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3,4–dihydro–2H–1,3–benzoxazines and their oxo–derivatives
chemistry and bioactivities

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Abstract: 3,4–Dihydro–2H–1,3–benzoxazines derivatives are a significant class of
heterocycles with a particular awareness due to their remarkable biological
activities in humans, plant as well as in animals and also, they are naturally
occurrence. Because of alteration in the benzoxazines skeleton, beside their
comparative chemical simplicity and accessibility, make these compounds to
be suitable sources of other bioactive compounds. Resulting in the discovery of
a wide set of these compounds that have a broad biological activity such as
antifungal, antibacterial, anti–HIV, anticancer, anticonvulsant, anti–inflammatory
and so on. Subsequently, this review herein gives a brief overview of
derivatives of 3,4–dihydro–2H–1,3–benzoxazines monomers and their oxo–
derivatives chemistry and bioactivities.

Keywords: benzo–1,3–oxazines; synthesis; reactions; biological activities

INTRODUCTION

Benzo–1,3–oxazine are bicyclic skeleton in which a oxazine ring is annu-
lated with a benzene ring. A number of isomeric structures are possible
depending upon the positions and the degree of oxidation rate of the ring system.
The two isomeric structures 1 and 2 (2H– and 4H–benz–1,3–oxazine) in addition
to another one 3 (2,3– dihydro–2H–benz–1,3–oxazine) are illustrated in Fugu-
re 1. This review is focused on 3,4–dihydro–2H–benz–1,3–oxazines and their
oxo–derivatives.

3,4–Dihydro–2H–benz–1,3–oxazines exist in two basic conformations semi–
chair (A) and semi–boat (B) structures as shown in Figure 2. According to the
orientation of the substituent at the nitrogen atom, so each conformation exists
into another two forms.2

On the other hand, the dihydro–1,3–benzoxazine monomers are synthesized
by not only by traditional Mannich condensation methods3,4 of phenol, amine,
and formaldehyde, but also cyclo–addition\textsuperscript{5,6} and other methods. Interestingly, several works have been performed to investigate of reactant ratios\textsuperscript{7,8} reactant structures\textsuperscript{9,10} solvent effect\textsuperscript{11} temperatures of reaction\textsuperscript{12} and reaction duration\textsuperscript{13}.

![Chemical structures of 1,3–benzoxazine.](image1)

Figure 1. Chemical structures of 1,3–benzoxazine.

![Half chair (A) and Half boat (B) conformations.](image2)

Figure 2. 3,4–Dihydro–2H–1,3–oxazines conformations\textsuperscript{2}

All previous studies\textsuperscript{14,15} demonstrated that, these factors have an important role on the synthesis and the properties of benzoxazine (such as low yield and poor purity), resulting in limitation on the development of benzoxazines chemistry. Subsequently, these problems need further efforts and studies\textsuperscript{10,16}.

Furthermore, benzoxazine nucleus not only is present in many pharmacologically active molecules, medicinally significant derivatives and natural products but also they have been used as intermediates for the synthesis of other heterocyclic scaffold of bioactive compounds\textsuperscript{17}. Also, several of 1,3–benzoxazines (Figure 3) show interesting biological and pharmaceutical properties\textsuperscript{18,19}. Moreover, these derivatives are very valuable in the chemistry of natural products due to the formation of acetal–glycosides in plant\textsuperscript{20} which act as a plant’s own resistance factor towards insects, pests, fungi and other microbial diseases\textsuperscript{21}.

In this frame, the collected data in this review is focused on the 3,4–dihydro–2H–1,3–benzoxazine monomers and their one–derivatives chemistry and bioactivities.

![Benzoxazines with biological and pharmaceutical properties.](image3)

Figure 3. 1,3–Benzoxazines with biological and pharmaceutical properties.
2H–1,3–BENZOXAZINE DERIVATIVES SYNTHESIS AND BIOACTIVITIES

2. SYNTHESIS OF 1,3–BENZOXAZINE DERIVATIVES

2.1. Synthesis of 3,4–dihydro–2H–1,3–benzoxazines

The synthesized 3, 4–dihydro–2H–1,3–benzoxazine through one–pot Mannich reaction by the reaction of a substituted phenol with formaldehyde and aliphatic or aromatic monoamines/diamines has been performed (Scheme 1). It was found that, the importance role of the basicity of the amine on the rate of the reaction. Thus weakly basic amine will react faster than the strongly basic amine.

![Scheme 1: Synthesis of 1,3–benzoxazines by Mannich reaction.](image)

This synthetic method can be carried out either in solvent such as dioxane/water, absolute ethanol, methanol and so on or solventless. The use of organic solvent increases the cost of the products and causes some environmental problems. Further, the solvent residue in the products leads to problems during the handling of the benzoxazine synthesis. To overcome these drawbacks, the solventless synthesis was developed at the melt condition. The reaction mechanism and kinetics of this method were suggested by Liu and Ishida for the preparation a large quantity of benzoxazine monomers.

