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Advances in the synthetic strategies of benzoxazoles using 2-aminophenol as a precursor: an up-to-date review

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Benzoxazole is a resourceful and important member of the heteroarenes that connects synthetic organic chemistry to medicinal, pharmaceutical, and industrial areas. It is a bicyclic planar molecule and is the most favorable moiety for researchers because it has been extensively used as a starting material for different mechanistic approaches in drug discovery. The motif exhibits a high possibility of broad substrate scope and functionalization to offer several biological activities like anti-microbial, anti-fungal, anti-cancer, anti-oxidant, anti-inflammatory effects, and so on. There has been a large upsurge in the synthesis of benzoxazole *via* different pathways. The present article presents recent advances in synthetic strategies for benzoxazole derivatives since 2018. A variety of well-organized synthetic methodologies for benzoxazole using 2-aminophenol with aldehydes, ketones, acids, alcohols, isothiocyanates, *ortho*-esters, and alkynones under different reaction conditions and catalysts, *viz.* nanocatalysts, metal catalysts, and ionic liquid catalysts, with other miscellaneous techniques has been summarized.

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1. Introduction

For over a century, heterocyclic compounds have been a privileged area of research in organic chemistry as they have high significance in industrial and medicinal fields to help human society to thrive.[1,2] Heterocyclic scaffolds are momentous for drug discovery and evolution.[3–5] Among all U.S. FDA (United States Food and Drug Administration) approved small-molecule drugs, 75% of the drugs contain nitrogen heteroatoms.[6]

Oxazole is an unsaturated five-membered heterocycle that contains O and N heteroatoms at positions 1 and 3, separated by

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[a] 1,3-oxazole [b] benzo[*d*]oxazole

Fig. 1 Structural formulae of [a] oxazole and [b] benzoxazole.

a C-atom (Fig. 1a), and was first developed in 1947.[7,8] Benzoxazole (Fig. 1b) is a fused bicyclic aromatic planar heterocycle containing benzene and a 1,3-oxazole ring structure.[9,10] The benzene ring is planar and composed of six carbon atoms, while the 1,3-oxazole ring contains one atom each of oxygen (O) and nitrogen (N). The fusion of these rings creates a bridging structure, resulting in a fused bicyclic system with aromatic properties.[7–10] The characteristics of benzoxazole[11,12] are depicted in Table 1.

It is an overarching framework of numerous biologically active compounds that are involved in synthetic, agrochemical, pharmaceutical, and material chemistry.[13,14] This skeleton is prominent in synthetic compounds and exhibits a broad range of biological activities, such as antimicrobial,[15] antitubercular,[16] antioxidant,[17] antifungal,[18] anti-inflammatory,[19] anti-allergic,[20] antihyperglycemic,[21] antidepressant,[22] cytotoxic agents,[23,24] anticonvulsant,[25] and analgesic agents.[26] They are isosteres of

Table 1 Characteristics of benzoxazole

Molecular formula	C_7H_5NO
IUPAC name	1,3-Benzoxazole
Molecular weight	119.121 g mol^{-1}
Melting point	27–30 °C
Boiling point	182 °C
Density	1.2 ± 0.1 g cm^{-3}
Appearance	White to light yellow solid
Odor	Similar to pyridine
Solubility	Insoluble in water

