novel Cocrystals and Eutectics of the Antiprotozoal Tinidazole: Mechanochemical Synthesis, Cocrystallization, and Characterization. Cryst Growth Des. 2020;20(5).

24] Fesatidou M, Petrou A, Athina G. Heterocycle Compounds with Antimicrobial Activity. Curr Pharm Des. 2020;26(8).

25] Rusu A, Moga IM, Uncu L, Hancu G. The Role of Five-Membered Heterocycles in the Molecular Structure of Antibacterial Drugs Used in Therapy. Vol. 15, Pharmaceutics. 2023;15(11):2554

26] Khalil A, Jaradat N, Hawash M, Issa L. In Vitro Biological Evaluation of Benzodioxol Derivatives as Antimicrobial and Antioxidant Agents. Arab J Sci Eng. 2021;46(6).

27] Hawash M, Jaradat N, Abualhasan M, Qaoud MT, Joudeh Y, Jaber Z, et al. Molecular docking studies and biological evaluation of isoxazole-carboxamide derivatives as COX inhibitors and antimicrobial agents. 3 Biotech. 2022;12(12).

28] Hawash M, Jaradat N, Abualhasan M, Qneibi M, Rifai H, Saqfelhait T, et al. Evaluation of Cytotoxic, COX Inhibitory, and Antimicrobial Activities of Novel Isoxazole-carboxamide Derivatives. Lett Drug Des Discov. 2022;20(12).

29] Joshi S, Singh Bisht A, Juyal D. Systematic scientific study of 1, 3-oxazole derivatives as a useful lead for pharmaceuticals: A review. ~ 109 ~ The Pharma Innovation. Journal [Internet]. 2017 ;6(1):109–17. Available from: www.thepharmajournal.com

30] Neha K, Ali F, Haider K, Khasimbi S, Wakode S. Synthetic approaches for oxazole derivatives: A review. Synthetic Communications. 2021;51(23):3501-3519

31] Walsh EJ. Book Notes: Heterocyclic Chemistry, 3rd ed. (Gilchrist, Thomas L.). J Chem Educ. 1997;74(12).

32] Zhang HZ, Gan LL, Wang H, Zhou CH. New Progress in Azole Compounds as Antimicrobial Agents. Mini-Reviews in Medicinal Chemistry. 2016;17(2).

33] Peng XM, Cai GX, Zhou CH. Recent Developments in Azole Compounds as Antibacterial and Antifungal Agents. Curr Top Med Chem. 2013;13(16).

34] Zhang HZ, Zhao ZL, Zhou CH. Recent advance in oxazole-based medicinal chemistry. Eur J Med Chem. 2018 Jan 20;144:444–92.

35] Synthesis and biological activity of 4-(4-hydroxybenzylidene)-2-(substituted styryl) oxazol-5-ones and their o -glucosides. Journal of Population Therapeutics and Clinical Pharmacology. 2023;30(12).

36] B. S. Rawat, Shrawan K. Shukla. Synthesis and evaluation of some new thiazole/oxazole derivatives for their biological activities. World Journal of Pharmacy and Pharmaceutical Sciences. 2016;5(8).

37] Liang Z, Zhang D, Ai J, Chen L, Wang H, Kong X, et al. Identification and synthesis of N′-(2-oxoindolin-3-ylidene) hydrazide derivatives against c-Met kinase. Bioorg Med Chem Lett. 2011;21(12).

38] Tiwari S, Ahamad A, Alauddin S. Synthesis of some 2-[2,4′-dioxo-spiroindole-3,2′-thiazolidin- 3′-yl] alkanoic acid/3-substituted indolo[2,3-b]oxazin-2-ones and 3-substituted arylidene indolo[2,3-b]oxazin-2-ones as fungicides. Indian Journal of Chemistry - Section B Organic and Medicinal Chemistry. 2014;53(3).

39] Tiwari S, Pathak P, Sagar R. Efficient synthesis of new 2,3-dihydrooxazole-spirooxindoles hybrids as antimicrobial agents. Bioorg Med Chem Lett. 2016;26(10).