Furthermore, the influence of substituent attached to phenol or aniline on oxazine ring stability and equilibrium constant has been also investigated and studied in the literatures.

In the solventless method, the all reactants are mixed together, heated, and maintained at above their melting point using paraformaldehyde to maintain the reaction stoichiometry. Additionally, in the case of reactants with high melting point, toluene or 1,4–dioxane are necessary utilized as solvents. The better yield and purity were obtained on using a two-step methods by reaction of aliphatic amine and formaldehyde at low temperature first then add of the phenol derivative.

On the other hand, the kinetics and details study of 3,4–dihydro–2H–3–phenyl–1,3–benzoxazine synthesis by Mannich reaction were investigated. It was observed that, N–hydroxymethyl aniline (HMA) is considered the key intermediate. HMA then reacts with phenol to give second intermediate (3) which reacts with formaldehyde to form benzoxazines. However, HMA reacts with other intermediates and reactants to form byproducts as shown in Scheme 2. So, this research observed that, the formation and the mechanism of benzoxazines synthesis beside the formation of byproducts well need further investigations.
Scheme 2. Possible path ways for the benzoxazines synthesis by Mannich reaction.\textsuperscript{16}

Also, due to the presence of water, polar solvents and used high temperatures, the formation of oligomers are considered the main drawbacks in benzoxazine synthesis by Mannich reaction.\textsuperscript{32,10}

To minimized the previous drawbacks in the synthetic methods of 3,4–dihydro–2H–3–phenyl–1,3–benzoxazine monomers via Mannich condensation, numerous study efforts have been focused on two approaches: the use suitable synthetic method or use a catalyst.

Herein, the different synthetic approaches for these derivatives have been studied as described in Schemes 3a to 3c.\textsuperscript{35}

From the previous, there are three general synthetic methods for the preparation of benzoxazine monomers, one–pot, two–step and three–step Mannich reactions.

**One-pot**

Scheme 3a. Illustrate one–pot synthetic method for the preparation of benzoxazine.
Scheme 3b. Illustrate two-pot synthetic method for the preparation of benzoxazine

Scheme 3c. Illustrate three-pot synthetic method for the preparation of benzoxazine
2.1.1 One–step Mannich condensation

Traditionally, benzoxazine synthesis was carried out using one–pot multi-component reactions by Bruke. This method has been generalized and studied because of its simplicity and diversity of substituents on both phenol and amine. For example, nitro, halogentic, cyano, aldehyde, carboxyl, alkenyl, maleimide groups etc. can be adopted onto benzoxazine by using functional phenols/amines leading to produce a large variety of functional benzoxazines. Furthermore, by using of bisphenol and/or diamine compounds, bifunctional benzoxazines can be obtained. As another advantage of solventless one–pot method, it avoids the solvent residue that may cause serious defects during processing, saves the solvent and its recovery cost, and there is no worry about the solubility of raw materials in organic solvent. As example, the compound (1) was prepared by one–step Mannich reaction.

Furthermore, one–pot reactions are simple, easy handling and avoiding isolation and purification of intermediates, maximizes the yield, minimize solvent, and enhance the greenness of the transformations. Consequently, they have become a popular tool in the synthesis of complex heterocyclic molecules.

![Scheme 4](image)

As the modification of one–pot Mannich reaction has been developed via the oxidative hydroxylation of arylboronic acids and subsequent coupling with paraformaldehyde and amines in good to excellent yields with a variety of functional groups Scheme 4.

The synthesis of dihydro–1,3–benzoxazines were obtained via one–pot condensation of α– or β–naphthol, aniline and formaldehyde using thiamine hydrochloride (VB₁) as catalyst.
The preparation of a novel tetrafunctional oxazine monomer (2) contains 1,3–benzoxazine and fluorene–oxazine was performed through one–step Mannich condensation reaction.\textsuperscript{48} 

Additionally, benzoxazine monomers were synthesized in high purity and good yield through one–pot reaction from the reaction of bisphenol with paraformaldehyde and isomeric butylamines as indicated in Scheme 5.\textsuperscript{49}

Nonvolatile ecofriendly solvent (Brønsted acidic ionic liquid BF\(_4\)), and as catalytic reagent for the one-pot green synthesis of isoxazolyl–3, 4–dihydro–2\(H\)–1, 3–benzoxazines (3) has been studied. This method afford excellent yield in short reaction time, and avoids multistep synthesis.\textsuperscript{50}
Moreover, 3,4–dihydro–2H–1,3–benzoxazines were synthesized by one–pot from directed ortho–lithiation of phenols.\(^\text{51}\)

2. 1. 2. Two–step Mannich condensation

On the other hand, the two–step synthesis was performed in solvent and the procedure was first described by Holly and Cope.\(^\text{52}\) The reaction mechanism of this method proceeds by first adding amine to formaldehyde at lower temperatures to form an \(\text{N,N–dihydroxymethylamine}\), which then reacts with the labile hydrogen of the hydroxyl group and ortho–position of the phenol at the elevated temperature to form the oxazine ring.\(^\text{53}\) The slow reaction rate, large amount of solvent required for the synthesis due to the poor solubility of the reacting compounds are considered the disadvantages of this procedure in addition to increases the cost of the products and creates the environmental problems. To overcome these drawbacks, the solventless synthesis was developed.\(^\text{52}\)