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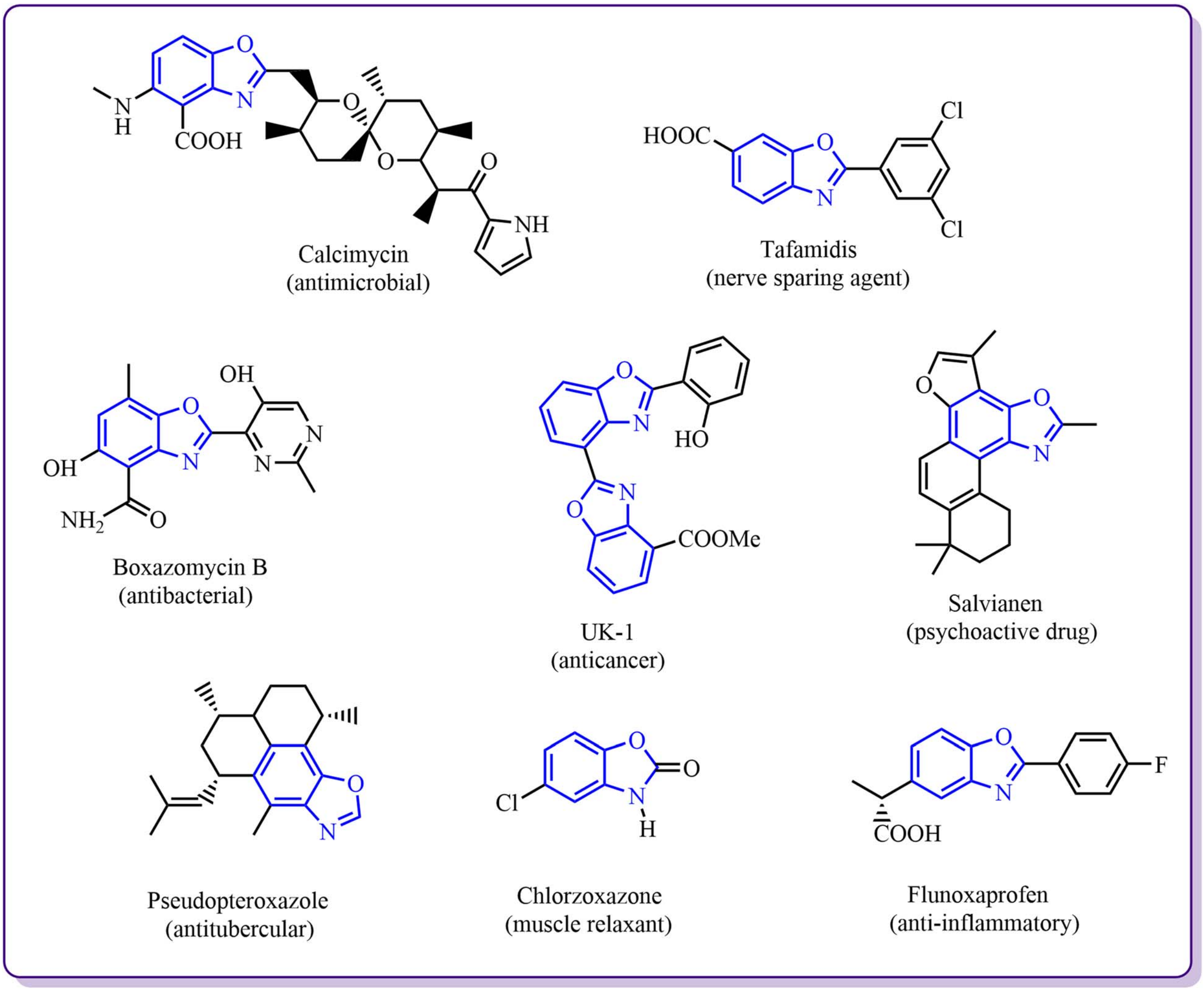


Fig. 2 Market-available drugs with a benzoxazole moiety.

the nucleic acid bases guanine and adenine that help them to easily interact with biological receptors in the human body.[27] There is a diverse range of market-available drugs (Fig. 2) that have benzoxazole as the leading moiety:[28] namely, calcimycin,[29] tafamidis,[30] boxazomycin B,[31] salvianen,[32] UK-1,[33] flunoxaprofen,[34] chlorzoxazone,[35] and pseudopteroxazole.[36] Its derivatives also act as whitening agents,[37] elastase inhibitors,[38] α-glucosidase inhibitors,[39] and fluorescent probes for different metal ions.[40] A diverse array of benzoxazole moieties has been discovered as isolated constituents of various natural product: closoxazole A and B, AJI9561, nataxazole, and nocarbenzoxazole G and F are examples of benzoxazole derivatives that have been found in natural sources[13,14] (Fig. 3).

They are one of the most favorable moieties in terms of synthetic aspects as they have a vast substrate scope and chemoselectivity.[41] They are generally prepared by the condensation of 2-aminophenol with acids and their derivatives,[42] oxidative coupling,[43] or other different methodologies.[44]

In the past few decades, a generous amount of research has been done on the synthesis and biological activity of benzoxazole derivatives. However, previous reviews have conveyed scattered information; therefore, there is a need for a systematic compilation of the most recent research. In this article, several methods of benzoxazole synthesis using 2-aminophenols with different compounds like aldehydes, acids and their derivatives, benzyl alcohol, alkynones, isothiocyanates, ketones, *ortho*-esters, amongst others are demonstrated. This review aims to accentuate several synthetic approaches from the last five years under different conditions to synthesize these scaffolds.