40] Srinivas A, Nagaraj A, Reddy CS. Synthesis and in vitro study of methylene-bis-tetrahydro [1,3] thiazolo[4,5- c]isoxazoles as potential nematicidal agents. Eur J Med Chem. 2010;45(6).

41] Moraski GC, Markley LD, Chang M, Cho S, Franzblau SG, Hwang CH, et al. Generation and exploration of new classes of antitubercular agents: The optimization of oxazolines, oxazoles, thiazolines, thiazoles to imidazo[1,2-a] pyridines and isomeric 5,6-fused scaffolds. Bioorg Med Chem. 2012;20(7).

42] Inamdar GS, Pandya AN, Thakar HM, Sudarsanam V, Kachler S, Sabbadin D, et al. new insight into adenosine receptors selectivity derived from a novel series of [5-substituted-4-phenyl-1,3-thiazol-2-yl] benzamides and furamides. Eur J Med Chem. 2013;63.

43] Abhale YK, Sasane A V., Chavan AP, Shekh SH, Deshmukh KK, Bhansali S, et al. Synthesis and antimycobacterial screening of new thiazolyl-oxazole derivatives. Eur J Med Chem. 2017;132.

44] Singh R, Nawale LU, Arkile M, Shedbalkar UU, Wadhwani SA, Sarkar D, et al. Chemical and biological metal nanoparticles as antimycobacterial agents: A comparative study. Int J Antimicrob Agents. 2015;46(2).

45] Shreedhara SH, Vagdevi HM, Jayanna ND, Raghavendra R. All rights reserved. International Journal of Pharma Research and Health Sciences [Internet]. 2017;5(6):2055–63. Available from: www.pharmahealthsciences.net

46] Rodríguez AD, Ramírez C, Rodríguez II, González E. Novel antimycobacterial benzoxazole alkaloids, from the West Indian Sea whip Pseudopterogorgia elisabethae. Org Lett. 1999;1(3).

47] Rida SM, Ashour FA, El-Hawash SAM, Elsemary MM, Badr MH, Shalaby MA. Synthesis of some novel benzoxazole derivatives as anticancer, anti-HIV-1 and antimicrobial agents 2005;40(9):949-959 Available from: www.elsevier.com/locate/ejmech

48] Sagheer OM, Saour KY, Ghareeb MM. Synthesis of oxoquinoline derivatives coupled to different amino acid esters and studying their biological activity as cytotoxic agents. Int J Pharm Pharm Sci. 2013;5(SUPPL.4).

49] Davidse LC. Benzimidazole Fungicides: Mechanism of Action and Biological Impact. Annu Rev Phytopathol. 1986;24(1).

50] Dannhardt G, Kiefer W, Krämer G, Maehrlein S, Nowe U, Fiebich B. The pyrrole moiety as a template for COX-1/COX-2 inhibitors inhibition / pyrrole derivatives / enzyme selectivity / structure-activity relationship. 2000;35(5): 499-510.

51] Jansen R, Sood S, Huch V, Kunze B, Stadler M, Müller R. Pyrronazols, metabolites from the myxobacteria Nannocystis pusilla

and N. exedens, are unusual chlorinated pyrone-oxazole-pyrroles. J Nat Prod. 2014;77(2).

52] Li J, Burgett AWG, Esser L, Amezcua C, Harran PG. Total synthesis of nominal diazonamides - Part 2: On the true structure and origin of natural isolates. Angewandte Chemie - International Edition. 2001;40(24).

53] Conti P, Dallanoce C, De Amici M, De Micheli C, Klotz KN. Synthesis of New Á 2-Isoxazoline Derivatives and their Pharmacological Characterization as-Adrenergic Receptor Antagonists1998; 6(4).