Afterwards, the two–step reaction involves via formations of perhydrotriazine (intermediate) which formed from the reaction of formaldehyde with benzylamine. This intermediate reacts with phenol and formaldehyde in acidic condition to give benzoxazines (Scheme 6).\(^\text{13}\) This method has been generalized with the proposed mechanism in the literature.\(^\text{10}\)

Additionally, another way was reported through the formation of \(\text{bis (alkoxy-methyl)alkylamine}\) as intermediate which obtained from the reaction of alkyl amine with alcohol (Scheme 7).\(^\text{54}\)

Notable, these methods cannot be used in the presence of a primary amine similar as one–pot methods. However, these methods were suitable in cases of reactive phenolic compounds, such as hydroxybenzaldehyde and hydroxybenzoic acid, so the primary amine may be used. Because of diversity of substituent on both phenol and amine a large variety of functional benzoxazines can be produced.

The synthesis of benzoxazine performed by two–step reaction, the formation of 1,3,5–tripentafluorophenylperhydro–1,3,5–triazine is involved in the first step, then the reaction between the acid–promoted cleavage of the perhydrotriazine with substituted phenol and formaldehydetake place. The latter step is considered the rate determining step reaction.\(^\text{55}\)
2H-1,3-BENZOXAZINE DERIVATIVES SYNTHESIS AND BIOACTIVITIES

Scheme 6. Benzoxazines synthesis with 1,3,5-hexahydrotriazine

Furthermore, 1,3,5-triphenylhexahydro-1,3,5-triazine (4) was formed during the solventless synthesis of benzoxazines as intermediate. Herein, the triazine can be used as a source of an amine instead of the direct use of a primary amine.\textsuperscript{10,56}

2.1.3. Three-step Mannich reaction

Brurke suggested reaction pathway of Mannich condensation: initially the \textit{N,N-dihydroxymethyl amine} (1) is formed then it converted into \textit{N-hydroxy-methyl} Mannich base (2) finally it reacts with phenol to generate 1,3-benzoxazines (Scheme 8).\textsuperscript{42,57,58}

Moreover, three–steps method was developed by imine formation between salicylaldehyde and the selected primary amines as first step; second step is the reduction of this imine into secondary amine and finally, is the ring closure using formaldehyde.\textsuperscript{59}
Advantage of this method is the ability to control each step and the usage of amines that are incompatible in classical methods. Further, the use of this method avoids the formation of undesirable oligomeric or polymeric species, thus leading to a simple workup and improving the yield and purity of the final product. As an example, salicylaldehyde or 4-aminophenol can be used as phenol or amine source respectively. Also, free phenol-containing benzoxazines can be also synthesized easily by this method. In addition, asymmetrical benzoxazine derivatives can be easily obtained by choosing suitable salicylaldehyde.

Furthermore, 1,3-benzoxazine derivatives were performed via dehydration of methylene glycol to formaldehyde molecule which reacts with Mannich base as indicated in Scheme 9.

Salicylaldehyde was condensed with the primary aromatic amines to give imine compounds which on reduction with NaBH₄ yielding intermediate (5) at room temperature. The compound (5) subsequently undergoes ring-closure reaction with paraformaldehyde in toluene at 60 °C to give benzoxazinemonomer by three-pot method.

Also, the kinetic of reaction between 2-phenylaminomethylphenol (phenol-aniline based Mannich base) and formaldehyde to benzoxazine has been studied. The results showed that, the reaction occurs rapidly and the reverse reaction occurs via hydrolysis of benzoxazine to Mannich base.
Moreover, the difunctional benzoxazine was prepared from the reaction of bis (ortho-hydroxybenzylamino)ethane (6) with formaldehyde. The advantage of this synthesis is the flexible substitution of functional groups on the oxazine ring. Also, another substitution on the oxazine ring can be achieved by the ring closure of salicylaldehyde with various aldehydes (aliphatic or aromatic) instead of formaldehyde. Additionally, the oxazine ring can be closed by the reaction of salicylaldehyde with not only aldehydes but also with methylene bromide also. Furthermore, this method enhances the formation of benzoxazine monomer only because its intramolecular cyclization permits the reaction condition to moderate, leading to minimize side reactions caused by high temperature. However, in the case of one–pot method sometimes requires relatively high temperature to close the oxazine ring leading to the formation of undesirable oligomeric or polymeric species.

