Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *86* (3) 213–246 (2021)
JSCS–5417
Survey

SURVEY

3,4-Dihydro-2*H*-1,3-benzoxazines and their oxo-derivatives – Chemistry and bioactivities

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(Received 30 May, revised 3 December 2018, accepted 11 January 2019)

Abstract: 3,4-Dihydro-2*H*-1,3-benzoxazines derivatives are a significant class of heterocycles with particular awareness due to their remarkable biological activities in humans, plants and animals, and also their natural occurrence. Alteration in the benzoxazine skeleton and their comparative chemical simplicity and accessibility, make these compounds suitable sources of other bioactive compounds, resulting in the discovery of a wide set of these compounds that have broad biological activity, such as antifungal, antibacterial, anti-HIV, anticancer, anticonvulsant, anti-inflammatory, *etc*. Subsequently, this review gives herein a brief overview of the chemistry and bioactivities of derivatives of 3,4--dihydro-2*H*-1,3-benzoxazine monomers and their oxo-derivatives.

Keywords: 1,3-benzoxazines; synthesis; reactions; biological activities.

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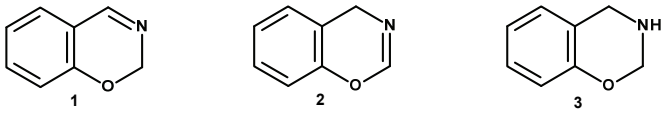
https://doi.org/10.2298/JSC180530001S

1. INTRODUCTION

1,3-Benzoxazine is a bicyclic skeleton in which an oxazine ring is annulated with a benzene ring. A number of isomeric structures are possible depending on the positions and the degree of oxidation of the ring system. The two isomeric structures **1** and **2** (2*H*- and 4*H*-1,3-benzoxazine) in addition to 2,3-dihydro-2*H*--1,3-benzoxazine (**3**) are illustrated in Fig. 1.[1] This survey is focused on 3,4--dihydro-2*H*-1,3-benzoxazines and their oxo-derivatives.



2*H*-1,3-benzoxazine 4*H*-1,3-benzoxazine 3,4-Dihydro-2*H*-1,3-benzoxazine

Fig. 1. Chemical structures of 1,3-benzoxazines.

3,4-Dihydro-2*H*-1,3-benzoxazines exist in two basic conformations, the semi-chair (A) and semi-boat (B) structures, as shown in Fig. 2. According to the orientation of the substituent at the nitrogen atom, each conformation exists in another two forms.[2]

On the other hand, the dihydro-1,3-benzoxazine monomers are synthesized not only by traditional Mannich condensation methods[3,4] of phenol, amine, and formaldehyde, but also by cycloaddition[5,6] and other methods. Interestingly,

several works have been performed to investigate the reactant ratios,[7,8] reactant structures,[9,10] solvent effect,[11] temperatures of reaction,[12] and reaction duration.[13]

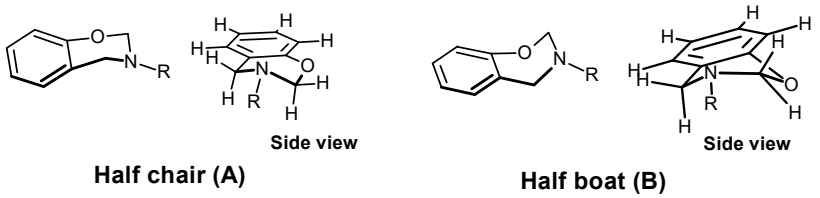


Fig. 2. Conformations of 3,4-dihydro-2*H*-1,3-benzoxazines.[2]

All previous studies[14,15] demonstrated that these factors play an important role in the synthesis and the properties of benzoxazine (such as, low yield and poor purity), resulting in limitation of the development of benzoxazine chemistry. Consequently, these problems need further efforts and studies.[10,16]

Furthermore, the benzoxazine nucleus is not only 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 bioactive compounds.[17] Furthermore, several 1,3-benzoxazines (Fig. 3) show interesting biological and pharmaceutical properties.[18,19] Moreover, these derivatives are very valuable in the chemistry of natural products due to the formation of acetal glycosides in plant[20] which act as a plant's own resistance factor towards insects, pests, fungi and other microbial diseases.[21] In this frame, the collected data in this survey is focused on the 3,4-dihydro-2*H*--1,3-benzoxazine monomers and their one-derivatives chemistry and bioactivities.

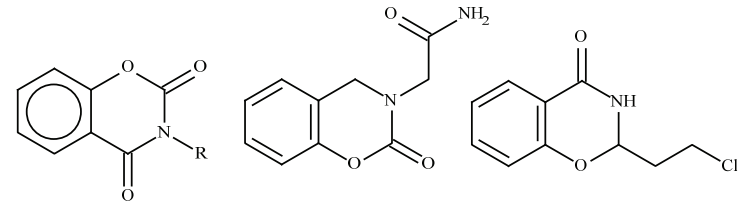
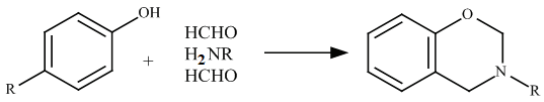


Fig. 3. 1,3-Benzoxazines with biological and pharmaceutical properties.

2. SYNTHESIS OF 1,3-BENZOXAZINE DERIVATIVES

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

3,4-Dihydro-2*H*-1,3-benzoxazines have been synthesized through the one-pot Mannich reaction of a substituted phenol with formaldehyde and aliphatic or aromatic monoamines/diamines (Scheme 1).[22] The importance of the role of the basicity of the amine on the rate of the reaction was found.[13,23] Thus a weakly basic amine will react faster than a strongly basic amine.[24]



Scheme 1. Synthesis of 1,3-benzoxazines by a Mannich reaction.

This synthetic method could be performed either in solvent,[25] such as dioxane/water,[26] absolute ethanol,[27,28] methanol,[29] *etc*., or solventless.[30,31] The use of an organic solvent increases the cost of the products and causes some environmental problems. Furthermore, 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 under melt condition.[32] The reaction mechanism and kinetics of this method were suggested by Liu and Ishida for the preparation large quantities of benzoxazine monomers.[24]

Moreover, the influence of substituent attached to phenol or aniline on the stability of the oxazine ring and the equilibrium constant has been investigated and studied in the literature.[24,26]

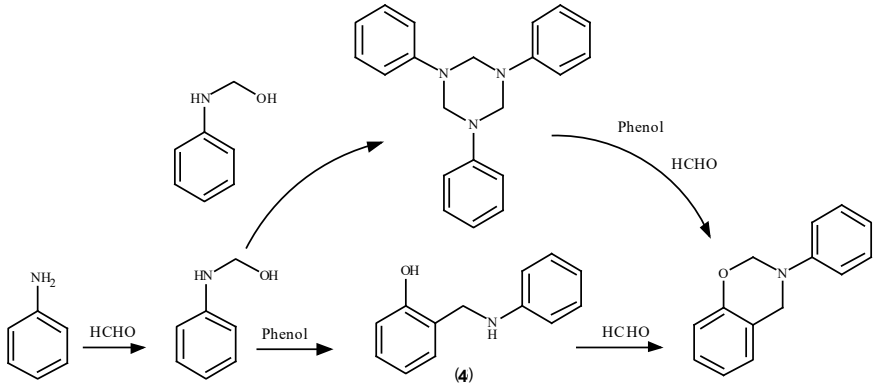
In the solventless method[30,33] all the reactants are mixed together, heated, and maintained at above their melting point using paraformaldehyde to maintain the reaction stoichiometry.[30] Additionally, in the case of reactants with high melting points, it is necessary to use toluene or 1,4-dioxane as solvents.[34] Better yield and purity were obtained using two-step methods by reaction of an aliphatic amine and formaldehyde at low temperature first before adding the phenol derivative.[32]

On the other hand, the kinetics and details of 3,4-dihydro-3-phenyl-2*H*-1,3--benzoxazine synthesis by the Mannich reaction were investigated.[16] It was observed that *N*-hydroxymethyl aniline (HMA) is considered the key intermediate. HMA then reacts with phenol to give a second intermediate (**4**) that reacts with formaldehyde to form benzoxazines. However, HMA reacts with other intermediates and reactants to form byproducts, as shown in Scheme 2. Thus, this research observed that the formation and the mechanism of benzoxazines synthesis besides the formation of byproducts will need further investigations.[16]

In addition, due to the presence of water, polar solvents and the high temperatures used, the formation of oligomers are considered the main drawbacks in benzoxazine synthesis by the Mannich reaction.[10,32]

