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Synthesis and Antimicrobial Applications of 1,3-Benzoxazine Derivatives: A Review

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Heterocyclic compounds, including 1,3-benzoxazine, have significant biological activity and multimodal therapeutic effects. 1,3-benzoxazine and its derivatives are a priority in medicine due to their bioactive compounds, but synthesis methods remain exploratory due to its efficacy. The synthesis of derivatives of 1,3-benzoxazine is still an important method in the pharmaceutical discovery because of its antimicrobial properties. The antimicrobial and its related properties have been well examined for their distinct structure. This study aims to review novel 1,3-benzoxazine and its derivatives for potent antimicrobial properties for pharmaceutical applications. 1,3-benzoxazine derivatives function against microorganisms, including bacteria and fungi. This review found that derivatives such as 1,3-oxazines have antifungal and antibacterial effects against several Gram-positive and Gram-negative bacteria, such as *Bacillus thuringiensis*, *Escherichia coli*, and *Fusarium oxysporum*. 3,4-dihydro-benzo[e] [1,3] oxazin-2-one derivatives showed significant antibacterial and antifungal activities. Thionated-1,3-benzoxzine showed antifungal activities against eight fungal strains, comparable to fluconazole fungicide. Therefore, exploring the 1,3-benzoxazine chemotype model for cannabinoid receptor 2 can offer deeper insights into new pharmaceutical properties and broad-spectrum applications in medicine. 1,3-benzoxazine chemotype and cannabinoid receptor 2 intersection can target pathogens and modulate immune responses, potentially improving immune system combating infections by regulating cytokine production and immune cell activity.

Keywords: 1,3-Benzoxazine; antimicrobial properties; derivatives; synthesis

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Heterocyclic compounds have a broad spectrum of biological activities, which has drawn great attention to scientific research in organic chemistry. Heterocycles make up most compounds of medicinal significance. They are used extensively in medicine and comprise the bulk of currently marketed medications. For example, the fused-bicyclic heterocyclic ring is one of the most important building blocks in medicinal chemistry. It can be found in many natural and synthetic drugs and is important for their pharmacological properties [1].

One class of fused-bicyclic heterocyclic compounds that has a lot of promise as an anti-microbial agent is 1,3-benzoxazine and its derivatives. The structural uniqueness of 1,3-benzoxazine has made it potent for pharmacological applications. It has been observed that benzoxazine derivatives, particularly those with the 1,3-position, have antitumor, antioxidant, anti-inflammatory, antimalarial, anti-plasmodial, antiplatelet, and anticonvulsant properties [2, 3, 4, 5, 6, 7, 8]. For example, methoxy 1,3-benzoxazine has been found in numerous pharmaceutically active molecules [9] such as analgesics, central nervous system medications, and calcium channel antagonists [10]. Additionally, 1,3-benzoxazine with the isoxazole group showed remarkable antifungal and antibacterial actions [11]. Due to these important properties, 1,3-benzoxazine and its derivatives have become the continuous focus and usage in medicine and a priority of the pharmacological industry. However, the methods of synthesis of 1,3-benzoxazine and its derivatives are still prone to exploration due to their structure and bioactive compounds, even with the progress made in the past decades. For instance, condensation of matching phenolic compounds, primary amine, and formaldehyde using either solventless or solution techniques is the usual synthetic procedure for producing 1,3-benzoxazine. However, there is a dearth of information on the efficacy of this method and its applicability for 1,3-benzoxazine synthesis for structural explorations for potential antimicrobial potent properties. There is no information on 1,3-benzoxazine antimicrobial properties for pharmaceutical applications. Thus, the aim of this study is to review the synthesis of novel 1,3-benzoxazine and its derivatives for potent antimicrobial and related properties for pharmaceutical applications.

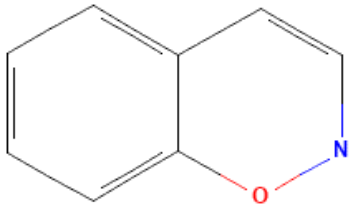
Description of 1,3-Benzoxazine Structure

1,3-Benzoxazine is a molecule having an oxazine ring, a six-membered heterocyclic ring with nitrogen and

oxygen atoms, fused with a benzene ring, as shown in Figure 1. 1,3-benzoxazine is numbered in accordance with the International Union of Pure and Applied Chemistry (IUPAC) of heterocyclic compounds, wherein the nitrogen atom comes after the oxygen atom as the prefix [12].

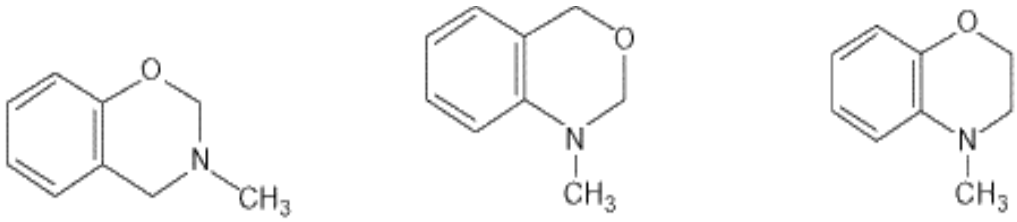
A benzene ring and an oxazine ring, a heterocyclic six-membered ring with a nitrogen atom and an oxygen atom, are joined to create benzoxazine [2]. Benzoxazine structures vary based on where the heteroatoms are located (Figure 2). For instance, the structure is traditionally designated as a 1,3-benzoxazine (3,4-dihydro-3-methyl-2H-1,3-benzoxazine) (structure a) (Figure 2a), while structure b is designated as a 3,1-benzoxazine (Figure 2b). The nitrogen position is numbered after the oxygen position. Structure c is therefore a 1,4-benzoxazine [6,9] (Figure 2c). This is due to the fact that benzoxazine, like in structure d, is initially a compound with a double bond. The conversion of 1,3 into 3,1, from structure a into b, is avoided in the IUPAC nomenclature, instead it is by counting in alphabetical order of the atoms in the oxazine ring.

The oxazine ring at the C3 position increases inhibitory activities and possibly some flexibility, according to this Structure-Activity Relationship (SAR) [6,9]. To boost the activity, π-stacking interactions appear to be important, which is why we used the Suzuki-Miyaura cross-coupling reaction to create a new series of molecules with aromatic groups. Anticipated molecules exhibited planarity and the ability to intercalate among various co-factors within the enzyme's pocket. This SAR study showed that the inhibitions observed by small electron-donating and electron-withdrawing groups were only minimal to maximum. According to substitution at the benzene ring, the analysis showed that all compounds displayed good to excellent antibacterial activity. 1,3-benzoxazine displayed the highest level of antibacterial potency against *Escherichia coli*, indicating that electron-withdrawing groups increase antibacterial potency while electron-donating groups increase antifungal potency [9]. The compound exhibiting heterocyclic six-membered ring substitution with a nitrogen atom and an oxygen atom at the C3 at 200 µM was found to exhibit the highest level of inhibition [10]. Planar structure and π-stacking interactions appeared to be the most advantageous properties for the development of possible ThyX inhibitors against microbial activities [9].



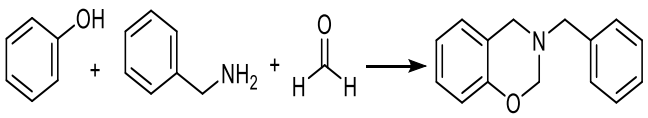
2D

Figure 1. Structure of 1,3-benzoxazine.



(a) 1,3-benzoxazine (b) 3,1-benzoxazine (c) 1,4-benzoxazine

Figure 2. Types of benzoxazine.



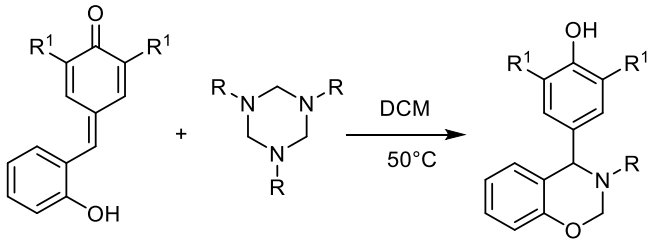
Scheme 1. One pot Mannich-type condensation of phenol, amines, and formaldehyde [13].