54] Reddy NB, Zyryanov G V., Reddy GM, Balakrishna A, Garcia JR, Camilo A, et al. Simulation results source for the identification of biological active compounds: synthesis, antimicrobial evaluation and SARs of three in one heterocyclic motifs. Medicinal Chemistry Research. 2018;27(8).

55] Kakkar S, Kumar S, Narasimhan B, Lim SM, Ramasamy K, Mani V, et al. Design, synthesis and biological potential of heterocyclic benzoxazole scaffolds as promising antimicrobial and anticancer agents. Chem Cent J. 2018 Sep 19;12(1).

56] Kakkar S, Tahlan S, Lim SM, Ramasamy K, Mani V, Shah SAA, et al. Benzoxazole derivatives: design, synthesis and biological evaluation. Chem Cent J. 2018;12(1).

57] Cappuccino J, Welsh C. Microbiology, a laboratory manual. Pearson Education Limited. 2018.

58] Ronad PM, Dharbamalla S, Hunshal R, Maddi V. Synthesis of Novel Substituted 7-(Benzylideneamino)-4-Methyl-2H-Chromen-2-one Derivatives as Anti-inflammatory and Analgesic Agents. Arch Pharm (Weinheim) [Internet]. 2008 Nov 1;341(11):696–700. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/ardp.200800057

59] Bolakatti GS, Maddi VS, Mamledesai SN, Ronad PM, Palkar MB, Swamy S. Synthesis and evaluation of anti-inflammatory and analgesic activities of a novel series of coumarin Mannich bases. Arzneimittel-Forschung/Drug Research [Internet]. 2008;58(10):515–20. Available from: http://www.thieme-connect.com/products/ejournals/html/10.1055/s-0031-1296551

60] Khode S, Maddi V, Aragade P, Palkar M, Ronad K, Mamledesai S, et al. Synthesis and pharmacological evaluation of a novel series of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agents. Eur J Med Chem. 2008;44:1682–8.

61] Yu D, Suzuki M, Xie L, Morris-Natschke SL, Lee KH. Recent progress in the development of coumarin derivatives as potent anti-HIV agents. Med Res Rev [Internet]. 2003 May 1;23(3):322–45. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/med.10034

62] Karalı N, Kocabalkanlı A, Gü A, Ates¸ A. Synthesis and antitubercular activity of 4-(3-coumarinyl)-3-cyclohexyl-4-thiazolin-2-one benzylidenehydrazones. Il Farmaco [Internet]. 2002;57:589–93. Available from: www.elsevier.com/locate/farmac

63] Ranjan Sahoo C, Sahoo J, Mahapatra M, Lenka D, Kumar Sahu P, Dehury B, et al. Coumarin derivatives as promising antibacterial agent(s). 2021;14(2):102922 Available from: https://doi.org/10.1016/j.arabjc.2020.102922

64] Kakkar S, Kumar S, Lim SM, Ramasamy K, Mani V, Shah SAA, et al. Design, synthesis and biological evaluation of 3-(2-aminooxazol-5-yl)-2H-chromen-2-one derivatives. Chem Cent J. 2018;12(1).

65] Latief BH, Al-Azzawi AM. Synthesis of new cyclic imides comprising antipyrine and thiazole cycles. Journal of Pharmaceutical Sciences and Research. 2018;10(12).

66] Synthesis and Antibacterial Screening of New Schiff Bases Based on N-(4-acetophenyl) Succinimide. IRAQI JOURNAL OF SCIENCE. 2017;58(4A).

67] Al-Azzawi AM, Sa'adi Hassan A. synthesis and antimicrobial activity of new succinimides bearing different heterocycles, international journal of research in pharmacy and chemistry [Internet]. 2014; 755-762. Available from: www.ijrpc.com

68] Abdel-Aziz AAM, El-Azab AS, Attia SM, Al-Obaid AM, Al-Omar MA, El-Subbagh HI. Synthesis and biological evaluation of some novel cyclic-imides as hypoglycaemic, anti-hyperlipidemic agents. Eur J Med Chem. 2011;46(9).