2. Synthesis of benzoxazole derivatives

The traditional approach for benzoxazole synthesis is the condensation of 2-aminophenol with various carbonyl compounds under different reaction conditions (Scheme 1). In this review, several protocols are discussed using 2-aminophenol as a major precursor with different substrates like aldehydes, acids and their derivatives, benzyl alcohol, alkynones, isothiocyanates, ketones, *ortho*-esters, amongst others.

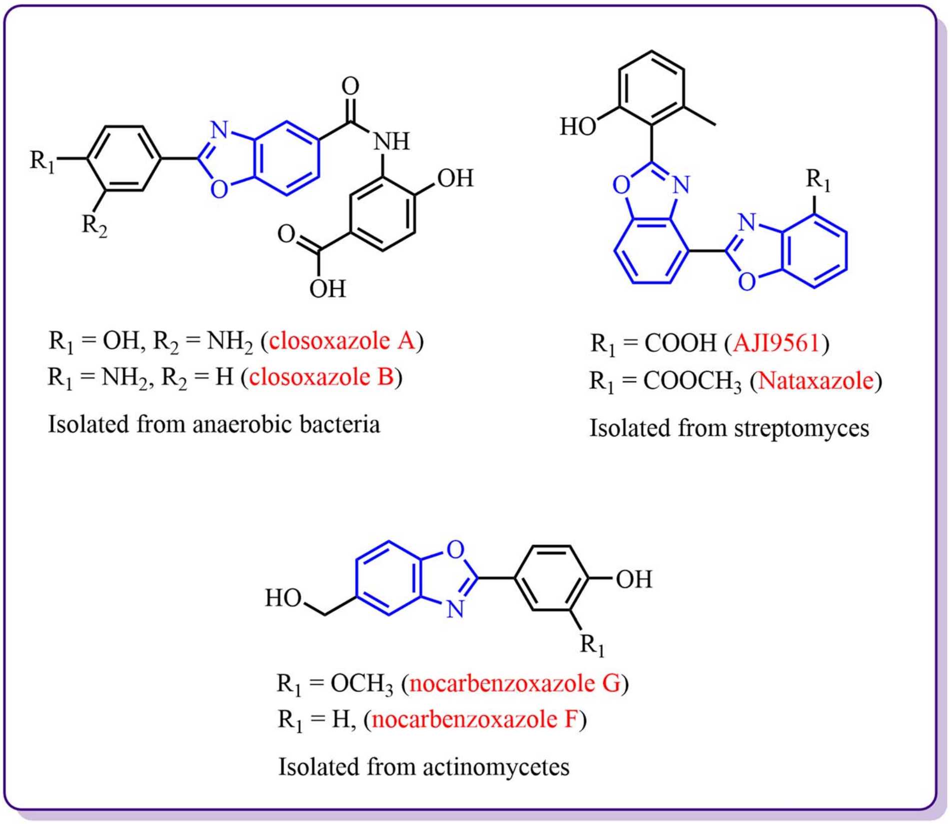
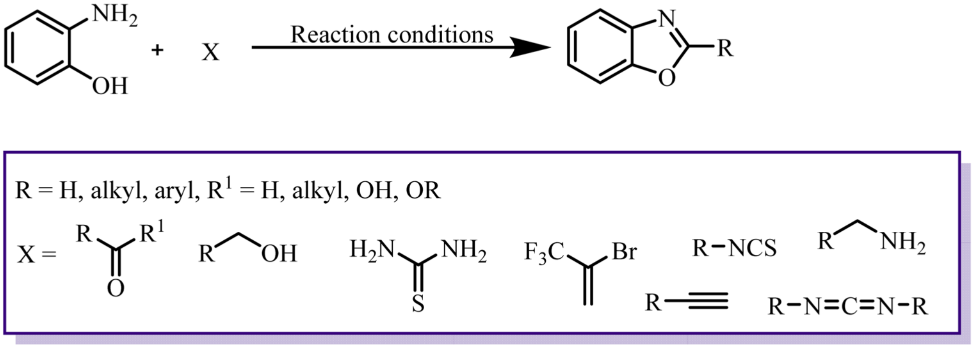


Fig. 3 Diversity of benzoxazole moiety in natural sources.