Methods of Synthesis

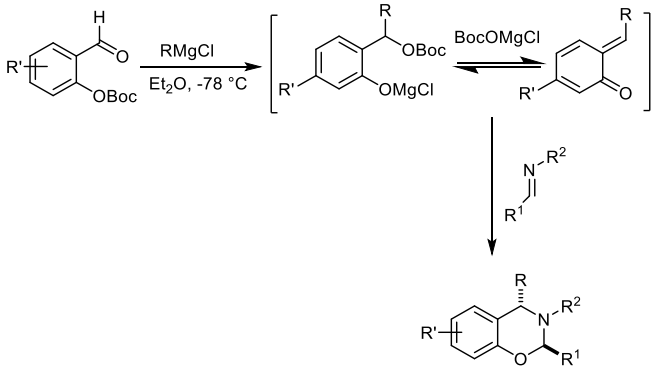
Numerous scientific procedures to produce 1,3-benzoxazine molecules have been documented. Trybuła used a Mannich base to produce 1,3-benzoxazine in 2020. As seen in Scheme 1, this procedure entails the condensation of three major components: formaldehyde, phenol, and primary amines [13, 14].

Moreover, hetero-aromatic cycloaddition of para-quinone methides can be used to create benzoxazine molecules (p-QMs). By using this method, important synthetic chemicals like 1,3-benzoxazine and other *O*,*N*-heterocyclic compounds can be synthesized. Under mild circumstances, the cycloaddition reaction of para-quinone methides (p-QMs) with hexahydro-1,3,5-triazine is conducted to synthesize substituted 1,3-benzoxazine in high yields; no ligands, base, or even catalyst is required, as shown in Scheme 2. Nevertheless, additional functionalization of 1,3,5-triazine can also provide a range of derivatives of 1,3-benzoxazine [15]. Moreover, 1,3-benzoxazine could be easily obtained by benzannulation of imitates with orthohydroxyphenyl-substituted p-QMs using a $FeCl_3$ catalyst [16].

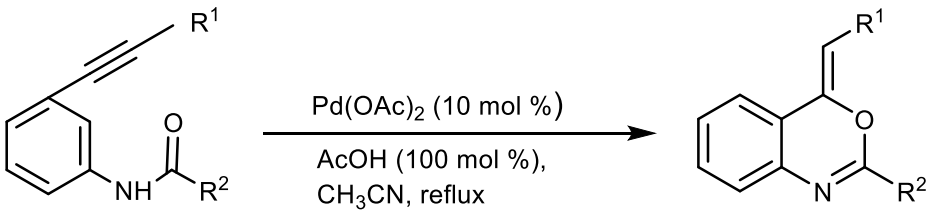
Moreover, a three-component one-pot synthesis using an imine, Grignard reagent, and o-OBoc salicylaldehyde can be used to synthesize 1,3-benzoxazine. In order to create o-Quinone Methides, an intermediate product, which is subsequently permitted to react with imine by nucleophilic addition, as indicated in Scheme 3, the reaction is carried out by directly adding a Grignard reagent to an o-OBoc salicylaldehyde in the presence of an imine [17].



Scheme 2. Synthesis of 1,3-benzoxazine via [4+2]-cycloaddition reaction [15].



Scheme 3. Synthesis of 1,3-benzoxazine via three components of o-OBoc salicylaldehyde, Grignard reagent and an imine [17].



Scheme 4. Synthesis of 1,3-benzoxazine via palladium-catalyzed cyclization [18].

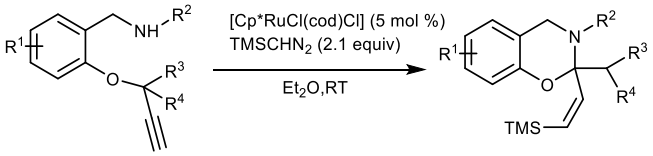
A synthesis of 1,3-benzoxazine has been achieved through the work of [66]. This approach was used to directly cyclize *N*-Acyl-o-alkynylanilines with various substituents in R [1] and R^2 using a palladium catalyst. This is thought to be a regioselective synthesis of 1,3-benzoxazine with good yields. On the other hand, using 100% acetic acid can hasten the reaction and provide the highest yield (Scheme 4) [18].

One alternative method to synthesize 1,3-benzoxazine derivatives is to directly cyclize ortho-(alkynyloxy)benzylamines using catalytic ruthenium carbenes in the presence of $TMSCHN_2$, which requires the rearrangement of an internal carbon in the starting material (see Scheme 5) [19]. Based primarily on the nucleophilic addition of amines to electrophilic metal carbenes employing catalytic metals like ruthenium, copper, and rhodium, researchers have improved this technology in some investigations to become a fresh way toward heterocycles [20].

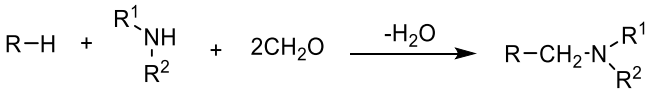
The multi-component Mannich type condensation reaction of formaldehyde, primary amines, and phenol in a single pot is a crucial synthesis technique for the production of derivatives of 1,3-benzoxazine. This can be attributed to the Mannich-type reaction's simplicity and adaptability for one-pot *β*-amino-carbonyl chemical synthesis. Because the Mannich type reaction is used in the synthesis of drugs and has several advantages over other methods, including ease of operation, low step count, low catalysis requirements, high chemical yields, readily available material, and environmental safety, it is regarded as a general and significant organic synthesis method. Furthermore, a wide range of 1,3-benzoxazine derivatives are accessible due to the substrate diversity on phenol and primary amines. The most attention has been drawn to solventless Mannish-type condensation in organic synthesis because it is an effective way to reduce reaction time while producing excellent products, without using or creating hazardous solvents, and it also saves capital on solvent recovery [21].

Synthesis of 1,3-Benzoxazine and its Derivatives

One of the most significant reactions in organic chemistry is generally acknowledged to be the Mannich-type reaction. The basic Mannich reaction consists of three main components: an aldehyde component (R-CHO) and primary or secondary amines; various substrates (R-H) containing at least one active hydrogen atom, such as phenols, esters, ketones, and carboxylic acids; and finally, a variety of compounds known as Mannich bases (Scheme 6). The world of medicinal chemistry has benefited greatly by the varied structure of Mannich bases [22]. Mannich derivatives are particularly valuable in the production of pharmaceutical goods such as antimalarial, antibacterial, and anti-inflammatory compounds. They can also increase the bioactivity of the therapeutic molecules [23, 24]. The final result of the Mannich reaction is the Mannich base, and its application in the synthesis of clinical pharmaceuticals, such as the antidepressant fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, procyclidine, ranitidine, and biperiden, is rapidly changing [25].

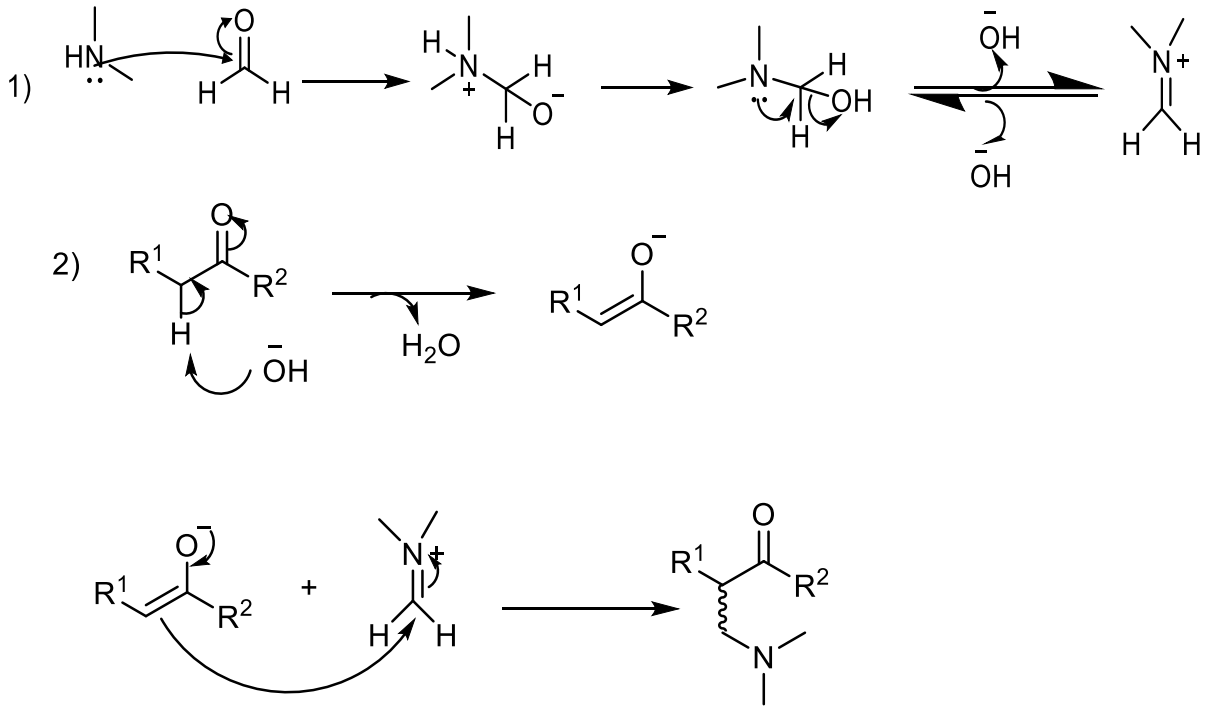


Scheme 5. Synthesis of 1,3-benzoxazine via ruthenium-catalyzed cyclization of *N*-substituted-ortho-(alkynyloxy)benzylamines [19].