On the other hand, for further limitation on the drawbacks of Mannich methods, many catalysts have been used for the growing of benzoxazines synthesis. As example: 2,3–diaryl–3,4–dihydro–2H–1,3–benzoxazines have been prepared in high yields from o–arylaminoethenylphenols and aromatic aldehydes in the presence of SnCl₂. Also, the condensation of hexa (methoxymethyl)melamine with mono or di–substituted phenols in p–xylene catalyzed by dinonylnaphthalenedisulfonic acid gave 1,3–benzoxazines. In addition, 3,4–dihydro–1,3–benzoxazines were synthesized by directed ortho–lithiation of phenols using ZnBr₂ as catalyst. Furthermore, Brønsted acidic ionic liquid BF₄⁻ has been used as a nonvolatile, ecofriendly solvent, and catalyst for the one–pot synthesis of substituted isoxazolyl–1,3–benzoxazines (7). The reaction gave excellent yield in short reaction time and avoids multistep synthesis. The recyclability of the catalyst makes the reaction economically and potentially able for commercial applications. Moreover, thiamine hydrochloride (VB₁) was used as versatile...
biodegradable and reusable catalyst in water as a universal solvent for the synthesis of benzoxazines. Finally, I$_2$/H$_2$O$_2$–promoted intramolecular C–O bond–formation reaction of a variety of 1–(aminoalkyl)–2–naphthols or 2–(aminoalkyl)phenols yielding the corresponding 1,3–oxazines. The reaction is simple, economic, and proceeds at room temperature in ethanol as solvent.

2.2. Synthesis of sulfone–scaffold benzoxazine monomer

On the other hand, the formation of byproducts (oligomers or polymers) in Mannich reaction has been considered beneficial in many industrial usages in spite of being considered drawback in the preparation of benzoxazine monomers. Thus, 3,4–dihydro–1,3–benzoxazines can yield polymeric structures through ring–opening of the cyclic monomers. These polymeric structures are commercially important and widely applied in the areas of coatings, adhesives, microelectronics, and aerospace etc. One example of commercially important polysulfones (PSU) are a class of polymers with excellent features e.g. thermal stability, durability in harsh conditions, oxidation, pH and temperature resistance, ease of process ability and good film properties.

Sulfone–scaffold 3,4–Dihydro–2H–1,3–benzoxazines (6) were prepared in high purity from 4,4′–diaminodiphenyl sulfone (7), bisphenolsulfone (8) or polysulfone and paraformaldehyde and phenol using high boiling point nonpolar solvent. See Figure 4.

Figure 4. Sulfone–based 1,3–benzoxazines, diaminodiphenyl sulfone and bisphenolsulfone
2.3. Synthesis of bio–based benzoxazine monomer

Interestingly, the raw materials for the synthesis of benzoxazine derivatives are almost always derived from petroleum oil. With the fast consuming of petroleum oil and increasingly serious environmental pollution, the utilization of bio–based feedstock to prepare green these derivatives has more attention in all domain.\textsuperscript{74,75}

In benzoxazines synthesis, the renewable starting materials are used due to their availability, low toxicity, and relative low cost. Thus, natural occurring phenol such as chavicol,\textsuperscript{76} Guaiacol,\textsuperscript{77} cardanol+\textsuperscript{78,79} and lignocelluloses\textsuperscript{80,81} are used in the synthesis of 1,3–benzoxazines (Figure 5).

![Figure 5. The structures of some natural occurring phenol](image)

2.2. Synthesis of 4H–1,3–benzoxazine–2–one

The benzoxazinones are performed by one–pot reaction of 2–naphthol, aldehydes and urea, in the presence of various catalysts such as iodine (Scheme 10), P\textsubscript{2}O\textsubscript{5} and Yb (OTf)\textsubscript{3},\textsuperscript{82} cellulose sulfuric acid,\textsuperscript{83} cyanuric chloride,\textsuperscript{84} phosphomolybdic acid,\textsuperscript{85} pyridinium-based ionic liquid,\textsuperscript{86} thiamine hydrochloride,\textsuperscript{87} zinc triflate,\textsuperscript{88} montmorillonite K10,\textsuperscript{89} zinc oxide,\textsuperscript{90} TMSCl/NaI,\textsuperscript{91} guanidine hydrochloride\textsuperscript{92} and so on.

![Scheme 10. One–pot Mannich using iodine as catalyst](image)
On the other hand, by condensation of amino–alkynaphthols with phosgene\(^{93}\) or carbonyl di–imidazole\(^{94}\) in the presence of triethylamine, the 1,3–oxazin–2–one derivatives were produced in moderate yields. Also, the 1,3–benzoxazin–2–ones \((8)\) were prepared by reaction of 2–hydroxyphenyl–substituted enones and isocyanates using bisguanidinium salt as catalyst.\(^{95}\)

Additionally, the 1,3–benzoxazine–2–one was synthesized from the reaction of substituted slicylaldehyde with primary amine and aldehyde. As example, the spiropyrans based on benzoxazine \([4]\) were synthesized from the reaction of compound \((A)\) with compound \((B)\) using protonated acetic acid \([\text{MeC(OH)}_2]^+\ ClO_4^-\) as catalyst, as indicated in Scheme 11.\(^{96}\)

![Scheme 11. Synthesis of spiropyrans based on 1,3–benzoxazine–2–one](image)

Also, 3, 4–dihydro–2H–1,3–oxazin–2–ones have been synthesized by intramolecular cyclization of arylcarbamates which produced from the reaction of aryl isocyanate and corresponding 2–nitroethenyl phenols under basic condition.\(^{97}\)
Via the reaction of salicyaldehyde/2–hydroxyacetophenone or its hydrazones and substituted urea or substituted semicarbazide under solventless microwave irradiation the 1,3–benzoxazine–2–ones were synthesized by one–pot method (Scheme 12).