69] Latief BH, Al-Azzawi AM. synthesis and antimicrobial activity screening of new cyclic imides comprising antipyrine and oxazole cycles. Biochem Cell Arch. 2019;19(2).

70] Zhang W, Liu W, Jiang X, Jiang F, Zhuang H, Fu L. Design, synthesis and antimicrobial activity of chiral 2-(substituted-hydroxyl)-3-(benzo[d]oxazol-5-yl) propanoic acid derivatives 2011; 46(9), 3639-3650. 2011;

71] Davyt D, Serra G. Thiazole and Oxazole Alkaloids: Isolation and Synthesis. Mar Drugs [Internet]. 2010;8:2755–80. Available from: www.mdpi.com/journal/marinedrugs

72] Ichiba T, Yoshida WY, Scheuer PJ, Higa T, Gravalos DG. Hennoxazoles: Bioactive Bisoxazoles from a Marine Sponge. J Am Chem Soc [Internet]. 1991;113(8):3173–4. Available from: https://pubs.acs.org/doi/pdf/10.1021/ja00008a056

73] Yokokawa F, Asano T, Shioiri T. Total synthesis of the antiviral marine natural product (-)-hennoxazole A. Org Lett. 2000;2(26).

74] Shiomi K, Arai N, Shinose M, Takahashi Y, Yoshida H, Iwabuchi J, et al. New Antibiotics Phthoxazolins B, C and D Produced by Streptomyces sp. KO-7888. J Antibiot (Tokyo). 1995 Jul 25;48(7):714–9.

75] The Macrocidins: Novel Cyclic Tetramic Acids with Herbicidal Activity Produced byPhomamacrostoma. Journal of Natural Products, 2003; 66(12), 1558–1561 | 10.1021/np030193e [Internet]. Available from: https://doi.org/10.1021/np030193e

76] Chlorosis Inducing Phytotoxic Metabolites: New Herbicides from Phoma macrostoma. Natural Products for Pest Management, 2006;37–47 Available from: http://dx.doi.org/10.1021 [Internet].

77] Kemkuignou BM, Treiber L, Zeng H, Schrey H, Schobert R, Stadler M. Macrooxazoles a–d, new 2,5-disubstituted oxazole-4-carboxylic acid derivatives from the plant pathogenic fungus phoma macrostoma. Molecules. 2020;25(23).

78] Katariya KD, Vennapu DR, Shah SR. Synthesis and molecular docking study of new 1,3-oxazole clubbed pyridyl-pyrazolines as anticancer and antimicrobial agents. J Mol Struct. 2021;1232.

79] Rajendra Prasad Y, Kumar GVS, Chandrashekar SM. Synthesis and biological evaluation of novel 4,5-dihydropyrazole derivatives as potent anticancer and antimicrobial agents. Medicinal Chemistry Research [Internet]. 2013 May 2;22(5):2061–78. Available from: https://link.springer.com/article/10.1007/s00044-012-0191-y

80] Abid M, Azam A. Synthesis, characterization and antiamoebic activity of 1-(thiazolo[4,5-b]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivatives. Bioorg Med Chem Lett. 2006 May 15;16(10):2812–6.

81] Ali MA, Yar MS, Kumar M, Pandian GS. Synthesis and antitubercular activity of substituted novel pyrazoline derivatives. Nat Prod Res [Internet]. 2007 Jun;21(7):575–9. Available from: https://www.tandfonline.com/doi/abs/10.1080/14786410701369367

82] Güzeldemirci NU, Ilhan E, Küçükbasmaci Ö, Satana D. Synthesis and antimicrobial evaluation of new 3-alkyl/aryl-2-[((α, α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinones. Arch Pharm Res [Internet]. 2010 Feb 27;33(1):17–24. Available from: https://link.springer.com/article/10.1007/s12272-010-2221-y

83] Amr AGE, Mohamed AM, Mohamed SF, Abdel-Hafez NA, Hammam AEFG. Anticancer activities of some newly synthesized pyridine, pyrane, and pyrimidine derivatives. Bioorg Med Chem. 2006 Aug 15;14(16):5481–8.