R[1]= alky
R[2]= alkyl or H
R= aryl or H

Scheme 6. General representation of Mannich-type reaction.



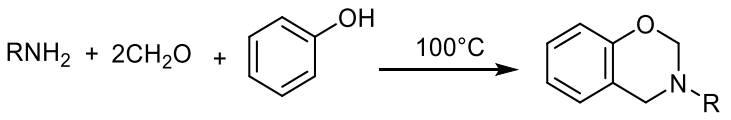
Scheme 7. Mechanism of Mannich-type chemical reaction [26].

The substitution of an aminomethyl or a modified aminomethyl group for the reactive hydrogen atom is the primary process involved in Mannich condensation. Compounds with acidic proton hydrogen atoms, such as aldehydes, ketones, phenols, esters, acids, and acetylenes, are designated by the R-H group.

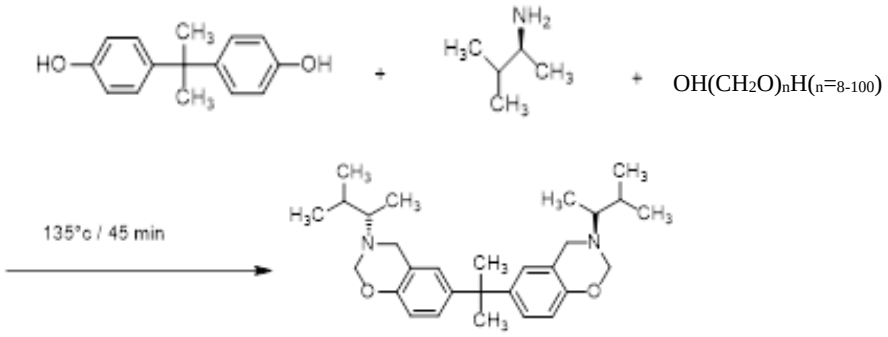
The Mannich reaction mechanism has been the subject of numerous studies. The mechanism is essentially composed of two primary phases. The first step is the condensation of the formaldehyde and amine groups, which produces an iminium ion. As an example, a ketone undergoes tautomerization in the second step to become an enol form, which can then attack an iminium ion to produce the β-amino-carbonyl molecule known as Mannich base, which is shown in Scheme 7 [26].

The first benzoxazine was produced without the use of a solvent based on Ishida approach [27]. A range of primary amines and substituted phenol and paraformaldehyde were used in the chemical process. In the solventless technique, paraformaldehyde is employed in place of a 37% formaldehyde solution in water to raise the reaction temperature to almost 100 degrees Celsius, allowing for the easy melting of all the reactants [28]. On the other hand, the formaldehyde aqueous solution is ideal for a solvent method in which the formaldehyde water solution combines with a solvent that is compatible with water [27]. But in a solvent system, the solvent makes up around 10% of the weight of the reactants, which explains why the chemical reaction takes so long to complete. Because the reactants in the solventless system make up all of the mixture in the reaction medium, the reaction rate is accelerated and can happen in minutes as opposed to hours [27]. Scheme 8 provides a description of the solventless reaction.

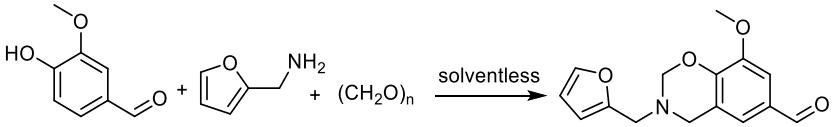
According to Liu and Chou [29], bisphenol-A combined with paraformaldehyde [$OH(CH_2O)_nH(_{n=8-100})$] and primary amines such as S-(+)-3-methyl-2-butylamine and rac-(±)-3-methyl-2-butylamine can be used to synthesize difunctional chiral and achiral benzoxazine monomers with double chiral centers in just one step without the use of solvents, as illustrated in Scheme 9. Chiral and achiral benzoxazine were subjected to a study on their curing kinetics, and the results showed that their curing behavior and thermal characteristics differed [29].



Scheme 8. Synthesis of 1,3-benzoxazine [27].



Scheme 9. Synthesis of 1,3-benzoxazine derivative [29].



Scheme 10. Synthesis of furan containing 1,3-benzoxazine [32].

Numerous researchers have been interested in 1,3-benzoxazine with furan groups because of the furan moiety's impact on the chemical reaction involved in polymerization. The thermal characteristics of polybenzoxazine can be enhanced by increasing the cross-linking density through the electrophilic aromatic substitution of the furan moiety [30, 31]. [32] produced bio-based benzoxazine by a green solventless process using vanillin, paraformaldehyde, and furfuryl amine. The furan moieties from the amine were then linked to the nitrogen atom of the oxazine ring, as seen in Scheme 10.

Moreover, Ishida and Rodriguez [27] used a solventless method to synthesize a range of mono-, di-, and tri-functional 1,3-benzoxazine compounds (Figure 3). The primary amines, paraformaldehyde, and bisphenol-A have all been used to create the precursors. Regarding the benzoxazine monomeric compounds displayed in Figure 3, the di-functional benzoxazine serves as a proficient illustration of the solventless procedure, which can be utilized to manufacture any of the compounds. Since the solventless technique uses a heterogeneous system, the reactants may consist of liquid-gas, solid-liquid, or solid-solid [28]. Reactants can be either all solid, melting at a moderate temperature to form a homogeneous solution quickly and synthesizing 1.3-benzoxazine, or one reactant, generally an amine, can be a liquid. As a result, the solid components dissolve in the liquid component; the addition of a tiny quantity of solvents helps to facilitate reactant control.

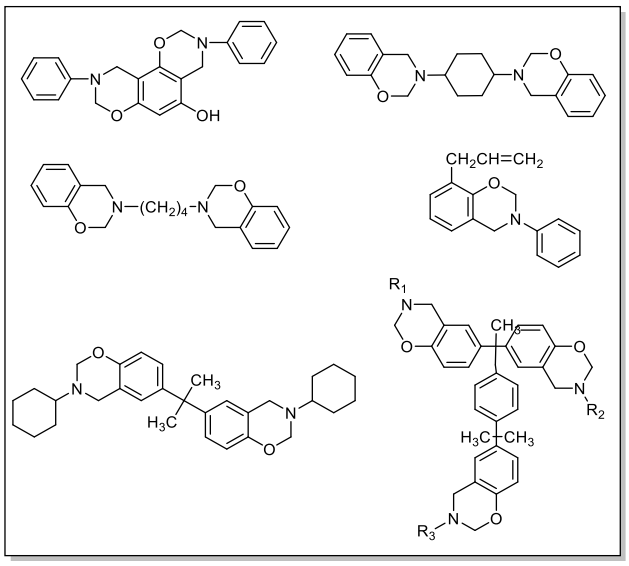
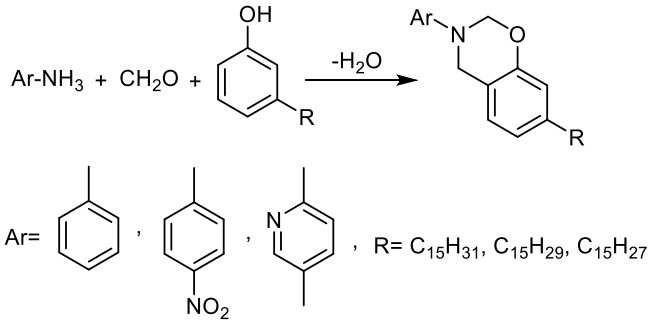
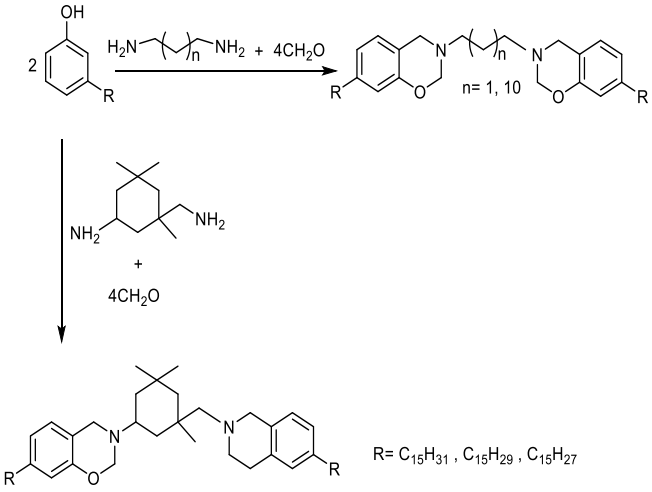