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

Herein, the different synthetic approaches for these derivatives have been studied as described in Scheme 3a–c.[35]



Scheme 2. Possible pathways for the synthesis of benzoxazines by the Mannich reaction.[16]

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

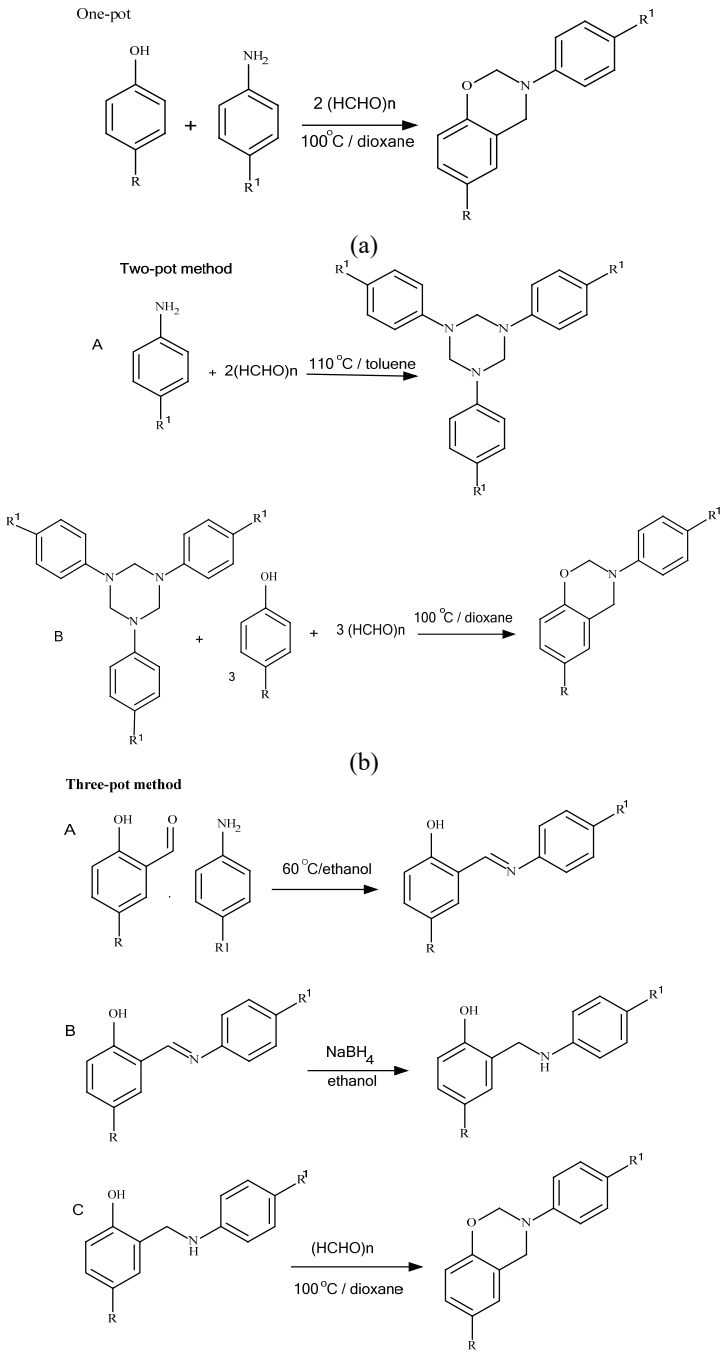
2.1.1. One-step Mannich condensation

Traditionally, benzoxazine synthesis was realized using the one-pot multi-component reactions of Burke.[3] This method has been generalized and studied because of its simplicity and diversity of substituents on both the phenol and the amine. For example, nitro,[35] halogenic,[36] cyano,[37] aldehyde,[38] carboxy,[39] alkenyl,[40] maleimide[41] groups, *etc.* could be adopted onto benzoxazine by using functional phenols/amines, leading to the production of a large variety of functional benzoxazines. Furthermore, by the use of bisphenol and/or diamine compounds, bifunctional benzoxazines could be obtained.[42] Another advantage of the solvent-free, one-pot method is that it avoids solvent residues, which may cause serious defects during processing, saves on solvent and its recovery costs, and there is no worry about the solubility of raw materials in an organic solvent.[32] As example, compound **5** was prepared in a one-step Mannich reaction (Fig. 4).[43]

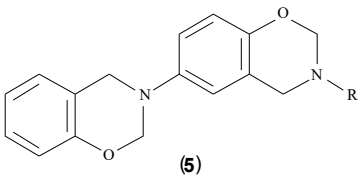
Moreover, one-pot reactions are simple, easy to handle and avoid isolation and purification of intermediates, maximize the yield, minimize solvent, and enhance the greenness of the transformations.[44] Consequently, they have become a popular tool in the synthesis of complex heterocyclic molecules.[45]

A modification of the one-pot Mannich reaction was 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.[46]

The synthesis of dihydro-1,3-benzoxazines were obtained *via* one-pot condensation of α- or β-naphthol, aniline and formaldehyde using thiamine hydrochloride as catalyst.[47]

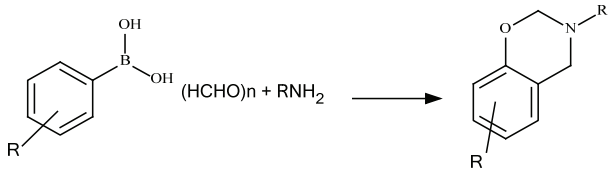


Scheme 3. Illustration of the one-pot (a), two-pot (b) and three-pot (c) synthetic method for the preparation of benzoxazine.



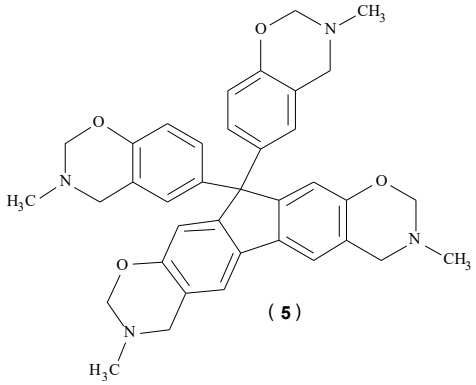
(**5**)

Fig. 4. Structure of compound **5**.



Scheme 4. Synthesis of 1,3-benzoxazines using arylboronic acids.

The preparation of a novel tetrafunctional oxazine monomer (**6**) containing 1,3-benzoxazine and fluorene-oxazine was performed through a one-step Mannich condensation reaction (Fig. 5).[48]



(**5**)

Fig. 5. Structure of compound **6**.

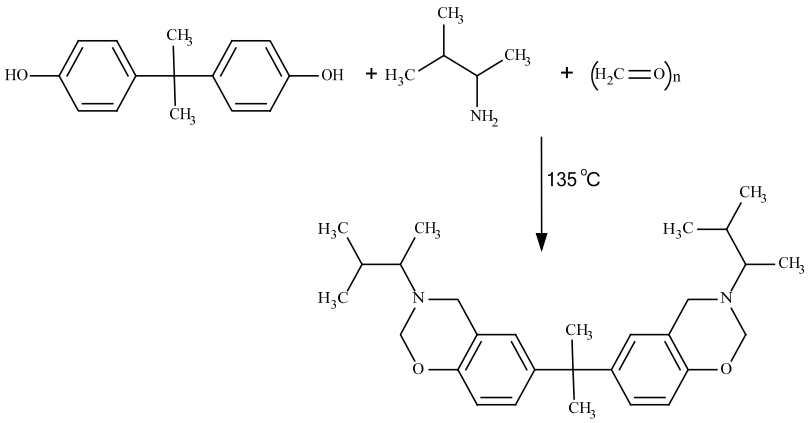
Additionally, benzoxazine monomers were synthesized in high purity and good yield through one-pot reactions from the reaction of bisphenol A with paraformaldehyde and isomeric butylamines, as indicated in Scheme 5.[49]

The Brønsted acidic ionic liquid [HMIm]BF_4 was used as a nonvolatile ecofriendly solvent and catalytic reagent for the one-pot green synthesis of isoxazolyl-3,4-dihydro-2*H*-1,3-benzoxazines (**7**, Fig. 6). This method afforded excellent yields in short reaction times, and avoids multistep synthesis.[50]

Moreover, 3,4-dihydro-2*H*-1,3-benzoxazines were synthesized in one pot by the directed *ortho*-lithiation of phenols.[51]