84] Mohareb RM, Zaki MY, Abbas NS. Synthesis, anti-inflammatory and anti-ulcer evaluations of thiazole, thiophene, pyridine and pyran derivatives derived from androstenedione. Steroids. 2015 Jun 1;98: 80–91.

85] GRAYER RJ. Flavanoids. 1989 Jan 1;1:283–323.

86] Grotewold E. The science of flavonoids. The Science of Flavonoids. 2006;1–273.

87] Bhale PS, Chavan H V., Dongare SB, Shringare SN, Mule YB, Nagane SS, et al. Synthesis of extended conjugated indolyl chalcones as potent anti-breast cancer, anti-inflammatory and antioxidant agents. Bioorg Med Chem Lett. 2017 Apr 1;27(7):1502–7.

88] Kumar H, Devaraji V, Joshi R, Jadhao M, Ahirkar P, Prasath R, et al. Antihypertensive activity of a quinoline appended chalcone derivative and its site-specific binding interaction with a relevant target carrier

protein. RSC Adv [Internet]. 2015 Jul 29;5(80):65496–513. Available from: https://pubs.rsc.org/en/content/articlehtml/2015/ra/c5ra08778c

89] Gómez-Rivera A, Aguilar-Mariscal H, Romero-Ceronio N, Roa-De La Fuente LF, Lobato-García CE. Synthesis and anti-inflammatory activity of three nitro chalcones. Bioorg Med Chem Lett. 2013 Oct 15;23(20):5519–22.

90] Khan SA, Asiri AM. Green synthesis, characterization and biological evaluation of novel chalcones as anti bacterial agents. Arabian Journal of Chemistry. 2017 May 1;10:S2890–5.

91] Bukhari S, Franzblau S, Jantan I, Jasamai M. Current Prospects of Synthetic Curcumin Analogs and Chalcone Derivatives Against Mycobacterium Tuberculosis. Med Chem (Los Angeles). 2013 Sep 14;9(7):897–903.

92] Muhammed MT, Kuyucuklu G, Kaynak-Onurdag F, Aki-Yalcin E. Synthesis, Antimicrobial Activity, and Molecular Modeling Studies of Some Benzoxazole Derivatives. Lett Drug Des Discov. 2022;19(8).

93] Aksenov NA, Aksenov A V., Nadein ON, Aksenov DA, Smirnov AN, Rubin M. One-pot synthesis of benzoxazoles via the metal-free ortho-C–H functionalization of phenols with nitroalkanes. RSC Adv [Internet]. 2015 Aug 21;5(88):71620–6. Available from: https://pubs.rsc.org/en/content/articlehtml/2015/ra/c5ra15128g

94] Zilifdar F, Foto E, Ertan-Bolelli T, Aki-Yalcin E, Yalcin I, Diril N. Biological evaluation and pharmacophore modeling of some benzoxazoles and their possible metabolites. Arch Pharm (Weinheim). 2018 Feb 1;351(2):1700265. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/ardp.201700265

95] Sondhi SM, Singh N, Kumar A, Lozach O, Meijer L. Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff's bases. Bioorg Med Chem. 2006;14(11).

96] Baytaş S, Nermin N, Dural T, Özkan Y, Bolkan Şimşek H, Gürsel T, et al. Synthesis, anti-inflammatory, antiplatelet and in silico evaluations of (E)-3-(3-(2,3-dihydro-3-methyl-2-oxo-3H-benzoxazole-6-yl)-1-phenyl-1H-pyrazole-4-yl) acrylamides 2012. Available from: https://journals.tubitak.gov.tr/chem/vol36/iss3/2

97] Temiz-Arpaci Ö, Yildiz I, Özkan S, Kaynak F, Aki-Şener E, Yalçin I. Synthesis and biological activity of some new benzoxazoles. Eur J Med Chem. 2008;43(7).