Figure 3. Mono-functional, di-functional, and tri-functional 1,3- benzoxazines.



Scheme 11. Synthesis of mono-1,3-benzoxazine from cardanol and its derivatives [32].



Scheme 12. Synthesis of bis-1,3-benzoxazine from cardanol and its derivatives [32].

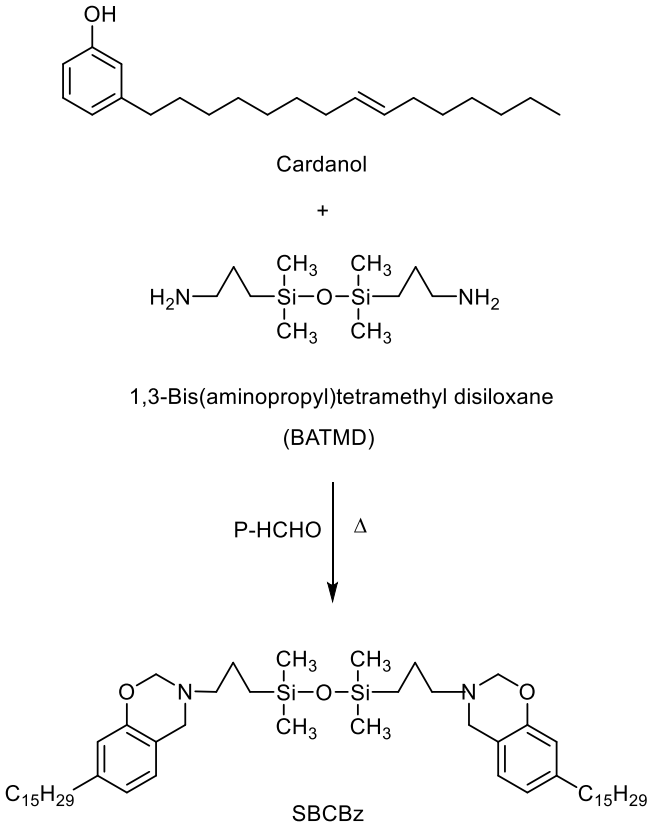
In a different work, solventless methods were used to produce new mono-1,3-benzoxazine and bis-1,3-benzoxazine from cardanol and its derivatives. As shown in Schemes 11 and 12, the syntheses were carried out by cyclizing cardanol and its derivatives with formaldehyde and aromatic primary amins, without producing any detectible byproducts [33].

A green solvent-free method (Scheme 13) was reported by Selvaraj et al. [34], utilizing amine-modified siloxane, 1,3-bis(aminopropyl) tetramethyldisiloxane, cardanol, and p-formaldehyde to synthesize siloxane-containing cardanol-1,3-benzoxazine. The inorganic siloxane linkage joins two monomers of organic benzoxazine. Benzoxazine monomer with siloxane (Si-O-Si) linkage has demonstrated excellent thermal performance [35].

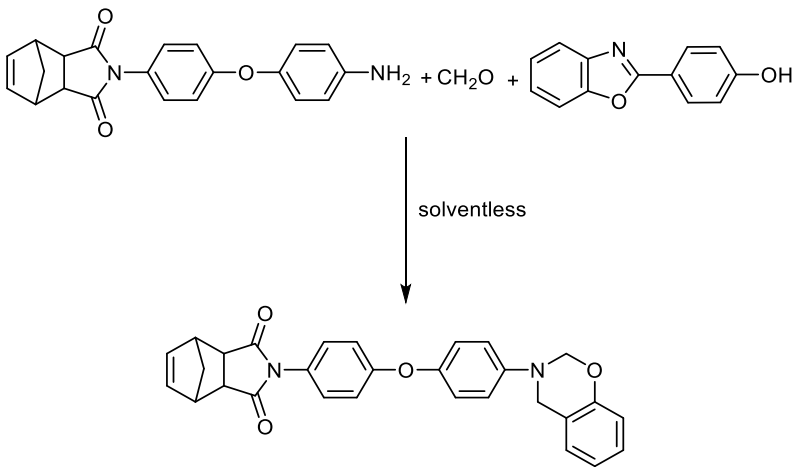
Green techniques were used to prepare a novel cardanol-based benzoxazine having nadimide functionality in its backbone structure, as shown in Scheme 14. The nitrobenzene (N-Bz) was achieved by condensation of three reactants: cardanol, paraformaldehyde, and nadimide-based amine [32]. To produce the benzoxazine resin, the elements were dissolved in cardanol, which can be used as a solvent. Because nadimide has better thermal characteristics and less viscosity than regular benzoxazine monomer, it has drawn interest when combined with the benzoxazine structure [36].

Synthetic Process and Reactions

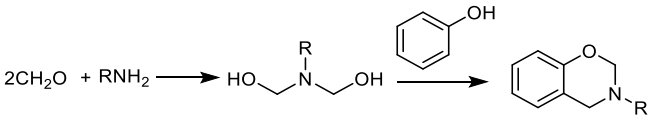
Benzoxazine can be prepared in a variety of synthetic ways. Formaldehyde and *o*-hydroxybenzylamine were condensed to synthesize 1,3-benzoxazine structure [14]. The Mannich condensation of phenol and formaldehyde with a range of primary amines in the molar ratio 1:2:1 in dioxane was then further studied by Trybuła [13; Scheme 15]. In order to carry out Mannich condensation, formaldehyde must first undergo condensation with primary amines to produce N,N-dihydroxymethylamine. This amine can then combine with phenol to produce benzoxazine molecule [37]. Numerous 1,3-benzoxazine derivatives can be produced using a variety of substituted phenol and primary amines [38].



Scheme 13. Synthesis of siloxane-containing cardanol-1,3-benzoxazine [34].



Scheme 14. Synthesis of nadimide-containing 1,3-benzoxazine [32].



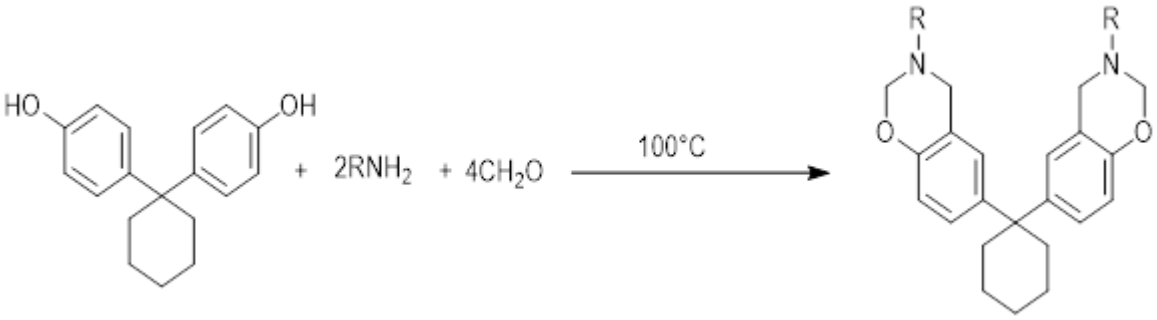
Scheme 15. Synthesis of 1,3-benzoxazine [13].