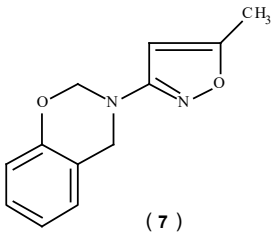
2.1.2. Two-step Mannich condensation

On the other hand, the two-step synthesis, first described by Holly and Cope,[52] is performed in solvent. The reaction by this method proceeds by first



Scheme 5. Synthesis of benzoxazines from bisphenol A.

adding amine to formaldehyde at lower temperatures to form an *N*,*N*-dihydroxymethylamine, which then reacts with the labile hydrogen of the hydroxyl group on the *ortho*-position of the phenol at an elevated temperature to form the oxazine ring.[53] The slow reaction rate and the 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 increasing the costs of the products and creating environmental problems. To overcome these drawbacks, the solvent-free synthesis was developed.[32]



(**7**)

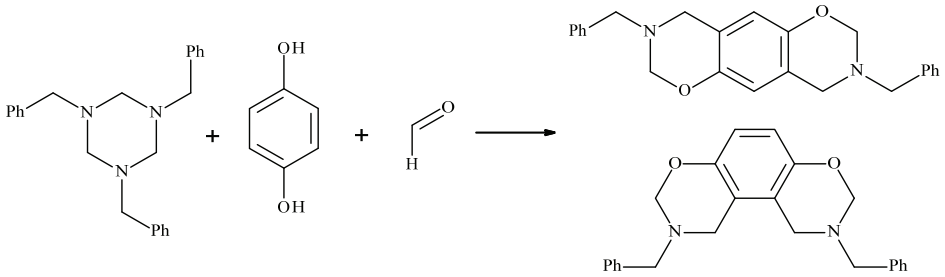
Fig. 6. Structure of compound **7**.

Thereafter, the two-step reaction involved the formation of perhydrotriazine (intermediate) in the reaction of formaldehyde with benzylamine. This intermediate reacts with phenol and formaldehyde in acidic condition to give benzoxazines (Scheme 6).[13] This method has been generalized with the proposed mechanism in the literature.[10]

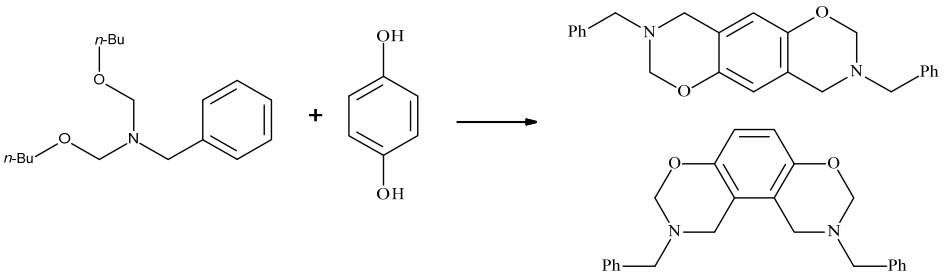
Additionally, another way was reported through the formation of bis(alkoxymethyl)alkylamine as intermediate, which was obtained in the reaction of alkyl amine with alcohol (Scheme 7).[54]

Notably, these methods cannot be used in the presence of a primary amine similar as one-pot methods. However, these methods were enabled in cases of reactive phenolic compounds, such as hydroxybenzaldehyde and hydroxybenzoic

acid, allowing a primary amine to be used. Due to the diversity of substituents on both the phenol and the amine, a large variety of functional benzoxazines could be produced.



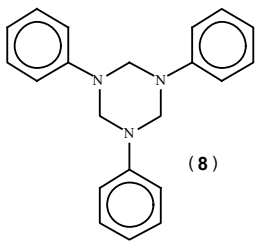
Scheme 6. Synthesis of benzoxazines with 1,3,5-hexahydrotriazine.



Scheme 7. Synthesis of benzoxazines with bis(alkoxymethyl)alkylamine.

In the synthesis of benzoxazine in a two-step reaction, the first step involved the formation of 1,3,5-tris(pentafluorophenyl)perhydro-1,3,5-triazine, then the reaction between the acid-promoted cleavage of the perhydrotriazine with substituted phenol and formaldehyde occurred. The latter step is considered the rate determining step reaction.[55]

Furthermore, 1,3,5-triphenylhexahydro-1,3,5-triazine (**8**, Fig. 7) was formed as intermediate during the solventless synthesis of benzoxazines. This triazine could be used as an amine source instead of the direct use of a primary amine.[10,56]

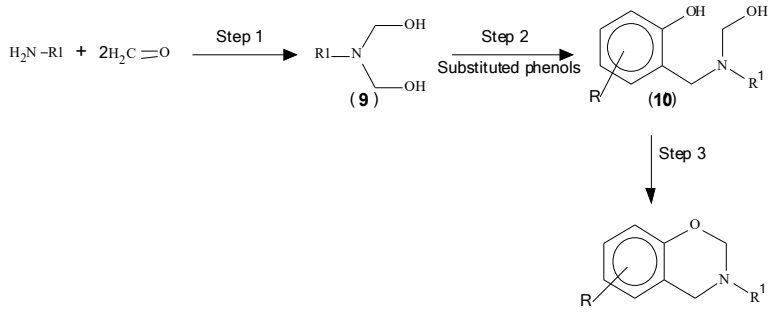


(**8**)

Fig. 7. Structure of compound **8**.

2.1.3. Three-step Mannich reaction

Brurke suggested a reaction pathway for a Mannich condensation, *i.e.*, initially, *N*,*N*-dihydroxymethylamine (**9**) is formed that is then converted into a *N*-hydroxymethyl Mannich base (**10**), which finally reacts with phenol to generate 1,3-benzoxazines (Scheme 8).[42,57,58]

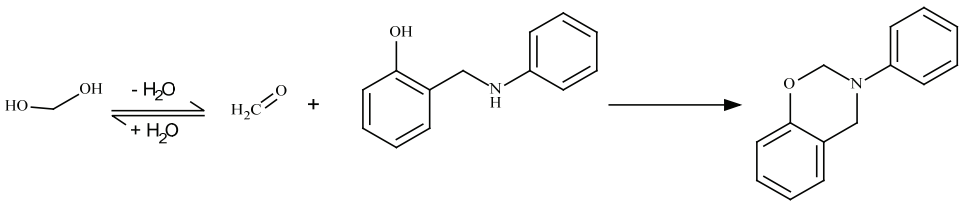


Scheme 8. Three-step Mannich reaction for the synthesis of 1,3-benzoxazines.

Moreover, a three-step method was developed by imine formation between salicylaldehyde and the selected primary amine as first step. The second step is the reduction of this imine into secondary amine and finally, ring closure using formaldehyde.[59]

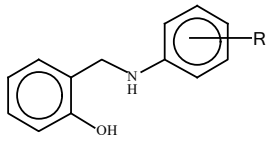
The advantage of this method is the ability to control each step and the usage of amines that are incompatible in classical methods. Furthermore, the use of this method avoids the formation of undesirable oligomeric or polymeric species, thus leading to a simple workup and improving the yield and purity of the final product. As an example, salicylaldehyde[59] or 4-aminophenol can be used as the phenol or amine source, respectively. In addition, free phenol-containing benzoxazines can also be synthesized easily by this method. Moreover, asymmetrical benzoxazine derivatives can easily be obtained by choosing a suitable salicylaldehyde.[60]

Furthermore, 1,3-benzoxazine derivatives were formed *via* dehydration of methylene glycol to formaldehyde, which reacts with a Mannich base as indicated in Scheme 9.[26]



Scheme 9. Three-step Mannich reaction for the synthesis of 1,3-benzoxazines.

Salicylaldehyde was condensed with primary aromatic amines to give imine compounds which on reduction with $NaBH_4$, yielded intermediate **11** at room temperature (Fig. 8). Compound **11** subsequently undergoes ring-closure reaction with paraformaldehyde in toluene at 60 °C to give benzoxazine monomer by a three-pot method. [27,58]

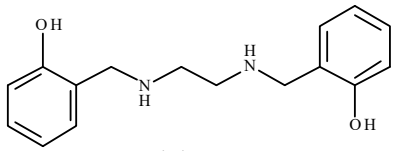


(**11**)

Fig. 8. Structure of compound **11**.