**Scheme 12.** Synthesis of 1,3–benzoxazine–2–ones from salicyaldehyde/2–hydroxyacetophenone

2. 3. Synthesis of 2H–1,3–benzoxazine–4–one

The condensation of acid halide with salicylamides in the presence of pyridine using boiling xylene as solvent the substituted 1, 3–benzoxazine–4–ones have been developed by one–step. In addition, two–step method by refluxing the salicylamide with aroyl chloride in pyridine followed by cyclization of the isolated intermediate by hydrogen chloride.

Further, by carbonylation–cyclization of ortho–halophenols and cyanamide or by treatment of the corresponding 2–hydroxycarboxamides with a formaldehyde/formic acid mixture, the corresponding 4H–1,3–benzoxazine–4–ones were synthesized. The 2–trichloromethyl and 2–dichloromethylene–2H–1,3–benzoxazine derivatives were obtained via intramolecular cyclization of N– (α–aryloyxirichloroethyl)imidoyl chlorides through dehydrochlorination. Also, 2–aryl–2–trifluoromethy–2,3–dihydro–4H–benzoxazin–4–ones were synthesized via intramolecular thermal cyclization of N– (1–aryl–2,2,2–trifluoroethylidene)–o– (3–alkoxyphenyl)urethanes which produced from the reaction of 1–aryl–2,2,2–trifluoroethylisocyanates with 3–alkoxyphenols (Scheme 13).
Moreover, synthesis of 2,3-dihydro-4H-benzoxazine-4-ones have been performed by intermolecular cyclization reactions of o-halobenzamides, LiOH and dichloromethane using copper-catalyzed tandem as catalyst.\textsuperscript{104}

2. 4. Synthesis of 1,3-benzoxazine-2,4 (3H) -diones

The 1,3-benzoxazine-2,4 (3H)-diones have been synthesized from the reaction of acardic acids with triphosgene,\textsuperscript{105} from the reaction of phthaloyl chlorides with acetone oxime\textsuperscript{106} or from the reaction of salicylate esters with isocyanates.\textsuperscript{107}

Reaction of 2-hydroxybenzonitrile with isocyanates\textsuperscript{108} using triethylamine as catalyst has been performed to obtain the target compounds as in Scheme 14.

Scheme 14. Synthesis of 1,3-Benzoxazine-2,4 (3H) -diones from 2-hydroxybenzonitrile and isocyanates
3. CHEMISTRY OF 1,3–BENZOXAZINE DERIVATIVES

3.1. Unusual behavior of ortho–functional

The formation of intramolecular five–membered ring H–bond between the NH of amide group and oxygen of oxazine ring (Figure 6) is considered as unusual behavior of ortho–functional benzoxazine.\textsuperscript{109}

![Figure 6](image)

Figure 6. The intramolecular five – membered ring H–bond in benzoxazines

Also, it was observed that, o–methyl substituted benzoxazine dimers as shown in (Figure 7),\textsuperscript{10,11} trimer or tetramer exhibit intramolecular hydrogen bonding.\textsuperscript{112}

![Figure 7](image)

Figure 7. The molecular structure of a pair of methyl benzoxazine dimers

Interestingly, the o–substituted benzoxazine dimers is used as novel ligands for rare earth metal ion e.g. Ce (III) ion. It was found that, the substituted groups on para–positions of benzoxazine dimers do not affect the formation of complexes.\textsuperscript{113}

3.2. Ring opening of benzoxazines

The dihydro–derivatives are more stable than the 1,3–benzoxazines towards acidic agents. The ring opening ability depends on the basicity of the oxygen and nitrogen atoms.\textsuperscript{114} In the compounds with active hydrogen such as indoles,
carbazole, imides, and aliphatic nitro compounds even phenol (Scheme 15), thiols (Scheme 16) or carboxylic acids, the auto–ring opening occurs as shown in Scheme 15, 16 and 17. The benzoxazines ring opening is beginning by protonation of oxygen and nitrogen atoms as indicated in Scheme 17.

Further, ring opening is promoted by irradiation with UV (Scheme 18) resulting in the formation of two chromophoric systems (3H–indolium cation and 4–nitrophenolate anion moiety).

In addition, the ring opening reaction of substituted benzoxazine would easily happen by heating due to the stabilization of the iminium ion by resonance as indicated in Scheme 19.
2H-1,3-BENZOXAZINE DERIVATIVES SYNTHESIS AND BIOACTIVITIES

Scheme 18. Ring opening of 1,3-oxazine ring upon irradiation

Scheme 19. The stabilization of the iminium ion by resonance

3. 3. RING–CHAIN TAUTOMERISM

The 1-(substituted-phenyl)-3-alkyl-2,3-dihydro-1H-naphth-1,3-oxazines undergoes ring-chain tautomerism, resulting in predominates the trans- (12) over the cis–conformation (13) through the compound (14) as shown in Scheme 20.