Scheme 1 A general mechanism for benzoxazole synthesis.

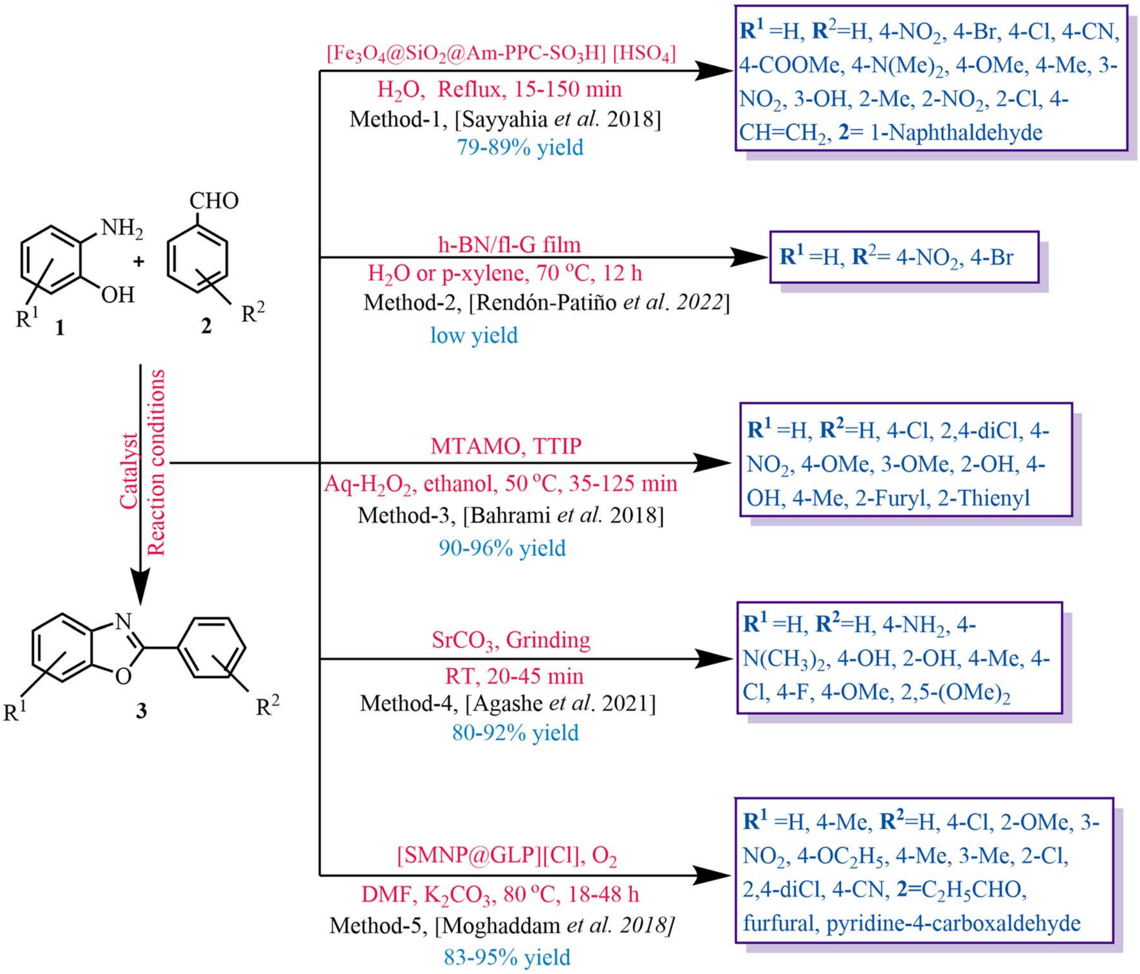
2.1. Reaction of 2-aminophenol with aldehydes

In this part of the review, benzoxazole synthesis using 2-aminophenol with different aldehydes under various circumstances and with catalysts like nanocatalysts, metal catalysts, ionic liquid catalysts, and a few other catalysts are demonstrated.

2.1.1. Nanocatalyzed synthesis. Nanocatalysts are metal-supported nanoparticles which play a major role in the catalysis process. They are used in several organic transformations due to their special properties like high reactivity, high surface area, selectivity, stability at high temperature, and reusability, and they also give optimal yields as they show escalated mixing with reactants and are furthermore readily separated. Several methods for benzoxazole synthesis using nanocatalysts are summarized here.