Furthermore, the kinetics of the reaction between 2-[(phenylamino)methyl]-phenol (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 the benzoxazine to the Mannich base.[26]

Moreover, a di-functional benzoxazine was prepared in the reaction of 1,2-bis-(*ortho*-hydroxybenzylamino)ethane (**12**, Fig. 9) with formaldehyde.[61] The advantage of this synthesis is the flexible substitution of functional groups on the oxazine ring. In addition, another substitution on the oxazine ring could be achieved by ring closure of salicylaldehyde with various aldehydes (aliphatic or aromatic) instead of formaldehyde.[62] Moreover, the oxazine ring could be closed by the reaction of salicylaldehyde not only with aldehydes but also with methylene bromide.[63] Furthermore, this method enhances the formation of benzoxazine monomer only because its intramolecular cyclization permits the reaction conditions to moderate, leading to the minimization of side reactions caused by high temperatures. However, in the case of a one-pot method, sometimes relatively high temperature are required to close the oxazine ring leading to the formation of undesirable oligomeric or polymeric species.

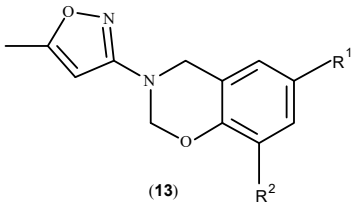


(**12**)

Fig. 9. Structure of compound **12**.

On the other hand, for further limitation on the drawbacks of Mannich methods, many catalysts have been used for the growing number of benzoxazines syntheses. As example, 2,3-diaryl-3,4-dihydro-*2H*-1,3-benzoxazines have been prepared in high yields from *o*-(arylaminomethyl)phenols and aromatic aldehydes in the presence of $SnCl_4$.[27] In addition, the condensation of hexakis(methoxy-methyl)melamine (HMMM) with mono- or di-substituted phenols in *p*-xylene

catalyzed by di-nonylnaphthalenedisulfonic acid[64] gave 1,3-benzoxazines. Finally, I_2/H_2O_2-promoted intramolecular C–O bond formation reaction of a variety of 1-(aminoalkyl)-2-naphthols or 2-(aminoalkyl)phenols yielded the corresponding 1,3-oxazines. The reaction is simple, economic, and proceeds at room temperature in ethanol as solvent.[65]



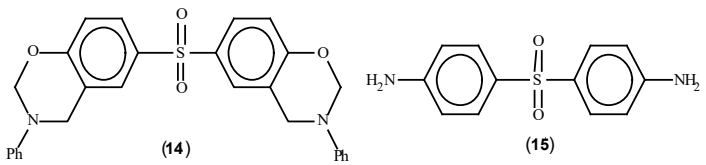
(13)

Fig. 10. Structure of compound **13**.

2.2. Synthesis of a sulfone-scaffold benzoxazine monomer

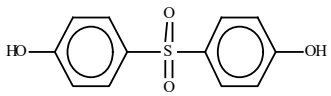
On the other hand, the formation of byproducts (oligomers or polymers) in Mannich reactions has been considered beneficial in many industrial usages in spite of being considered a drawback in the preparation of benzoxazine monomers. Thus, 3,4-dihydro-2*H*-1,3-benzoxazines can yield polymeric structures through ring-opening of the cyclic monomers. These polymeric structures are commercially important and widely applied in the areas of coatings, adhesives, microelectronics, aerospace, *etc*.[66,67] One example of commercially importance are polysulfones (PSU), 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.[68,69]

Sulfone-scaffold 3,4-dihydro-2*H*-1,3-benzoxazines (**14**) were prepared in high purity from 4,4′-diaminodiphenyl sulfone (**15**),[70,71] 4,4′-sulfonylbisphenol (**16**)[25] or polysufone[72] and paraformaldehyde and phenol using a high boiling point, nonpolar solvent, see Fig. 11.



(14)

(15)



(16)

Fig. 11. Sulfone-based 1,3-benzoxazines, 4,4′-diaminodiphenyl sulfone and 4,4′-sulfonylbisphenol.

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 consumption of petroleum oil and the increasingly serious environmental pollution, the utilization of bio-based feedstock for the green preparation of these derivatives has gained more attention in all domains.[73,74]

In the synthesis of benzoxazines, renewable starting materials are used due to their availability, low toxicity, and relatively low cost. Thus, naturally occurring phenols, such as chavicol,[75] guaiacol,[76] cardanol[77,78]and lignocelluloses,[79,80] are used in the synthesis of 1,3-benzoxazines (Fig. 12).

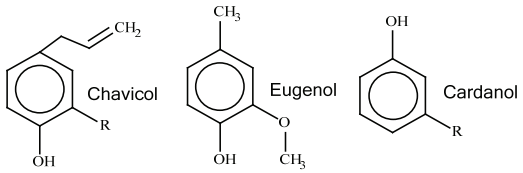
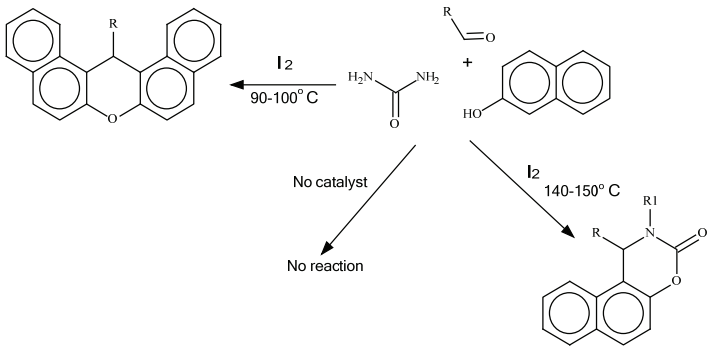


Fig. 12. The structures of some naturally occurring phenols.

*2.4. Synthesis of 4*H*-1,3-benzoxazin-2-ones*

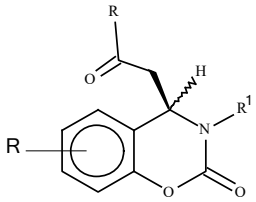
The benzoxazinones were prepared in the one-pot reaction of 2-naphthol, an aldehyde and urea in the presence of various catalysts such as iodine (Scheme 10), P_2O_5 and $Yb(OTf)_3$,[81] cellulose sulfuric acid,[82] cyanuric chloride,[83] phosphomolybdic acid,[84] pyridinium-based ionic liquid,[85] thiamine hydrochloride,[86] zinc triflate,[87] montmorillonite K10,[88] zinc oxide,[89] TMSCl/NaI,[90] guanidine hydrochloride,[91] *etc*.



Scheme 10. One-pot Mannich reaction using iodine as catalyst.

On the other hand, by condensation of (aminoalkyl)naphthols with phosgene[92] or 1,1′-carbonyl diimidazole[93] in the presence of triethylamine, 2*H*-1,3--oxazin-2-one derivatives were produced in moderate yields. In addition, 1,3-

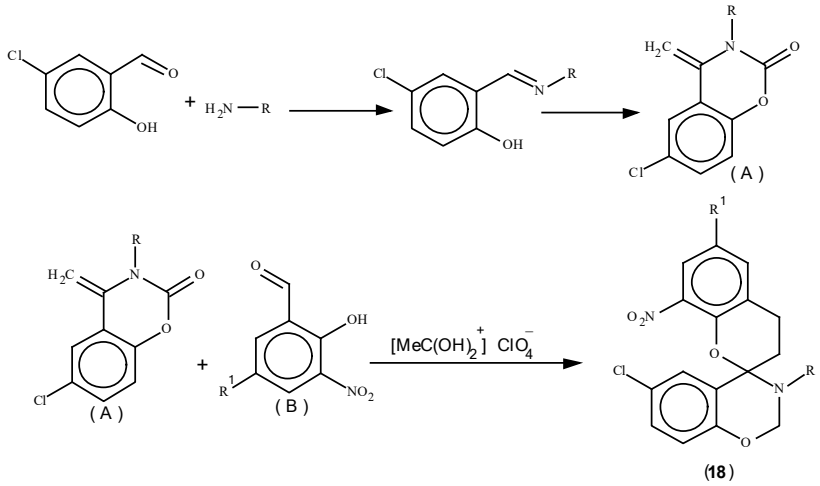
-benzoxazin-2-ones (**17**, Fig. 13) were prepared by reaction of 2-hydroxyphenyl-substituted enones and isocyanates using bisguanidinium salt as catalyst.[94]



(**17**)

Fig. 13. Structure of compounds **17**.