Scheme 20. 3, 4-dihydro-2H-1, 3-benzoxazine epimerization

4. REACTION OF 1,3-BENZOXAZINE DERIVATIVES

4. 1. Hydrolysis with HCl

The benzoxazine derivatives (31) are hydrolyzed by HCl to give 2-aminopyridine (32) or N–2-pyridylsalicylamide (33) depending on concentration of acid as indicated in Scheme 21.

Scheme 21. Effect of acids on benzoxazine derivatives
4. 2. Salt formation

The salt formation of 1,3–benzoxazines have been prepared by acidic cyclization of disalicylamide\textsuperscript{125} or by acylation of \textit{o–aminophenyl diphenylcarbinol} with carboxylic acids in the presence of perchloric acid\textsuperscript{126} producing 1,3-benzoxazinium perchlorate (9).

\[ \text{[Reaction Diagram]} \]

4. 2. 1. Reaction of 4H–1,3–benzoxazin–4–onium salts

Interestingly, benzoxazin–4–onium perchlorate (15) reacts with dialdehyde methyl 3,5–diformal–2,4–dihydroxybenzoate (16) in glacial acetic acid obtaining spiropyran of 1,3–benzoxazine series (5) through the formation of intermediate styryl salt (17). This intermediate has been isolated and then cyclized under the action of triethylamine in anhydrous diethyl ether to yield the compound (18) as shown in Scheme 22.\textsuperscript{127,128}

\[ \text{[Reaction Diagram]} \]

Scheme 22. Reaction of 4H–1,3–benzoxazin–4–onium salts with 3,5–diformal–2,4–dihydroxybenzoate

4. 3. Reaction with alkylhalides

1,3–Benzoxazine–2,4–dione was reacted with alkyl halide in the presence of K\textsubscript{2}CO\textsubscript{3}\textsuperscript{129,130} yielding \textit{N–substituted} derivatives (Scheme 23).
4. 4. Nucleophilic substitution reaction

4. 4. 1. Reaction with pyridine–N oxide

2,2-Dimethyl-3–(2–pyridyl)–4–oxo–4H–1,3–benzoxazine (19) was produced by refluxing of 4–chloro–derivative of benzoxazine (20) with two mole of pyridine–N–oxide in methylene chloride through nucleophilic substitution reaction then rearrangement\textsuperscript{124} (Scheme 24).

4. 4. 2. Reaction with organometallic compounds

2,2–Dimethyl–1,3–benzoxazin–4–one derivatives react with organometallic compounds by nucleophilic substitution as shown in Scheme 25.\textsuperscript{131}

Scheme 23. Reaction of 1,3–benzoxazine–2,4–dione with alkyl halide

Scheme 24. Reaction of substituted–1,3–benzoxazines with pyridine–N–oxide

Scheme 25. Reaction of 1,3–benzoxazin–4–ones with organometallic compounds
5. BIOLOGICAL ACTIVITIES

Benzoxazinone and their derivatives are a significant class of heterocyclic compounds, because many of these derivatives display diverse biological activities.

5.1. Antiviral Therapy

Elbasvir (10)\textsuperscript{1,132,133} is potent inhibitor of the HCV NS5A protein and it used in combination with grazoprevir for the treatment of hepatitis C virus (HCV) NS3/4A.\textsuperscript{134} Also, Grazoprevir/elbasvir plus ribavirin were examined as new treatment option for patients after failure of triple therapy containing an earlier-generation protease inhibitor.\textsuperscript{135}

5.2. Anti–tuberculosis activity

The antimycobacterial activity various substituted 3–phenyl–2H–benzoxazine–2,4 (3H)–dithiones and 3–(phenyl)–4–thioxo–2H–benzoxazine–4 (3H)–diones have been studied using a quantum molecular similarity approach. The replacement of the oxo–group by the thioxo–group in position 4 on the benzoxazin–2,4–dionering increases the activity, as well as the similar replacement in position 2.\textsuperscript{136,137} In vitro antimycobacterial activity against Mycobacterium tuberculosis, Mycobacterium avium and two strains of Mycobacterium kansasi were studied. Further, the antimycobacterial activity increased with the replacement of the carbonyl group by the thiocarbonyl group in the starting 3–(4–alkylphenyl)–2H–1,3–benzoxazine–2,4 (3H)–diones.\textsuperscript{138,139}