Formaldehyde, monophenol, and monoamines have been used to synthesize monofunctional benzoxazines [39, 40], whereas bisphenol, monoamines, and formaldehyde have been used to synthesize difunctional benzoxazines [50, 51, 52]. Benzoxazine was originally synthesized as a difunctional [53, 54] because difunctional benzoxazines are more malleable in their molecular structure than

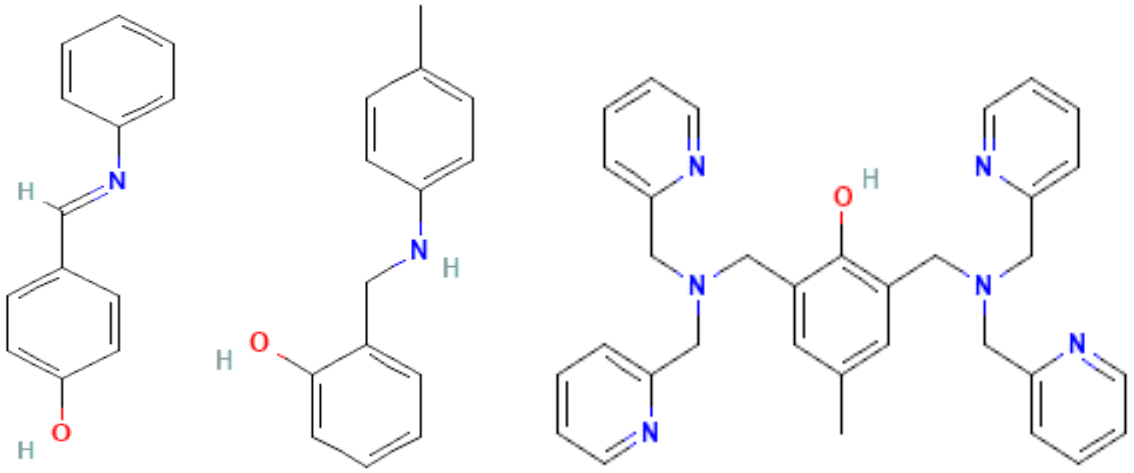
monofunctional monomers, a greater range of performance in polybenzoxazines can be achieved [55]. Research usually aims to produce benzoxazine monomers with functional groups to enhance the performance of benzoxazine-based products. Ohashi's approach, on the other hand, was thought to be the most thorough way for synthesizing 3,4-dihydro-1,3-benzoxazine [56, 57]. Subsequently, other adjustments were made to this basic technique. For instance, a solventless approach was explored to synthesize 1,3-benzoxazine molecules [57]. The 1,3-benzoxazine compounds can be synthesized in just one step with a solventless approach, which also offers reduced health hazards due to the lack of harmful solvents, less byproducts, a quick reaction time, and good yield [58; Scheme 16].

Primary amine and formaldehyde react to form the extremely reactive intermediate N,N-dihydroxymethylamine [10,14,16,26,30,31]. This intermediate then combines with other reactants or intermediates to form tertiary amine compounds. The end products contain the three secondary amine compounds **2, 4**, and **6** (Figure 4). The benzoxazine monomer hydrolysis reaction can account for the generation of compound **4**. The intermediate in the synthesis of benzoxazine is N-hydroxymethyl aniline (HMA). HMA is more credible intermediate. It can be further converted to compounds **2, 4**, and **6** (Figure 4). Moreover, HMA might be a key step in the production of benzoxazine.

The most likely pathway of the reaction could be as follows: formaldehyde combines with primary amine to form HMA, which subsequently reacts with additional reactants and intermediates to produce the final products. The creation of an active intermediate HMA, which results from the reaction between formaldehyde and primary amine, is the primary reaction in the synthesis of benzoxazine [30,31].



Scheme 16. Synthesis of 1,3-benzoxazine derivative. Molecular Formula = C_8H_7NO; Molecular Weight = 133.15 g/mol; XLogP3-AA = 1.1; Monoisotopic Mass = 133.052763847 g/mol.



(2) **(4)** **(6)**

Figure 4. N,N-dihydroxymethylamine as intermediate product of 1,3-benzoxazine synthesis. (**2**) 4-((Phenylamino) methyl)phenol; Molecular Formula = $C_{13}H_{11}NO$; Molecular Weight = 197.23 g/mol; XLogP3 = 2.5; Monoisotopic Mass = 197.084063974 g/mol. (**4**) 2-((Phenylamino)methyl)phenol; Molecular Formula = $C_{14}H_{15}NO$; Molecular Weight = 213.27 g/mol; XLogP3-AA = 3.4; Monoisotopic Mass = 213.115364102 g/mol. (**6**) 2,6-Bis((phenylamino) methyl) phenol; Molecular Formula = $C_{33}H_{34}N_6O$; Molecular Weight = 530.7 g/mol; XLogP3-AA = 3.4; Monoisotopic Mass = 530.27940973 g/mol [10,14,16,46].

Biological Significance of 1,3-Benzoxazine Derivatives

Heterocyclic compounds are abundant in nature with tremendous significance to life due to their widespread presence in several natural products like vitamins, hormones, and antibiotics [59]. The wide range of biological activities of 1,3-*O*,*N*-heyterocyles give them a special role in medical chemistry. Numerous derivatives of 1,3-benzoxazine derivatives have been produced and tested for their biological activity. Hence, studies have reported on a wide range of biologically active 1,3-benzoxazine derivative replacements. Analgesic, antitubercular, anticonvulsant, antibacterial, and anti-HIV properties have been reported for 1,3-oxazine [60, 61, 62, 63]. The benzoxazine moieties found in 1,3-oxazine derivatives are known to exhibit biological activity, as evidenced by their anticancer [64, 65], antimicrobial [64, 66], antifungal [64, 67], antiphlogistic drug [68, 69], antihypertensive effects [7, 70], and anti-osteoclastic bone resorption activity [71].

Ferrocenyl 1,3-benzoxazine (**1)** (Figure 6) was recently synthesized by the researchers, and it shows potency against the HCC70 breast cancer cell line [72]. Additionally, benzoxazine having aminoquinoline moiety (**2)** was shown to have antimalarial and anti-plasmodium properties [73]. Additionally, spirocycle-1,3-benzoxazine with *N*-hydroxyacrylamides moiety (**3**) has strong anticancer activity against HCT-116 human tumor xenografts [74]. 3-Benzyl-1,3-benzoxazine-2,4-dione (**4)** has been observed to function as an inhibitor of allosteric mitogen-activated kinase (MEK) [75]. Furthermore, there is hope that 2-morpholino-1,3-benzoxazine (**5)** will have encouraging antiplatelet aggregation activity [76]. Conversely, the oxo-derivative of 1,3-benzoxazine (**6)** functions as an anticonvulsant and can lessen the convulsive action of bicuculline; this compound may be a novel GABA mimic [77]. 1,3-benzoxazine has also been reported to exhibit antidepressant, antidiabetic, and hypolipidemic effects [78, 79, 80]. Additionally, to treat obesity, 1,3-benzoxazine and its derivatives function as pancreatic lipase inhibitors [81, 82]. Because of the biological features of synthetic *O,N*-heterocyclic 1,3-benzoxazine chemicals, there is a growing interest in developing their derivatives for use in pharmaceutical applications. Figure 5 displays a few of the 1,3-benzoxazine ring system structures along with an explanation of their biological importance.