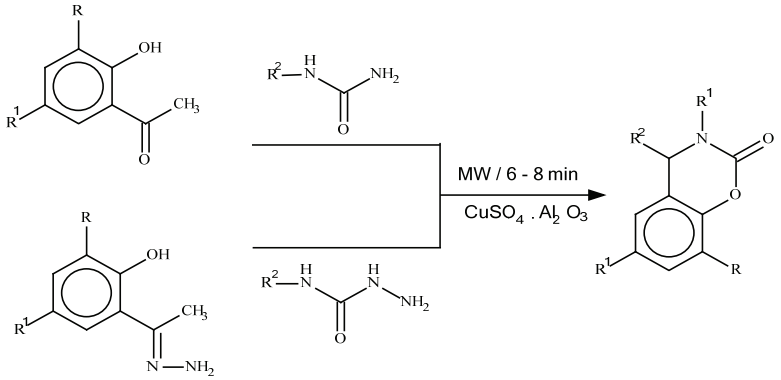
Furthermore, 2*H*-1,3-benzoxazine-2-ones were synthesized in the reaction of substituted salicylaldehydes with a primary amine and an aldehyde. As example, spiropyrans based on benzoxazinone (**18**) were synthesized in the reaction of compound (A) with compound (B) using protonated acetic acid $[MeC(OH)_2]^+ClO_4^-$ as catalyst, as indicated in Scheme 11.[95]



Scheme 11. Synthesis of spiropyrans based on 2*H*-1,3-benzoxazin-2-one.

In addition, 3,4-dihydro-2*H*-1,3-oxazin-2-ones were synthesized by intramolecular cyclization of aryl carbamates, which were produced from the reaction of aryl isocyanate and the corresponding 2-(nitroethenyl)phenol under basic conditions.[96]

Via the reaction of salicylaldehyde/2-hydroxyacetophenone or its hydrazones and substituted urea or substituted semicarbazide under solventless microwave irradiation,[97] 2*H*-1,3-benzoxazin-2-ones were synthesized in a one-pot method (Scheme 12).

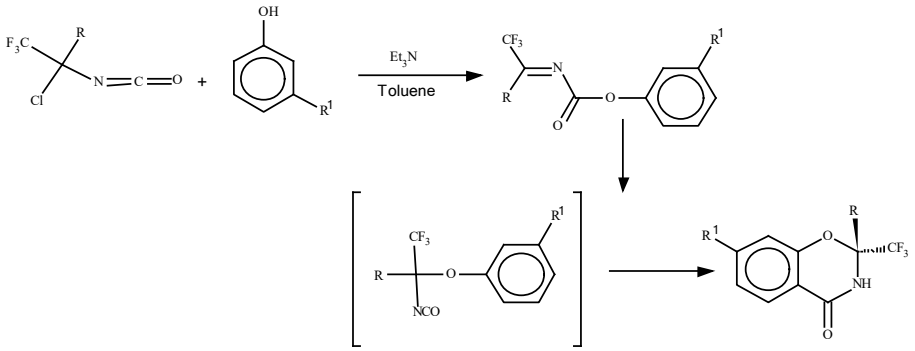


Scheme 12. Synthesis of 2*H*-1,3-benzoxazin-2-ones from salicylaldehyde/2-hydroxyacetophenone.

*2.5. Synthesis of 2*H*-1,3-benzoxazin-4-one*

In the condensation of an acid halide with salicylamides in the presence of pyridine using boiling xylene as solvent, substituted 2*H*-1,3-benzoxazin-4-ones were formed in one-step. They were also formed in a two-step method by refluxing the salicylamide with aroyl chloride in pyridine followed by cyclization of the isolated intermediate by hydrogen chloride.[98]

Furthermore, by carbonylation-cyclization of *ortho*-halophenols and cyanamide[99] or by treatment of the corresponding 2-hydroxycarboxamides with a formaldehyde/formic acid mixture,[100] the corresponding 4*H*-1,3-benzoxazin-4--ones were synthesized. 2-(Trichloromethyl) and 2-(dichloromethylene)-2*H*-1,3-benzoxazine derivatives were obtained *via* intramolecular cyclization of *N*-(*α*-aryloxytrichloroethyl)imidoyl chlorides through dehydrochlorination.[101] Additionally, 2-aryl-2-(trifluoromethyl)-2,3-dihydro-4*H*-benzoxazin-4-ones were synthesized *via* intramolecular thermal cyclization of 3-alkoxyphenyl *N*-(1-aryl-2,2,2-trifluoroethylidene)carbamates, which were produced in the reaction of 1-aryl-2,2,2-trifluoroethyl isocyanates with 3-alkoxyphenols (Scheme 13).[102]



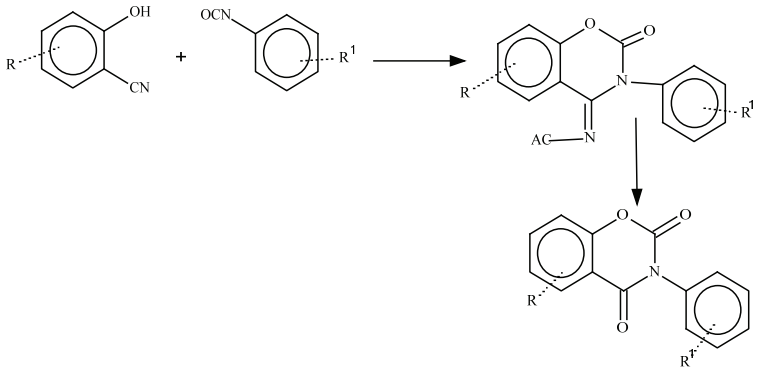
Scheme 13. Synthesis of 2-aryl-2-(trifluoromethyl)-2,3-dihydro-4*H*-benzoxazin-4-ones.

Moreover, 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones have been synthesized by intermolecular cyclization reactions of *o*-halobenzamides, LiOH and dichloromethane using copper-catalyzed tandem reaction.[103]

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

The 2*H*-1,3-benzoxazine-2,4(3*H*)-diones were synthesized from the reaction of acardic acids with triphosgene,[104] from the reaction of phthaloyl chlorides with acetone oxime[105] or from the reaction of salicylate esters with isocyanates.[106]

Reaction of 2-hydroxybenzonitrile with isocyanates[107] using triethylamine as catalyst has been performed to obtain the target compounds as in Scheme 14.



Scheme 14. Synthesis of 2*H*-1,3-benzoxazine-2,4(3*H*)-diones from 2-hydroxybenzonitrile and isocyanates.

3. CHEMISTRY OF 1,3-BENZOXAZINE DERIVATIVES

3.1. Unusual behavior of ortho-functional benzoxazines

The formation of intramolecular five-membered ring H-bond between the NH of the amide group and the oxygen of the oxazine ring (Fig. 14) is considered as unusual behavior of *ortho*-functional benzoxazines.[108]

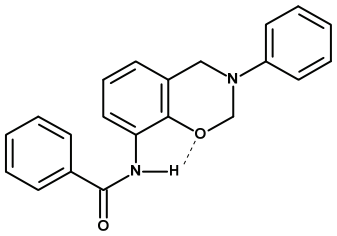


Fig. 14. The intramolecular five-membered ring H-bond in benzoxazines.

Furthermore, it was observed that, *o*-methyl-substituted benzoxazine dimers, as shown in Fig. 15,[109,110] trimers or tetramers exhibit intramolecular hydrogen bonding.[111]

Interestingly, the *o*-substituted benzoxazine dimers are used as novel ligands for rare earth metal ions, *e.g.*, the Ce(III) ion. It was found that, the substituted groups on the *para*-positions of benzoxazine dimers do not affect the formation of complexes.[112]

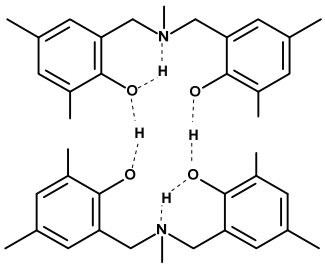
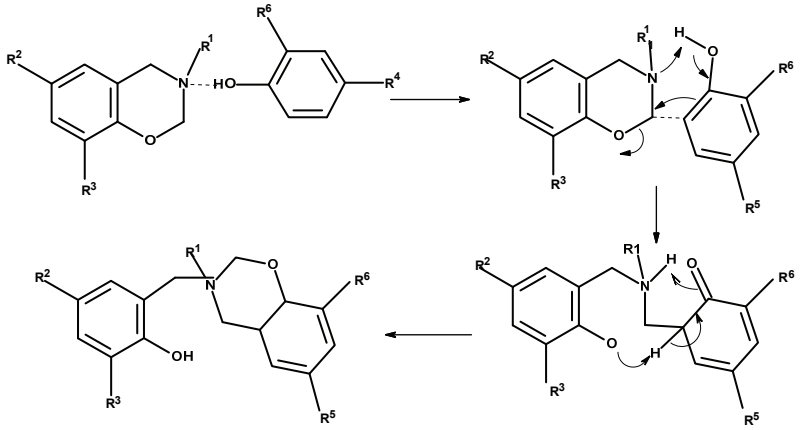


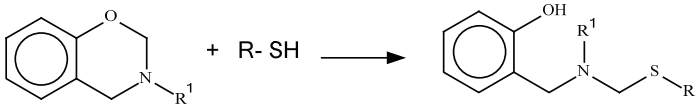
Fig. 15. The molecular structure of a pair of methyl benzoxazine dimers.