98] Taşcı M, Temiz-Arpaci O, Kaynak-Onurdag F, Okten S. Synthesis and antimicrobial evaluation of novel 5-substituted-2 -(p-tert-butylphenyl) benzoxazoles. 2018;57:385–9. Available from: http://nopr.niscpr.res.in/handle/123456789/43822

99] Keivanloo A, Abbaspour S, Sepehri S, Bakherad M. Synthesis, Antibacterial Activity and Molecular Docking Study of a Series of 1,3-Oxazole-Quinoxaline Amine Hybrids. Polycycl Aromat Compd. 2022;42(5).

100] Zificsak CA, Hlasta DJ. Tetrahedron report number 691 Current methods for the synthesis of 2-substituted azoles. 2004;60(41), 8991-9016.

101] Undevia SD, Innocenti F, Ramirez J, House L, Desai AA, Skoog LA, et al. A phase I and pharmacokinetic study of the quinoxaline antitumour Agent R(+)XK469 in patients with advanced solid tumours 2008; 44(12), 1684-1692.

102] Vicente E, Lima LM, Bongard E, Charnaud S, Villar R, Solano B, et al. Synthesis and structureeactivity relationship of 3-phenylquinoxaline 1,4-di-N-oxide derivatives as antimalarial agents. 2008; Available from: http://www.elsevier.com/locate/ejmech

103] Kim YB, Kim YH, Park JY, Kim SK. Synthesis and biological activity of new quinoxaline antibiotics of echinomycin analogues §. Bioorg Med Chem Lett. 2004;14:541–4.

104] Jaung JY. Synthesis and halochromism of new quinoxaline fluorescent dyes. Dyes and Pigments. 2006;71(3).

105] Justin Thomas KR, Velusamy M, Lin Jiann T, Chuen CH, Tao YT. Chromophore-labeled quinoxaline derivatives as efficient electroluminescent materials. Chemistry of Materials. 2005;17(7).

106] Shanbhag GS, Bhargava A, Pal Singh G, Joshi SD, Singh Chundawat N. Synthesis, molecular simulation studies, in vitro biological assessment of 2-substituted benzoxazole derivatives as promising antimicrobial agents. Turk J Chem. 2023;47(1).

107] Zilifdar Foto F, Foto E, Ertan-Bolelli T, Yildiz I. Biological activity and ADME/Tox prediction of some 2-substituted benzoxazole derivatives. Bioorg Chem. 2022;123.

108] Charifson PS, Grillot AL, Grossman TH, Parsons JD, Badia M, Bellon S, et al. Novel dual-targeting benzimidazole urea inhibitors of DNA gyrase and topoisomerase IV possessing potent antibacterial activity: Intelligent design and evolution through the judicious use of structure-guided design and stucture-activity relationships. J Med Chem. 2008;51(17).

109] Axford LC, Agarwal PK, Anderson KH, Andrau LN, Atherall J, Barker S, et al. Design, synthesis and biological evaluation of a-substituted isonipecotic acid benzothiazole analogues as potent bacterial type II topoisomerase inhibitors. Bioorg Med Chem Lett [Internet]. 2013;23:6598–603. Available from: http://doi.org/10.1016/j.bmcl.2013.10.058

110] Reddy GM, Kumari AK, Reddy VH, Garcia JR. Novel pyranopyrazole derivatives comprising a benzoxazole core as antimicrobial inhibitors: Design, synthesis, microbial resistance and machine aided results. Bioorg Chem. 2020;100.

111] Oksuzoglu E, Tekiner-Gulbas B, Alper S, Temiz-Arpaci O, Ertan T, Yildiz I, et al. Some benzoxazoles and benzimidazoles as DNA topoisomerase I and II inhibitors. J Enzyme Inhib Med Chem. 2008;23(1).