Sayyahi *et al.*[45] introduced a new magnetic solid acid nanocatalyst ($[Fe_3O_4@SiO_2@Am\text{-}PPC\text{-}SO_3H][HSO_4]$) for benzoxazole synthesis (**3**) using 2-aminophenol (**1**) and aldehyde (**2**) in water under reflux conditions for about 45 min and found 79–89% yield. The catalyst can be easily separated and used for 4 consecutive runs with significant catalytic activity. High yield, shorter reaction time, and ambient reaction conditions are additional benefits of the present protocol (Scheme 2; method 1).

Thin-layered nano h-BN/fl-G films were prepared and applied as an active catalyst to the synthesis of benzoxazole



Scheme 2 Nanocatalyzed synthesis of benzoxazole derivatives.

derivatives (**3**) by Rendón-Patiño and co-authors.[46] The coupling of 2-aminophenol (**1**) and *p*-substituted benzaldehyde (**2**) in water/*p*-xylene at 70 °C showed a low yield of the desired product. The authors further devised an experiment for the reusability of the catalyst for 5 sequential cycles. Low yields and less substrate scope are the demerits of this method (Scheme 2; method 2).

In 2018, Bahrami *et al.*[47] proposed a condensation reaction of 2-aminophenol (**1**) and aromatic aldehydes (**2**) in the presence of aqueous H_2O_2, ethanol, TTIP (titanium tetraisopropoxide), and the catalyst MTAMO (mesoporous titania–alumina mixed oxide) at 50 °C to give 2-substituted benzoxazole (**3**). The authors concluded that the reaction gave excellent yields (90–96%) in a short reaction time. The advantages of this procedure are that it is efficient and eco-friendly, and has an inexpensive catalyst with ease of operation (Scheme 2; method 3).

Agashe *et al.*[48] synthesized a nanomaterial strontium carbonate from strontium nitrate, sodium hydroxide, and ethylene glycol in distilled water *via* a hydrothermal reaction. The synthesized $SrCO_3$ was used as a catalyst for the synthesis of benzoxazole derivatives (**3**) from 2-aminophenol (**1**) and substituted benzaldehyde (**2**) *via* a grindstone method using a mortar and pestle at RT for 20 min to obtain a high yield in solvent-free conditions. The reusability of the catalyst, short reaction time, high yield, and eco-friendly approach are the characteristics of the present protocol (Scheme 2; method 4).

Moghaddam and co-workers[49] reported a one-pot synthesis of 2-phenyl benzoxazole (**3**) catalyzed by a palladium-supported [SMNP@GLP] [Cl] nanocatalyst. The reaction between 2-aminophenol (**1**) and aldehydes (**2**) in the presence of O_2, K_2CO_3, and DMF solvent at 80 °C with stirring for 18 h gave good to excellent yields. The authors synthesized 18 derivatives with 83–95% yield. This [SMNP@GLP] [Cl] nanocatalyst can be reused for 6 consecutive runs without losing its efficiency and gave a better yield than other methods. Effortless synthesis, high yield, good atom economy, and eco-friendliness are the specific benefits of this method but a long reaction time (18–48 h) is a major limitation of this method (Scheme 2; method 5).

Kumar and co-authors[50] demonstrated a β-carboline scaffold consisting of benzoxazole synthesis (**5**) by the reaction between 1-formyl-9*H*-pyrido[3,4-*b*] indole (**4**) and 2-aminophenol (**1**) catalyzed by nano-ZnO using DMF as a solvent at 100 °C to give moderate yields. Operational simplicity and easy workup are special characteristic features of this approach. Low yields and high temperatures are major drawbacks of this method (Scheme 3).

The synthetic strategy for benzoxazole developed by Agashe *et al.* was found to be highly efficient among the described nanocatalyzed protocols.

2.1.2. Metal-catalyzed synthesis. Transition-metal-supported catalysts are widely used in organic transformations as they enhance the reaction rate by lowering the energy barrier between the reactants and the products. They are often used in reactions like reduction, oxidation, and coupling, amongst others. Metal catalysts are recyclable, provide a high yield, and are easy to handle. However, transition-metal-catalyzed reactions have a heavy environmental impact due to the extraction and depletion of rare metal resources, by-products, and the generation of large amounts of waste. Here, several metal-catalyzed benzoxazole synthesis methodologies are demonstrated.