3.2. Ring opening of benzoxazines

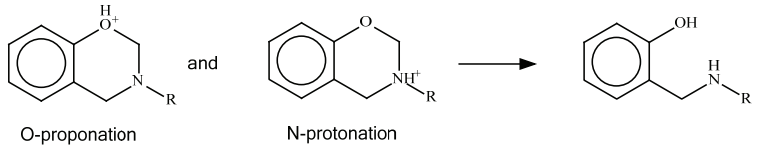
The dihydro-derivatives are more stable than the 1,3-benzoxazines towards acidic agents. The ring opening ability depends on the basicity of the oxygen and nitrogen atoms.[113] In compounds with an active hydrogen, such as indoles, carbazole, imides, and aliphatic nitro compounds, even phenol (Scheme 15),[114,115] thiols (Scheme 16)[116] or carboxylic acids,[117] auto-ring opening occurs as shown in Schemes 15–17. The benzoxazines ring opening begins with protonation of oxygen and nitrogen atoms,[118] as indicated in Scheme 17.



Scheme 15. The mechanism of benzoxazines ring opening.

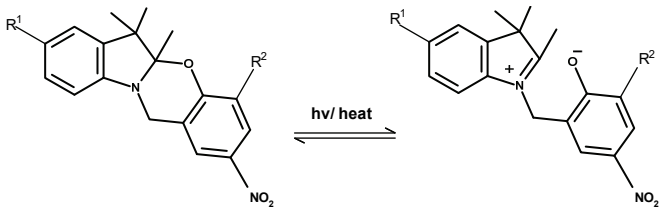


Scheme 16. The auto-ring opening reaction of 1,3-benzoxazines.



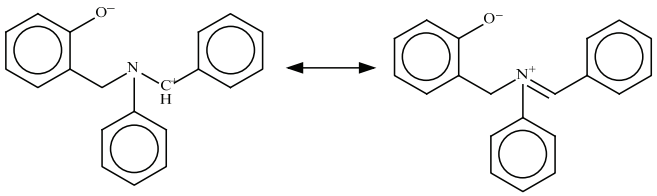
Scheme 17. The benzoxazines ring opening by protonation of oxygen and nitrogen atoms.

Furthermore, ring opening is promoted by irradiation with UV radiation (Scheme 18),[119,120] resulting in the formation of two chromophoric systems (the 3*H*-indolium cation and the 4-nitrophenolate anion moiety).[119]



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

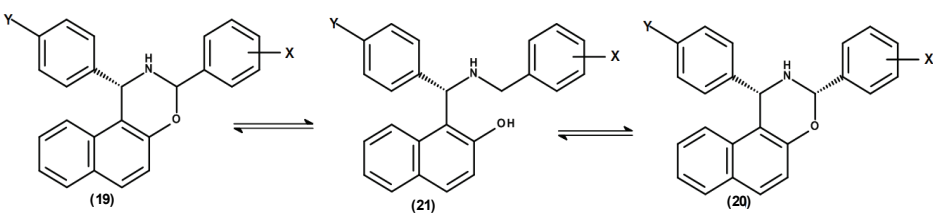
In addition, the ring opening reaction of substituted benzoxazine would readily occur by heating due to the resonance stabilization of the iminium ion, as indicated in Scheme 19.[121]



Scheme 19. The resonance stabilization of the iminium ion.

3.3. Ring-chain tautomerism

The 1-(substituted phenyl)-3-aryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines undergo ring–chain tautomerism, resulting in predominately the *trans*- (**19**) over the *cis*-configuration (**20**) through compound (**21**), as shown in Scheme 20.[122]

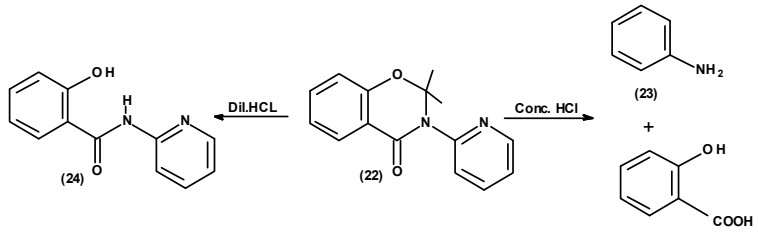


Scheme 20. Naphthoxazines epimerization.

4. REACTIONS OF 1,3-BENZOXAZINE DERIVATIVES

4.1. Hydrolysis with HCl

The benzoxazine derivatives (**22**) are hydrolyzed by HCl to give 2-amino-pyridine (**23**) or *N*-2-pyridylsalicylamide (**24**) depending on the concentration of the acid, as indicated in Scheme 21.[123]



Scheme 21. Effect of acids on benzoxazine derivatives.

4.2. Salt formation

The formation salts of 1,3-benzoxazines has been realized by acidic cyclization of disalicylamide[124] or by acylation of (*o*-aminophenyl)diphenylmethanol with carboxylic acids in the presence of perchloric acid,[125] producing l,3-benzoxazinium perchlorate **25**, Fig. 16.

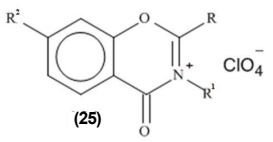


Fig. 16. Structure of compound **25**.

4.2.1. Reactions of 4-oxo-4*H*-1,3-benzoxazinium salts

Interestingly, 4-oxo-4*H*-1,3-benzoxazinium perchlorate **26** reacts with the dialdehyde potassium 3,5-diformyl-2,4-dihydroxybenzoate **27** in glacial acetic acid yielding the spiropyran of the 1,3-benzoxazine series through the formation of the intermediate styryl salt **28**. This intermediate has been isolated and then cyclized under the action of triethylamine in anhydrous diethyl ether to yield compound **29**, as shown in Scheme 22.[126,127]

4.3. Reaction with alkyl halides

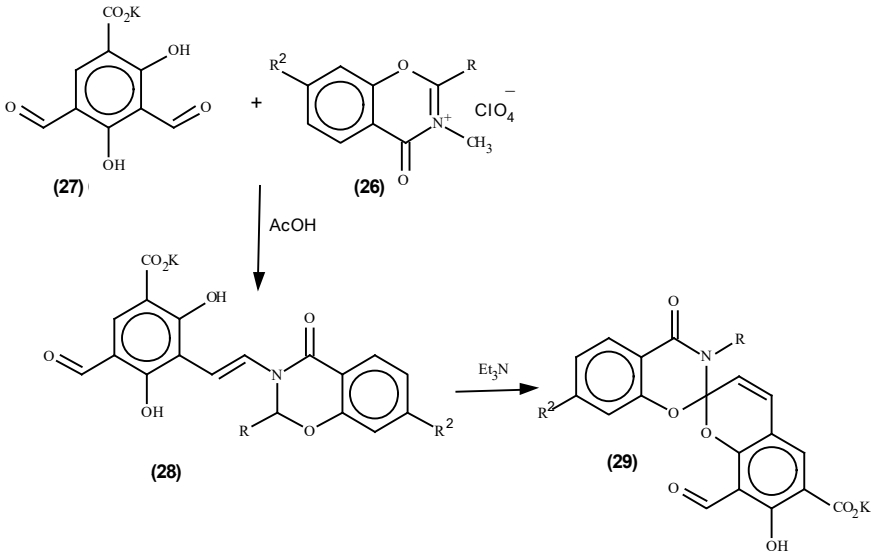
1,3-Benzoxazine-2,4-dione was reacted with alkyl halide in the presence of K_2CO_3[128,129] yielding *N*-substituted derivatives (Scheme 23).

4.4. Nucleophilic substitution reaction

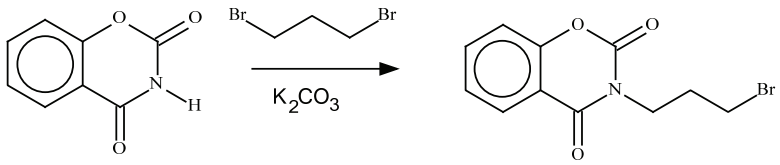
4.4.1. Reaction with pyridine *N*-oxide

2,3-Dihydro-2,2-dimethyl-3-(2-pyridyl)-4*H*-1,3-benzoxazin-4-one (**30**) was produced by refluxing the 4-chloro-derivative of benzoxazine (**31**) with two

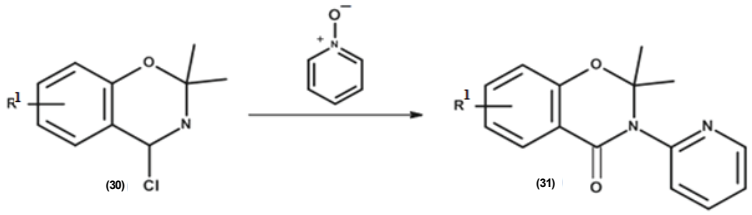
moles of pyridine *N*-oxide in dichloromethane through a nucleophilic substitution reaction followed by rearrangement[123] (Scheme 24).