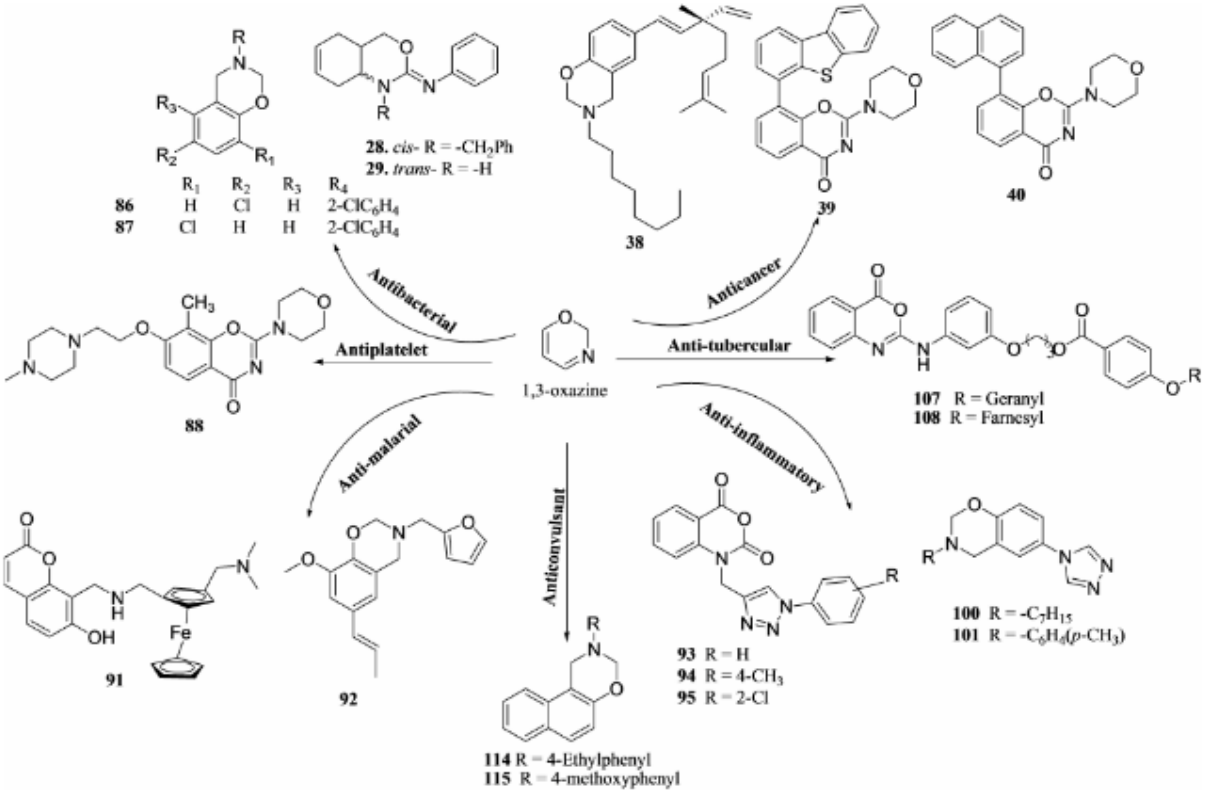


Figure 5. Biological properties of 1,3-oxazine derivatives [64].

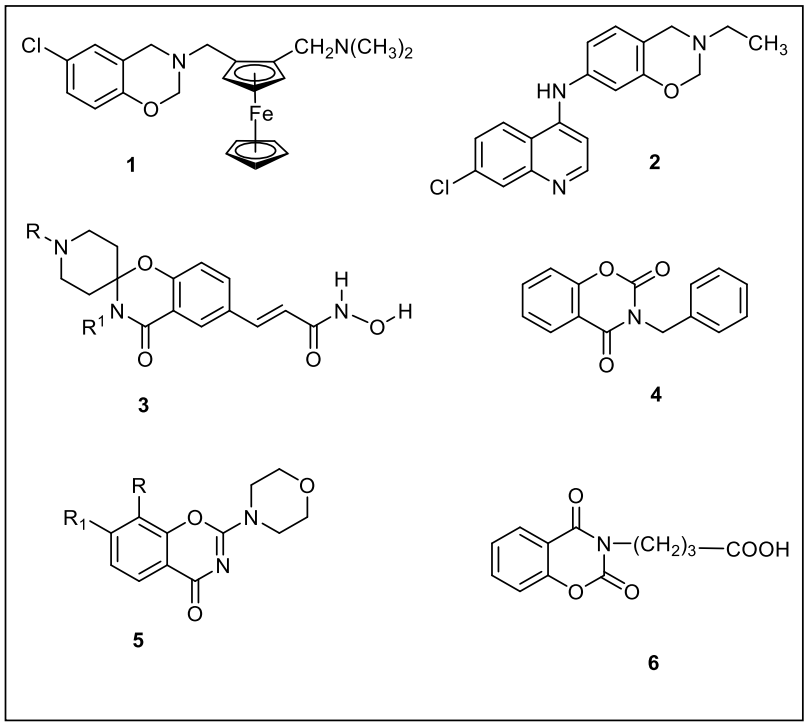
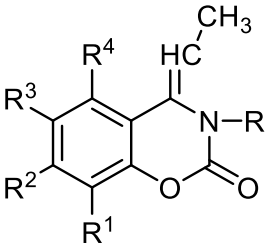


Figure 6. 1,3-benzoxazine ring system structures. (1) Antimalarial [82], (2) anti-plasmodial [43], (3) antitumor activity [44], (4) MEK inhibitor [45], (5) antiplatelet aggregation activity [46], and (6) anticonvulsant agent [47], as potential agent against HCC70 breast cancer cell line.

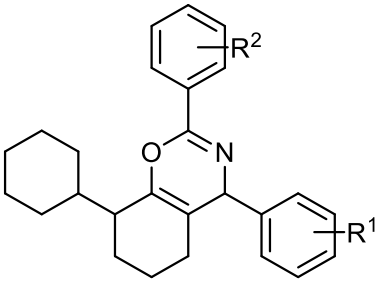
An antimicrobial substance is characterized as one that works against microorganisms by either eliminating or preventing the growth of microorganisms, such as fungi and bacteria. For example, chemicals that function against all kinds of microbes are referred to as antimicrobial substances. Conversely, the terms "antibacterial" and "antifungal" designate substances that have antibacterial and antifungal properties, respectively. Due to their intriguing microbiological characteristics, numerous substituted 1,3-oxazines have been reported in the literature. In the biological study, several series of 3,4-dihydro-benzo[e][1,3]oxazin-2-one derivatives **7a-m** (Figure 7) were synthesized and tested for antifungal and antibacterial properties against *Aspergillus niger*, *P. chrysogenum*, *F. moniliforme*, and *Aspergillus flavus*, as well as against *Escherichia coli*, *P. aeruginosa*, and *S. aureus*. Compounds **7c**, **7f**, **7h**, and **7m** showed strong antifungal activities [53].



7a-m

7	R^1	R^2	R^3	R^4	R	7	R^1	R^2	R^3	R^4	R
7a	H	H	H	H	C_6H_5	**7h**	I	H	Cl	H	*n*-C_3H_7
7b	H	H	Cl	H	C_6H_5	**7i**	I	H	Cl	H	*n*-C_4H_9
7c	H	H	Cl	H	*n*-C_4H_9	**7j**	I	H	Cl	H	*iso*-C_3H_7
7d	H	H	CH_3	H	*n*-C_4H_9	**7k**	I	H	Cl	H	C_6H_5
7e	H	CH_3	H	H	C_6H_4-CH_3	**7i**	I	H	CH_3	H	CH_2-C_6H_5
7f	I	H	CH_3	H	*n*-C_3H_7	**7m**	I	H	CH_3	H	*iso*-C_3H_7
7g	I	H	CH_3	H	*n*-C_4H_9						

Figure 7. 3,4-dihydro-benzo[e][1,3]oxazin-2-one derivatives **7a-m** [53].



8a-c

8	R^1	R^2
8a	*p*-	H
8b	Cl	H
8c	*P*-F	*p*-
	H	CH_3

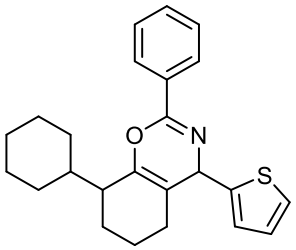


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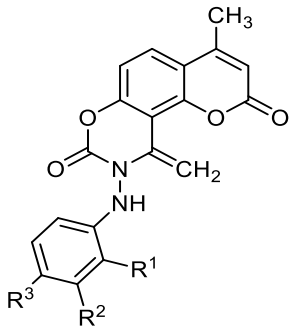
Figure 8. Tetrahydro-benzo[1,3]oxazines 8a-c and 4-(thiophen-2-yl)tetrahydrobenzo[1,3]oxazine 9 [54].

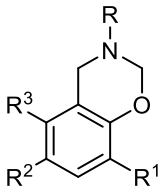


10a-g

10	R^1	R^2	R^3
10a	H	H	H
10b	OCH_3	H	H
10c	CH_3	H	H
10d	H	H	Cl
10e	NO_2	H	NO_2
10f	CH_3	H	CH_3
10g	H	CH_3	H

Figure 9. Coumarin-based 1,3-benzoxazine derivatives **10a-g** [40].