5.3. Fungicidal and pesticide activities

A series 2,3–disubstituted–3,4–dihydro–2H–1,3–benzoxazines was prepared by reaction of aza–acetalizations of aromatic aldehydes with 2–(N–substituted aminomethyl)phenols in the presence of TMSCl. The fungicidal activities were evaluated, and some of these compounds exhibited activity against Rhizoctonia solani.\textsuperscript{63} Additionally, a series of 2,3–diaryl–3,4–dihydro–2H–1,3–benzoxazines has been prepared in high yields from o–arylamidomethylphenols and aromatic...
aldehydes in the presence of SnCl\textsubscript{4}. Their fungicidal activities were investigated. Some of the products showed good fungicidal activities against \textit{Rhizoctonia solani}.\textsuperscript{27} Also, synthesis of novel naphtho[1,2-e][1,3] oxazines bearing an arylsulfonamide moiety were synthesized and evaluated for their anticancer and antifungal activities.\textsuperscript{140}

Furthermore, the substituted 8-hydroxy-3-phenyl-2H-1,3-benzoxazine-2,4 (3H) –diones were synthesized by cyclization of corresponding dihydro-N-phenylbenzamides with methyl chloroformate. Thionation of compounds was carried out by Lawesson's reagent. All compounds were tested \textit{invitro} for their antifungal activity against eight test strains. The compounds showed moderate activity.\textsuperscript{141}

In addition, the compounds 3-Nonyl-3, 4-dihydro-4-methyl-2H-1,3-benzoxazines and 3-Decyl-3,4-dihydro-4-methyl-2H-1,3-benzoxazines were studied and investigated as pesticides.\textsuperscript{142}

4. Anticonvulsive activities

4-[2H-1,3-benzoxazine-2,4 (3H) –dione]–butyric acid (BXDBA) shows a good anticonvulsive activity and its ability to block bicuculline–induced convulsions suggests that it could be a GABA\textsubscript{A} mimetic drug.\textsuperscript{143,144}

5. Antibacterial activities

\textit{N}-(benzyl carbamothioyl)-2-hydroxy substituted benzamides were synthesized using sodium bicarbonate and benzyl amine with 2-thioxo–substituted–1,3-benzoxazines. These derivatives were investigated as antibacterial, antifungal activities.\textsuperscript{145}

Moreover, a series of 1,2-bis (3,4-dihydrobenzo[e][1,3]oxazin–3 (4H) –yl)ethane derivatives (11) was synthesized via an eco–friendly Mannich type condensation–cyclization reaction of phenols or naphthols with formaldehyde and primary amines in water at ambient temperature. \textit{Invitro} antimicrobial activity of the synthesized compounds was assessed against six pathogenic fungi, two Gram-negative and two Gram-positive bacteria. Some of the screened compounds have shown significant \textit{invitro} antimicrobial effect.\textsuperscript{146}
The derivatives of benzofuranyl–1,3–benzoxazine and 1,3–benzoxazin–2–one was synthesized via coupling benzofuran with 1,3–benzoxazines and 1,3–benzoxazin–2–ones through –CONH– and –COCH2– bridges, respectively. The antimicrobial activity of these compounds was reported.\textsuperscript{147}

5. 6. Anticancer activities

Furthermore, naphtho[1,2–e][1,3]oxazines bearing arylsulfonamide moiety have been synthesized via a one–pot method and showed remarkable activities against MCF–7 (breast) and HCT116 (colon) cancers.\textsuperscript{140} Also, 1,3–benzoxazines, having flavone moiety at 3–position showed also activities against MCF–7.\textsuperscript{148}

2H–1,3–Oxazine–2,6 (3H)–dione (3–oxauracil) exhibits cytotoxic activity against cancer cell lines tested (pancreatic, colon, neuroendocrine, and nonsmall cell lung). These derivatives were studied as an inhibitor of selected neoplastic cell growth \textit{in vivo}.\textsuperscript{149}

In addition, a series of modified hexacyclic camptothecin derivatives containing a 1,3–oxazine ring was synthesized against nine human cancer cell lines. All compounds were assayed \textit{in vitro} against 13–fold more potent than camptothecin, and about six–fold more potent than topotecan toward HEPG–2. Furthermore, the \textit{N}–alkyl substituted derivatives were more potent than the \textit{N}–aryl and \textit{N}–benzyl substituted compounds.\textsuperscript{150}

The synthesis of 6–aryl, 8–aryl, and 8–aryl–6–chloro–2–morpholino–1,3–benzoxazines with potent activity against PI3K and DNA–PK was studied. A compound with 8–(naphthalen–1–yl) scaffold showed strong anti–proliferative activity against A498 renal cancer cells that warrants further investigation.\textsuperscript{151}

5. 7. Antihypertensive activities

The antihypertensive and cardiovascular properties of a new potassium channel opener, TCV–295 (12), were studied in rats and dogs. In conscious, spontaneously hypertensive rats (SHR), TCV–295, reduced blood pressure (BP) with low dose dependently and with slow onset of action were observed.\textsuperscript{152}

An efficient process for potassium channel opener, TCV–295, based on a 4–(2–pyridyl)–2H–1,3–benzoxazine ring formation from o–hydroxybenzoylpyridine by the NH4I/piperidine/2,2–dimethoxypropane system and the following selective pyridine–N–oxidation using dimethyldioxirane, has been examined.\textsuperscript{153}