Scheme 22. Reaction of 4-oxo-4*H*-1,3-benzoxazinium salts with 3,5-diformyl-2,4-dihydroxybenzoate.



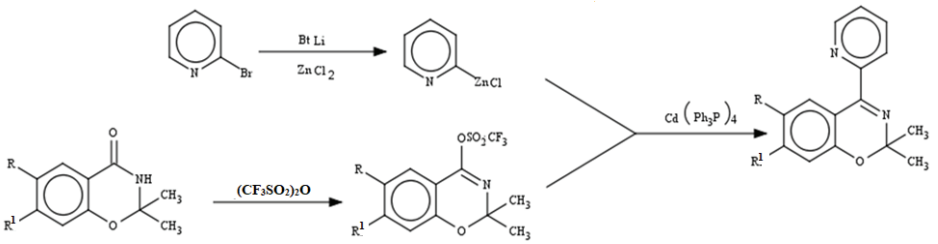
Scheme 23. Reaction of 1,3-benzoxazine-2,4-dione with alkyl halides.



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

4.4.2. Reaction with organometalic compounds

2,3-Dihydro-2,2-dimethyl-1,3-benzoxazin-4-one derivatives react with organometallic compounds by nucleophilic substitution as shown in Scheme 25.[130]



Scheme 25. Reaction of 1,3-benzoxazin-4-ones with organometalic compounds.

5. BIOLOGICAL ACTIVITIES

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

5. 1. Antiviral therapy

Elbasvir (**32**, Fig. 17)[131,132] is potent inhibitor of the HCV NS5A protein and is used in combination with grazoprevir for the treatment of the hepatitis C virus (HCV) NS3/4A.[133] In addition, grazoprevir/elbasvir plus ribavirin were examined as a new treatment option for patients after failure of triple therapy containing an earlier-generation protease inhibitor.[134]

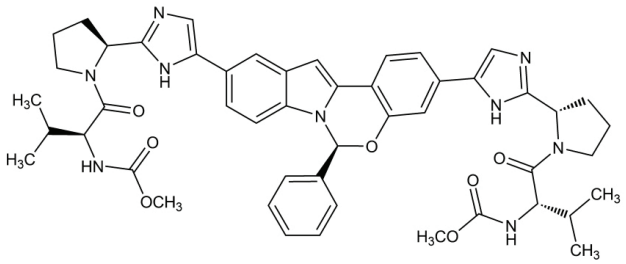


Fig. 17. Structure of elbasvir (**32**).

5.2. Anti-tuberculosis activity

The antimycobacterial activity of various substituted 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dithiones and 3-phenyl-2*H*-benzoxazine-2,4(3*H*)-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-dione ring increases the activity, as well as the similar replacement in position 2.[135,136] *In vitro* antimycobacterial activity against *Mycobacterium tuberculosis*, *M. avium* and two strains of *M. kansasii* were studied. Furthermore, the antimycobacterial activity increased with replacement of the carbonyl group by the thiocarbonyl group in the starting 3-(4-alkylphenyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-diones.[137,138]

5.3. Fungicidal and pesticide activities

A series of 2,3-disubstituted-3,4-dihydro-2*H*-1,3-benzoxazines was prepared by reaction of aza-acetalizations of aromatic aldehydes with *2*-(*N*-substituted aminomethyl)phenols in the presence of trimethylsilyl chloride (TMSCl). The fungicidal activities were evaluated, and some of these compounds exhibited activity against *Rhizoctonia solani*.[62] Additionally, a series of 2,3-diaryl-3,4--dihydro-2*H*-1,3-benzoxazines was prepared in high yields from *o*-arylamino-methylphenols and aromatic aldehydes in the presence of $SnCl_4$. Their fungicidal activities were investigated. Some of the products showed good fungicidal activities against *R. solani*.[27] Furthermore, novel naphtho[1,2-*e*][1,3]oxazines bearing an arylsulfonamide moiety were synthesized and evaluated for their anticancer and antifungal activities.[139]

Moreover, substituted 8-hydroxy-3-phenyl-2*H*-1,3-benzoxazine-2,4-(3*H*)--diones were synthesized by cyclization of the corresponding dihydroxy-*N*-phenylbenzamides with methyl chloroformate. Thionation of the compounds was performed using Lawesson's reagent. All compounds were tested *in vitro* for their antifungal activity against eight test strains. The compounds showed moderate activity.[140]

In addition, the compounds 3,4-dihydro-4-methyl-3-nonyl-2*H*-1,3-benzoxazines and 3-decyl-3,4-dihydro-4-methyl-2*H*-1,3-benzoxazines were studied and investigated as pesticides.[141]

5.4. Anticovulsive activities

2,4-Dioxo-2*H*-1,3-benzoxazine-3(4*H*)-butanoic acid (BXDBA) shows good anticonvulsive activity and its ability to block bicuculline-induced convulsions suggests that it could be a $GABA_A$ mimetic drug.[142,143]

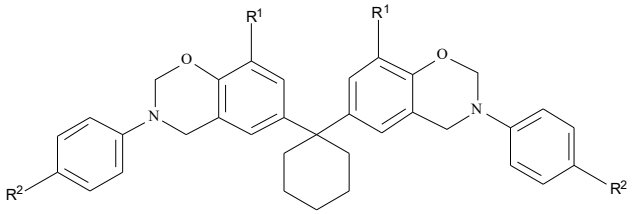
5.5. Antibacterial activities

Substituted *N*-[(benzylamino)thioxomethyl]-2-hydroxybenzamides were synthesized using sodium bicarbonate and benzyl amine with 2-thioxo-substituted-1,3-benzoxazines. These derivatives were investigated as antibacterial and antifungal agents.[144]

Moreover, a series of 3,3′-(1,2-ethanediyl)-bis[3,4-dihydro-2*H*-1,3-benzoxazine derivatives (**33**, Fig. 18) 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. *In vitro* 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 showed significant *in vitro* antimicrobial effects.[145]

Benzofuranyl-1,3-benzoxazines and benzofuranyl-1,3-benzoxazin-2-ones were synthesized *via* coupling benzofuran with 1,3-benzoxazines and 1,3-benzo-

xazin-2-ones through –CONH– and –$COCH_2$– bridges, respectively. The antimicrobial activity of these compounds was reported.[146]



(33)

Fig. 18. Structure of compound **33**.

5.6. Anticancer activities

Furthermore, naphtho[1,2-*e*][1,3]oxazines bearing a arylsulfonamide moiety, synthesized *via* a one-pot method, showed remarkable activities against MCF-7 (breast) and HCT116 (colon) cancers.[139] In addition, 1,3-benzoxazines having a flavone moiety at the 3-position also showed activities against MCF-7.[147]

2*H*-1,3-Oxazine-2,6(3*H*)-dione (3-oxauracil) exhibited cytotoxic activity against the tested cancer cell lines (pancreatic, colon, neuroendocrine and non-small cell lung). These derivatives were studied as an inhibitor of selected neoplastic cell growth *in vivo*.[148]

In addition, a series of modified hexacyclic camptothecin derivatives containing a 1,3-oxazine ring was synthesized. All compounds were assayed *in vitro* against nine human cancer cell lines. Some of these compounds showed about 13-fold greater potency than camptothecin, and about six-fold greater potency than topotecan toward HEPG-2. Furthermore, the *N*-alkyl-substituted derivatives were more potent than the *N*-aryl- and *N*-benzyl-substituted compounds.[149]

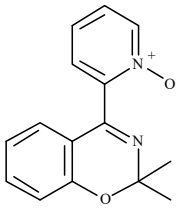
The synthesis of 6-aryl, 8-aryl, and 8-aryl-6-chloro-2-morpholino-1,3-benzoxazines with potent activity against PI3K and DNA-PK was studied. A compound with the 8-(naphthalen-1-yl) scaffold showed strong anti-proliferative activity against A498 renal cancer cells, which warrants further investigation.[150]

5.7. Antihypertinsive activities

The antihypertensive and cardiovascular properties of a new potassium channel opener, TCV-295 (**34**), were studied in rats and dogs. In conscious, spontaneously hypertensive rats (SHR), TCV-295 reduced blood pressure (BP) with a low dose dependence and with slow onset of action being observed.[151]

An efficient process for potassium channel opener TCV-295, based on 4-(2--pyridyl)-2*H*-1,3-benzoxazine ring formation from 2-(*o*-hydroxybenzoyl)pyridine derivative by the NH_4I/piperidine/2,2-dimethoxypropane system and subsequent selective pyridine-*N*-oxidation using dimethyldioxirane, was examined.[152]

In addition, to explore K^+ channel openers, a series of 1,3-benzoxazine derivatives with a 2-pyridine-1-oxide group at C4 (**34**, Fig. 19) was synthesized by one-pot 1,3-benzoxazine skeleton formation and 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 $BaCl_2$-induced and high KCl-induced contraction of rat aorta to identify potential K^+ channel openers, and also for oral hypotensive effects in spontaneously hypertensive rats.[130]



(34)

Fig. 19. Structure of compound **34**.