112] Heddle J, Maxwell A. Quinolone-binding pocket of DNA gyrase: Role of GyrB. Antimicrob Agents Chemother [Internet]. 2002;46(6):1805–15. Available from: https://journals.asm.org/doi/10.1128/aac.46.6.1805-1815.2002

113] Abdullahi A, Keng •, Yeong Y. Targeting disease with benzoxazoles: a comprehensive review of recent developments. Medicinal Chemistry Research [Internet]. 2024;33:406–38. Available from: https://doi.org/10.1007/s00044-024-03190-7

114] Mohamed MFA, Marzouk AA, Nafady A, El-Gamal DA, Allam RM, Abuo-Rahma GEDA, et al. Design, synthesis and molecular modeling of novel aryl carboximidamides and 3-aryl-1,2,4-oxadiazoles derived from indomethacin as potent anti-inflammatory iNOS/PGE2 inhibitors. Bioorg Chem. 2020;105.

115] Youssif BGM, Mohamed MFA, Al-Sanea MM, Moustafa AH, Abdelhamid AA, Gomaa HAM. Novel aryl carboximidamide and 3-aryl-1,2,4-oxadiazole analogues of naproxen as dual selective COX-2/15-LOX inhibitors: Design, synthesis and docking studies. Bioorg Chem. 2019;85.

116] Ibrahim TS, Almalki AJ, Moustafa AH, Allam RM, Abuo-Rahma GEDA, El Subbagh HI, et al. Novel 1,2,4-oxadiazole-chalcone/oxime hybrids as potential antibacterial DNA gyrase inhibitors: Design, synthesis, ADMET prediction and molecular docking study. Bioorg Chem. 2021;111.

117] Ibrahim TS, Moustafa AH, Almalki AJ, Allam RM, Althagafi A, Md S, et al. Novel chalcone/aryl carboximidamide hybrids as potent anti-inflammatory via inhibition of prostaglandin E2 and inducible NO synthase activities: design, synthesis, molecular docking studies and ADMET prediction. J Enzyme Inhib Med Chem. 2021;36(1).

118] Youssif BGM, Gouda AM, Moustafa AH, Abdelhamid AA, Gomaa HAM, Kamal I, et al. Design and synthesis of new triarylimidazole derivatives as dual inhibitors of BRAFV600E/p38α with potential antiproliferative activity. J Mol Struct. 2022;1253.

119] Biernacki K, Daśko M, Ciupak O, Kubiński K, Rachon J, Demkowicz S. Novel 1,2,4-oxadiazole derivatives in drug discovery. Pharmaceuticals. 2020; 13(6), 111

120] Rai NP, Narayanaswamy VK, Govender T, Manuprasad BK, Shashikanth S, Arunachalam PN. Design, synthesis, characterization, and antibacterial activity of {5-chloro-2-[(3-substitutedphenyl-1,2,4-oxadiazol-5-yl)-methoxy]-phenyl} -(phenyl)-methanones. Eur J Med Chem. 2010;45(6).

121] Janardhanan J, Meisel JE, Ding D, Schroeder VA, Wolter WR, Mobashery S, et al. In vitro and in vivo synergy of the oxadiazole class of antibacterials with β-lactams. Antimicrob Agents Chemother. 2016;60(9).

122] Pi H, Venter H, Russell CC, Young KA, McCluskey A, Page SW, et al. In Vitro Activity of Robenidine Analogues NCL259 and NCL265 against Gram-Negative Pathogens. Antibiotics. 2022;11(10).

123] ROSA MF da, MORCELLI ACT, LOBO VDS. 1,2,4-oxadiazole: A Brief Review from the Literature About the Synthesis and Pharmacological Applications. Visão Acadêmica. 2015;16(2).

124] Alsimaree AA, Sharaf M, Moustafa AH, Abd-El-Aziz A, Mohamed MAA, Malik MS, et al. Design, synthesis and preliminary antibacterial evaluation of novel 1,3-benzoxazole/carboximidamide- and 1,3-benzoxazole/3-aryl-1,2,4-oxadiazole hybrids. J Mol Struct. 2024 Aug 15;1310.