In addition, a series of 1, 3–benzoxazine derivatives with a 2–pyridine–1–oxide group at C4 (12) was synthesized to explore \textit{K}+ channel openers by one–pot 1, 3–benzoxazine skeleton formation using a palladium (0)–catalyzed carbon–carbon bond formation reaction of imino–triflates with organozinc reagents. The compounds were tested for vaso–relaxant activity using BaCl2–induced and high KCl–induced contraction of rat aorta to identify potential \textit{K}+ channel openers, and also for oral hypo–tensive effects in spontaneously hypertensive rats.\textsuperscript{131}
5.8. Antimalarial activities

A series of 6- (2–chloroquinolin–3–yl) –4–substituted–phenyl–6H–1, 3–oxazin–2–amines was synthesized and evaluated in vitro for antimalarial efficacy against chloroquine sensitive (MRC–02) as well as chloroquine resistant (RKL9) strains of *Plasmodium falciparum*.\(^{154}\)

The antimalarial activities of the resulting benzoxazines, their isosteric tetrahydroquinazoline derivatives, and febrifugine–based 1,3–quinazolin–4–ones were examined in vitro (against *Plasmodium falciparum*) and in vivo (against *Plasmodium berghei*).\(^{159}\)

5.9. Antidiabetic and hypolipidaemic activity

A series of 5–[4–[2–[2, 3–benzoxazine–4–one–2–yl]ethoxy]phenyl methyl]thiazolidine–2,4–diones was synthesized and investigated for their plasma glucose and plasma triglyceride lowering activity. Also the synthesized 2, 4–thiazolidinedione derivatives of 1, 3–benzoxazinone were evaluated for antidiabetic and hypolipidaemic potential. As example, DRF–2519 (13), has shown potent dual PPAR activation.\(^{155}\)
5. 10. Receptor antagonist activity

Synthesis and pharmacology of benzoxazines (14) were investigated as highly selective antagonists at M₄ Muscarinic Receptors.\textsuperscript{156}

![Chemical structure of (14)](image)

5. 11. Antidepressant activity

It was found that, 1,3–benzoxazine–2,4–diones (15) have binding affinities for 5–HT₁₅ and 5–HT₇ receptors.\textsuperscript{158} Further, Benzoxazine derivative, caroxazone (16), was investigated\textit{in vitro} and \textit{in vivo} as antidepressant (Ro 11–1163) and as specific and short–acting MAO–A inhibitor\textsuperscript{157}

![Chemical structure of (15)](image)

![Chemical structure of (16)](image)

5. 12. Anti–platelet aggregation activity

A series of 2,8–disubstituted benzoxazinones (17) was synthesized and studied as anti–platelet aggregation, via inhibition of superoxide anion generation and inhibition of neutrophil elastase release assays. It was found that, the synthesized compounds were more potent than aspirin on AA–induced platelet aggregation.\textsuperscript{158,159}
5.13. Miscellaneous activities

In addition, other benzoxazine compounds have an anti-inflammatory activities e.g. the compounds (18) and (19), analgesic and antipyretic properties such as chlorthenoxazin (20). Furthermore, these derivatives are used as specific inhibitors of the Tissue Factor (TF)/Factor Via (Via) – induced pathway of coagulation as reported in literature.

CONCLUSION

In conclusion, the synthetic potential and transformations of 3,4-dihydro-2H-1, 3-benzoxazines remains largely interested. The 3,4-dihydro-2H-1, 3-benzoxazines are flexible and toughness lead molecule to diverse workable site for substitution. Also, they exhibit wide range of biological activity such as herbicides and agricultural microbiocides as well as they have been pharmacological activities such as antitumor agents, antiretroviral therapy, anti-tubercular activity, antibacterial activity, anti-inflammatory activity, anti-convulsant activity etc. On the other hand, the growth of drug resistance is considered a major problem in
medicine and to overcome this status, it is requisite to synthesize new classes of compounds. Subsequently, the collected data in this review can be used to provide novel benzoxazine derivatives that could be utilized for the development of new compound to inhibit resistance of a drug for various diseases.

I Z В О Д

ХЕМИЈА И БИОЛОШКА АКТИВНОСТ 3,4–ДИХИДРО–2Н–1,3–БЕНЗОКСАЗИНИ И ЊИХОВИ ОКСО–ДЕРИВАТА

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Деривати 3,4–дихидро–2Н–1,3–бензоксазин и њихови оксо–деривата су природни производи и значајна класа хетероцикличких једињења посебно због њихове изузетне активности у хуманој медицини, фито–фармацији и ветерин. Услед могућности за надградњу бензоксазинске структуре, комаративне хемијске једноставности и доступности, ова једињења су подесан извор за нова биоактивна једињења. Резултати тога су истраживање и открића велике групе ових једињења која показују широк опсег биолошких активности, као што су антифунгална, антибактеријска, анти–ХИВ, антиканцерска, релаксациона, анти–инфламанторна и др. Овај преглед литературе даје кратак приказ деривата 3,4–дихидро–2Н–1,3–бензоксазина и њихових оксо–деривата, хемијску реактивност и биоактивност.

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