The antibacterial and antifungal properties of tetrahydro-benzo[1,3]oxazines **8a-c** and 4-(thiophen-2-yl)tetrahydrobenzo[1,3]oxazine **9** (Figure 8) were examined in a study against the bacterial species *Bacillus thuringiensis*, *Escherichia coli*, and the *Fusarium oxysporum* and the fungal species *Botrytis fabae*. Compounds **8a-c** showed strong activities against *B. thuringiensis*, while compounds **9** was found to showed relative activity against *Escherichia coli*. Additionally, the results of the antifungal activity showed that compound **8c** had a significant effect against *B. fabae* and *F. oxysporum* [54].



11a-n

11	R^1	R^2	R^3	R
11a	H	H	H	C_4H_9
11b	H	H	H	C_6H_{11}
11c	H	H	H	C_6H_5
11d	CH_3	H	H	C_6H_5
11e	H	CH_3	H	C_6H_5
11f	H	CH_3	H	4-$CH_3C_6H_4$
11g	H	CH_3	H	2-ClC_6H_4
11h	H	CH_3	H	4-ClC_6H_4
11i	H	CH_3	H	4-FC_6H_4
11j	H	Cl	H	C_4H_9
11k	H	Cl	H	C_6H_5
11l	H	Cl	H	4-$CH_3C_6H_4$
11m	H	Cl	H	2-ClC_6H_4
11n	Cl	H	Cl	2-ClC_6H_4

Figure 10. 3,4-dihydro-2H-benzo[e][1,3]oxazines **11a-n** [5].

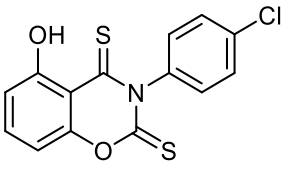
Another study evaluated in vitro antibacterial and antifungal activities of seven compounds of coumarin-based 1,3-benzoxazine derivatives **10a-g** (Figure 9), using ciprofloxacin and amphotericin B as standard antibacterial and antifungal agents, respectively [40]. The compounds were tested on many bacteria and fungi and showed that compounds with methoxy substituents have excellent efficacy against Gram-positive and Gram-negative micro-organisms. Compounds with dimethyl and chloro substituents inhibited the growth of *Aspergillus flavus, Cryptococcus neoformans, Aspergillus niger, Staphylococcus aureus, Staphylococcus pyogenes, Escherichia coli*, and *Pseudomonas aeruginosa*.

Additionally, the biological profiles of 3,4-dihydro-2H-benzo[e][1,3]oxazines **11a-n** (Figure 10) were examined in contrast to six different pathogenic fungi and two Gram-positive and two Gram-negative bacteria, and ampicillin as the reference antibacterial and antifungal agent. It was found that every chemical examined showed excellent potency against every tested microorganism. Compound **11m** had the highest level of inhibition against the six pathogenic fungi at concentrations ranging from 12.5 to 25 µg/ml. Meanwhile, compounds **11d–f** and **11k–l** demonstrated greater efficacy against Gram-negative *Escherichia coli* when compared to ampicillin, the reference medication [5].

Kategaonkar et al. [55] used eight different fungal strains to describe the antifungal activity of thionated 1,3-benzoxzine (compound **12**) (Figure 11). The substance exhibited actions comparable to the fungicide fluconazole against *Aspergillus fumigatus* and *Absidia corymbifera*. Furthermore, many substitutions have been used to synthesis several 1,3-benzoxazine derivatives in an effort to investigate their potential pharmaceutical properties [38]. For example, 1,3-benzoxazin-4-ones **13a-b** (Figure 11) with a 2-alkenyl/hydroxyl alkenyl chain substitution were prepared and their efficacy against *Aspergillus fumigatus* and *Absidia corymbifera* was assessed. It was also discovered that compounds **13a** and **13b** are excellent against Gram-negative and Gram-positive bacteria. These substances exhibited strong antifungal properties as well [38].

6-Acetyl-2H-Benzo[e][1,3] was assessed by Ning and Ishida [48]. In vitro tests were conducted to evaluate the antibacterial activity of oxizine-2, 4(3H)-Dione **14a-g** (Figure 12) against *Aspergillus niger, Candida albicans, Aspergillus clavatus*, and *Streptococcus pyogenes*. The results showed that these compounds have a good inhibitory effect on Gram-positive bacteria.

Gram-positive and Gram-negative bacteria were used to examine the antibacterial effects of 3, 4-dihydro-2H-1, 3-benzoxazines **15a** and **15b**, as shown in Figure 13. Compound **15a** was found to exhibit very good activity against *Acinetobacter anitratus* and good activity against *Bacillus subtilis* and *Staphylococcus epidermidis*. Additionally, it was discovered that the compound showed great potential as an antibacterial agent against *Escherichia coli*. Whereas, compound **15b** showed a modest level of action against *Escherichia coli, Staphylococcus epidermidis*, and *Bacillus subtilis* [56].



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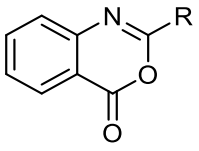
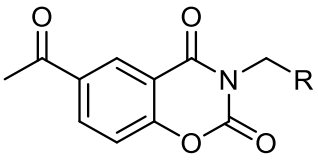


13a-b

13	R
13a	CH_3-$(CH_2)_5$-CH(OH)-CH_2-CH=CH-$(CH_2)_7$
13b	CH_3-$(CH2)_4$-CH=CH-CH_2-CH_2-CH(OH)-$(CH2)_7$

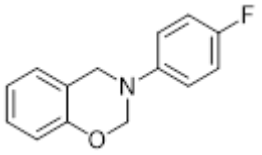
Figure 11. Thionated 1,3-benzoxzine (compound **12**) [55] and 2-alkenyl/hydroxyl alkenyl chain substituted 1,3-benzoxazin-4-ones **13a-b** [38].



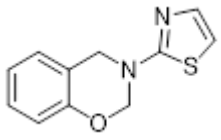
14a-g

14	R
14a	4-NO_2benzyl
14b	4-Cl benzyl
14c	Benzyl
14d	2,6-di-Cl benzyl
14e	2-Me benzyl
14f	3,5-di-Br benzyl
14g	4-CN benzyl

Figure 12. 6-Acetyl-2H-Benzo[e][1, 3] Oxazine-2, 4(3H)-Dione **14a-g** [48].



15a



15b

Figure 13. 3, 4-dihydro-2H-1, 3-benzoxazines **15a** and **15b** [56].

Moreover, 1-((1-(4-(2H-benzo[e][1,3]oxazin3 (4H)-yl) phenyl)ethylidene)amino)-6-((arylidene)amino) has been used to detect the in vitro antimicrobial activity of 1,3-benzoxazine derivatives, -4-(4chlorophenyl) -2-oxo-1,2-dihydropyridine and 3,5-dicarbonitriles **16a–j** (Figure 14). The experiment was conducted on strains of bacteria (*S. aureus, Staphylococcus pyogenes, Escherichia coli* and *P. aerogenosa*) and fungi (*C.albicans, Aspergillus niger* and *A. clavatus*). Based on substitution at the benzene ring, the analysis results showed that all compounds exhibited good to excellent antibacterial activity. Compound **16c** (R=4-NO_2) exhibited the highest level of antibacterial potency against *Escherichia coli*, indicating that electron-withdrawing groups increase antibacterial potency, whereas electron-donating

groups increase antifungal potency. Compounds **16d** and **16e**, containing the methoxy 3,4,5-$(OCH_3)_3$ and *N*,*N*′-$(CH_3)_2$ moieties, respectively, showed remarkable antifungal activity. Additionally, it was revealed that a molecular docking study was conducted against microbial DNA gyrase in order to provide additional information needed to enhance the antibacterial action of those compounds [57, 83].

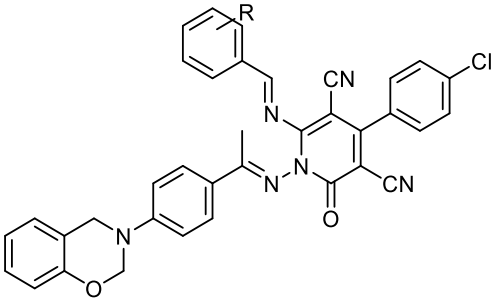
In summary, as 1,3-benzooxazine derivatives have made a substantial contribution to pharmacophore, there is a general agreement regarding their therapeutic qualities.