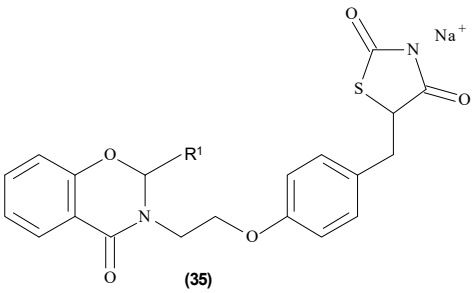
5.8. Antimalarial activities

A series of 6-(2-chloroquinolin-3-yl)-4-(substituted phenyl)-6*H*-1,3-oxazin-2-amines was synthesized and evaluated *in vitro* for antimalarial efficacy against chloroquine sensitive (MRC-02) and chloroquine resistant (RKL9) strains of *Plasmodium falciparum.*[153]

The antimalarial activities of the resulting benzoxazines, their isosteric tetrahydroquinazoline derivatives, and febrifugine-based quinazolin-4-ones were examined *in vitro* (against *P. falciparum*) and *in vivo* (against *P. berghei*).[138]

5.9. Antidiabetic and hypolipidaemic activity

A series of 5-{{4-[2-(4-oxo-2*H*-1,3-benzoxazin-3(4*H*)-yl)ethoxy]phenyl}methyl}thiazolidine-2,4-diones was synthesized and investigated for their plasma glucose and plasma triglyceride lowering activity. In addition the synthesized 2,4-thiazolidinedione derivatives of 1,3-benzoxazinone were evaluated for their antidiabetic and hypolipidaemic potential. For example, DRF-2519 (**35**, Fig. 20) showed potent dual PPAR activation.[154]



(35)

Fig. 20. Structure of compound **35**.

5.10. Receptor antagonist activity

The synthesis and pharmacology of benzoxazines (**36**, Fig. 21) were investigated as highly selective antagonists at M_4 muscarinic receptors.[155]

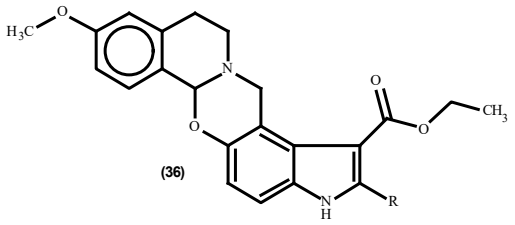


Fig. 21. Structure of compound **36**.

5.11. Antidepressant activity

It was found that 1,3-benzoxazine-2,4-diones (**37**, Fig. 22) have binding affinities for the 5-HT_{1A} and 5-HT_7 receptors.[128] Furthermore, the benzoxazine derivative caroxazone (**38**, Fig. 23), was investigated *in vitro* and *in vivo* as antidepressant (Ro 11-1163) and as a specific and short-acting MAO-A inhibitor.[156]

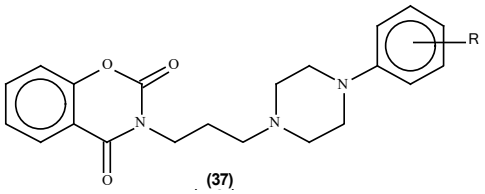


Fig. 22. Structure of compound **37**.

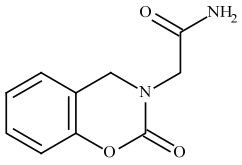


Fig. 23. Structure of compound **38**.

5.12. Anti-platelet aggregation activity

A series of 2,8-disubstituted benzoxazinones (**39**, Fig. 24) was synthesized and studied as anti-platelet aggregation agents *via* inhibition of superoxide anion generation and inhibition of neutrophile elastase release assays. It was found that, the synthesized compounds were more potent than aspirin on arachidonic acid-induced platelet aggregation.[157,158]

5.13. Miscellaneous activities

In addition, other benzoxazine compounds have anti-inflammatory activities, *e.g.*, compounds **40** and **41**,[30] and analgesic and antipyretic properties, such as

chlorthenoxazin (**42**), Fig. 25.[19,30] Furthermore, these derivatives are used as specific inhibitors of the Tissue Factor (TF)/Factor Via (Via)-induced pathway of coagulation, as reported in the literature.[159]

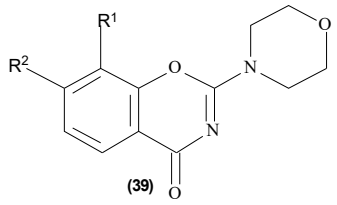


Fig. 24. Structure of compound **39**.

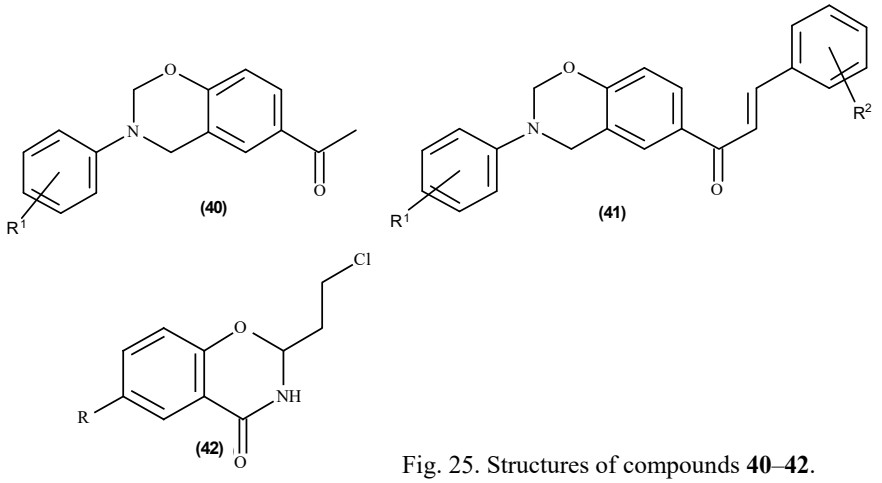


Fig. 25. Structures of compounds **40**–**42**.

CONCLUSIONS

In conclusion, the synthetic potential and transformations of 3,4-dihydro-2*H*--1,3-benzoxazines remain largely of interest. The 3,4-dihydro-2*H*-1,3-benzoxazines are flexible and tough, which lead the molecules to have diverse workable site for substitution. In addition, they exhibit a wide range of biological activities, such as herbicides and agricultural microbiocides, and they show diverse 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, the synthesis of new classes of compounds is a requisite. Consequently, the data collected in this review could be used to provide novel benzoxazine derivatives that could be utilized for the development of new compounds to overcome resistance of drugs for various diseases.

ИЗВОД

ХЕМИЈА И БИОЛОШКА АКТИВНОСТ 3,4-ДИХИДРО-2*H*-1,3-БЕНЗОКСАЗИНА И ЊИХОВИХ ОКСО-ДЕРИВАТА

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Деривати 3,4-дихидро-2*H*-1,3-бензоксазина су природни производи и значајна класа хетероцикличних једињења посебно због њихове изузетне активности у хуманој медицини, фитофармацији и ветерини. Услед могућности за надградњу бензоксазинске структуре, компаративне 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, антиинфламаторна и др. Овај прегледни чланак даје кратак приказ деривата 3,4-дихидро-2*H*-1,3-бензоксазина и њихових оксо-деривата, хемијску реактивност и биоактивност.

(Примљено 30. маја, ревидирано 3. децембра 2018, прихваћено 10. јануара 2019)

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