Pharmaceutical Applications of the Bioactive Compounds

Many 1,3-benzoxazines are used in the pharmaceutical industry and have interesting biological and medicinal properties, given the fact that 1,3-benzoxazine is one of the most important scaffolds in pharmaceutical chemistry. Compounds containing benzoxazine generally show several biological activities, such as antioxidant, anti-inflammatory, antimicrobial, and antituberculosis effects, among others [84, 85] (Table 1). The benzoxazine nucleus can be found in a wide range of naturally occurring products, pharmaceutically active molecules, and derivatives with therapeutic significance. The 1,3-benzoxazine nucleus, a flexible structure with numerous modification positions appropriate for the synthesis of a medium-sized focused library, was the center of the pharmaceutical industry's attention. Some studies developed and synthesized a group of 25 compounds of 1,3-benzoxazine and tested them in competitive binding and functional assays toward human CB1 and CB2, building on the 2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one scaffold as the starting point [10,54]. It has also been utilized as an intermediary in the production of other heterocyclic-scaffold bioactive chemicals.

The organic compounds, which are based on 1,2,3-triazoles and derived from 1,3-benzoxazine, have been found in several pharmaceutical products. These substances have shown a broad range of biological activities, such as antimicrobial, antimalarial, antibacterial, antifungal, and antiviral properties, due to their bio-isosteric effect [9,11,35,36,37,40,43,45,47]. Repurposed 1,3-benzoxazine scaffold with the addition of organometallic ferrocene has been used to develop a new class of chemicals with in vitro biological activities against breast cancer, malaria, and trypanosomiasis [82, 86]. As per reference [87], the addition of ferrocene to 1,3-benzoxazine compounds can result in the creation of multimodal therapeutic candidates to offer protective effects against many microorganisms (Table 1). The resultant ferrocenyl 1,3-benzoxazine compounds exhibited remarkable selectivity and efficacy against both chloroquine-sensitive and resistant strains of the parasite *Plasmodium falciparum* [2].

The benzoxazine structure has been applied pharmaceutically for drug discoveries. Some pharmaceutical researchers have identified several 1,3-benzoxazine and [1,4]-benzoxazinone-based compounds as potential new drugs. Examples include antibacterial agent A, neuroprotective agent B, and protective agent D in tissue culture and in vivo models of neurodegeneration [6]. Hence, it has been possible to successfully synthesize polybenzoxazines with improved structural properties, either by themselves or in combination with other compounds for further pharmaceutic explorations.



16	R
16a	4-OH
16b	3-NO_2
16c	4-NO_2
16d	3,4,5-$(OCH_3)_3$
16e	*N*,*N*′-$(CH_3)_2$
16f	4-F
16j	4-Br

Figure 14. 1,3-benzoxazine derivatives **16a-j** [57,58].

Table 1. Summary of 1,3-benzoxazine derivatives' antimicrobial activities and pharmaceutical properties.

Pharmaceutical properties	1,3-benzoxazine derivatives	Reference
Antimicrobial	Dihydro-2H-benzo-and naphtho-1, 3-oxazine	[5]
	Benzoxazine moieties	[64,66]
	1, 3-disubstituted-1H-naphtho [1, 2-e][1, 3] oxazine	[7]
	1-((1-(4-(2H-benzo[e][1,3]oxazin3(4H)-yl)phenyl)ethylidene)amino)-6-((arylidene)amino)	[57,58]
	Methoxy 1,3-benzoxazine	[8]
	Isoxazolyl-1, 3-benzoxazine	[11]
Antibacterial	Methoxy 1,3-benzoxazine	[9,10]
	Triazolyl benzoxazine	[6]
Antimalarial	Benzoxazine + aminoquinoline moiety	[73]
	Ferrocenyl 1, 3-oxazine	[82]
Anti-plasmodial	Benzoxazine + aminoquinoline moiety	[2,73]
Antitumor/ anticancer	Ferrocenyl 1,3-benzoxazine	[72,81]
	Spirocycle-1,3-benzoxazine with N-hydroxyacrylamides moiety	[74]
	Benzoxazine moieties	[64,65]
Antifungal	Benzoxazine moieties	[64,67]
Antiphlogistic	Benzoxazine moieties	[68,69]
Antiprotozoal	Ferrocenyl 1, 3-benzoxazine	[81]
Antitrypanosomal	Ferrocenyl 1, 3-oxazine	[82]

Future Prospect

The integration of 1,3-benzoxazine into ferrocene compounds is recommended by modern drug discovery prospects as a means of producing multimodal drugs with the inherent ability to provide protective effects against many microorganisms. Compared to commonly used organic drugs, 1,3-benzoxazine chemotypes display a variety of molecular properties, such as cannabinoid receptor 2 [83]. 1,3-benzoxazine derivatives, such as 1,3-oxazine ring, have been reported to modulate the glia and immune-stimulating cells by activating cannabinoid receptor type 2 activities [88]. The inflammatory response is decreased by its activation, which also function in restricting cell migration and the release of pro-inflammatory stimuli. As the cannabinoid receptor's endogenous ligand, anandamide shares many of THC's pharmacological characteristics. Cannabinoid type 2 receptor expression is mostly limited to periods of active inflammation. Research has demonstrated the potential of the cannabinoid type 2 receptor as a therapeutic target in models of diseases like neuropathic pain and neurodegenerative disorders like Alzheimer's disease, for which there are no approved treatments currently [89]. This is the outcome of the synergistic effects of the medicinal advantages provided by a nadimide or a siloxane, which has favorable high lipophilicity, chemical structure, thermal stability, and redox characteristics, along with the bioactivity stimulated by the organic pharmacophore.

The 1,3-benzoxazine scaffold, such as 1,3-benzoxazine chemotype for cannabinoid receptor 2, is attractive as a model for new bioactive in drug discovery [85]. In order to create new compounds with pharmaceutical applications for a range of infections, the 1,3-benzoxazine motif is a potential option to graft other biologically active molecules. These grafting approaches can include drug hybridization and repurposing. The identification of cannabinoid receptor 2 selectivity agonists is actively studied for effective modulation endocannabinoid signaling for medicinal applications [88, 90, 91]. There are still challenges with cannabinoid receptor 2 because of its strong similarity with cannabinoid receptor 1, and thus still uncertain molecular underpinnings of the agonist and antagonist shift. Hence, selectivity of cannabinoid receptor 2 agonist design is still difficult.

CONCLUSION

1,3-benzoxazine and its derivatives remain potent compounds with significant pharmaceutical applications. The 1,3-benzoxazine derivatives stand as the bridge between chemistry and medicine that can be further explored for many therapeutic targets and diagnoses. They have many biological properties that include antioxidant, anti-inflammatory, antimalarial, anti-plasmodial, antiplatelet, anticonvulsant, etc. found in various products. They also have antitumor properties. In addition, the synthesized 1,3-oxazines have antifungal and antibacterial properties against several Gram-positive and Gram-negative bacteria, such as *Bacillus thuringiensis*, *Escherichia coli*, and *Fusarium oxysporum*. 3,4-dihydro-benzo[e] [1,3] oxazin-2-one derivatives showed significant antibacterial and antifungal activities. Thionated-1,3-benzoxzine showed antifungal activities against eight fungal strains, comparable to fluconazole fungicide. They can be synthesized using formaldehyde

and o-hydroxybenzylamine condensing, Mannich condensation, and substitutions. Therefore, exploring the 1,3-benzoxazine chemotype model for cannabinoid receptor 2 can offer a deeper insight into the new pharmaceutical properties and broad-spectrum applications in medicine. This is because 1,3-benzoxazine and its derivatives can disrupt microbial processes or cell structures. The 1,3-benzoxazine chemotype and cannabinoid receptor 2 intersection have the potential to directly target pathogens and modulate the immune system. The cannabinoid receptor 2 in the immune system is primarily expressed in immune cells, such as macrophages and lymphocytes, whose modulation can influence immune responses, including antimicrobial defences. 1,3-benzoxazine derivatives can function as agonists or antagonists, depending on their chemical modifications and biological targets, and can interact with the cannabinoid receptor 2. The cannabinoid receptor 2 agonists or antagonists might improve the ability of immune system to combat infections caused by microorganisms by regulating cytokine production or immune cell activity. The 1,3-benzoxazine chemotype can create compounds mimicking receptor ligands by adding functional groups and optimizing the compounds through SAR studies to fit receptor binding pockets.

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