Suryavanshi and co-authors[51] utilized a metal oxide alumina catalyst for benzoxazole synthesis (**3**). 2-Aminophenol (**1**) and aldehyde (**2**) were stirred in acetonitrile solvent at room temperature for 5 h to attain a moderate yield (55–75%). The use of green solvents, recyclable catalysts, and a facile and eco-friendly synthesis are noteworthy advantages (Scheme 4; method 1).

In 2020, George and Sreekumar[52] prepared palladium complexes of dendronized amine polymer (EG–G*n*–Pd, $n = 0$, 1, and 2) catalysts for the synthesis of benzoxazoles (**3**). The reaction between 2-aminophenol (**1**) and benzaldehyde (**2**) with an EG–G2–Pd catalyst (10 mg) in ethanol at 50 °C for 3 h gave 88% product yield. The catalyst can be reused for 5 cycles with low degradation of catalytic activity, and a low amount of catalyst loading, air as an oxidant, and water as the only by-product are the unique merits of this protocol (Scheme 4; method 2).

In 2021, Wu *et al.*[53] demonstrated an $FeCl_3$-catalyzed aerobic oxidation reaction for the synthesis of 1-benzoxazolyl-*o*-carboranes (**3**) from 2-aminophenol (**1**) and 1-formyl-*o*-carborane (**2**) with toluene as a solvent at 110 °C for 24 h to give 50–96% yield depending on substitution. However, $AgNO_3$ as a co-oxidant provided an excellent yield of 91–99%. High yield, good atom economy, a facile synthetic approach, and operational simplicity are the main features of this approach (Scheme 4; method 3).

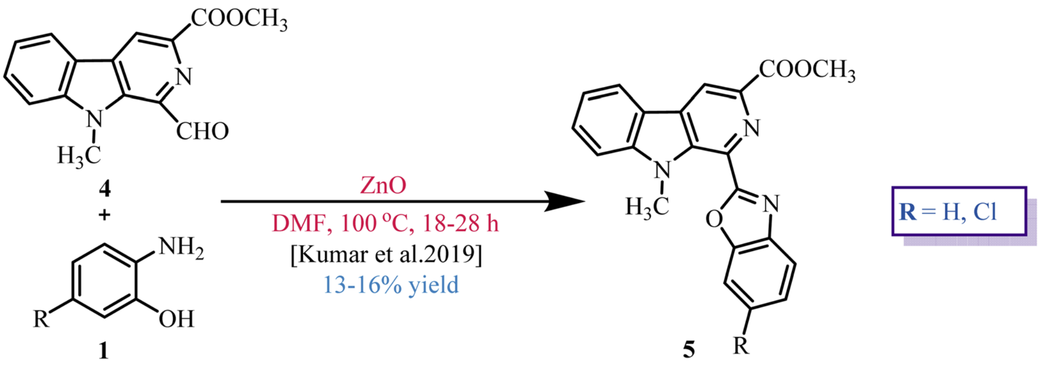
Jilani and co-workers[54] synthesized 2-substituted benzoxazole acetic acid derivatives (**3**) *via* an oxidative coupling reaction between methyl-3-amino-4-hydroxyphenylacetate (**1**) and aldehydes (**2**), catalyzed by lead tetraacetate in ethanol and the further addition of 90% NaOH solution in ethanol and water at RT for 3 h. Their cytotoxic activity against cancer cell lines, namely MCF-7 (human breast cancer cells) and HCT-116 (human colorectal carcinoma cells), was also evaluated. Cytotoxic activity was elevated in the presence of an acetic acid group at the fifth position on the benzoxazole moiety (Scheme 4; method 4).

In 2019, Layek *et al.*[55] prepared nickel(II) complexes of benzoyl hydrazones and used them as catalysts for the synthesis of 2-aryl benzoxazoles (**3**). The Ni(II) complex-assisted intramolecular cyclization of 2-aminophenol (**1**) and aromatic aldehydes (**2**) in the presence of DMF and K_2CO_3 at 80 °C for 3–4 h, provided 87–94% yields. A low amount of catalyst loading and high yield are the plus points of this method (Scheme 4; method 5).

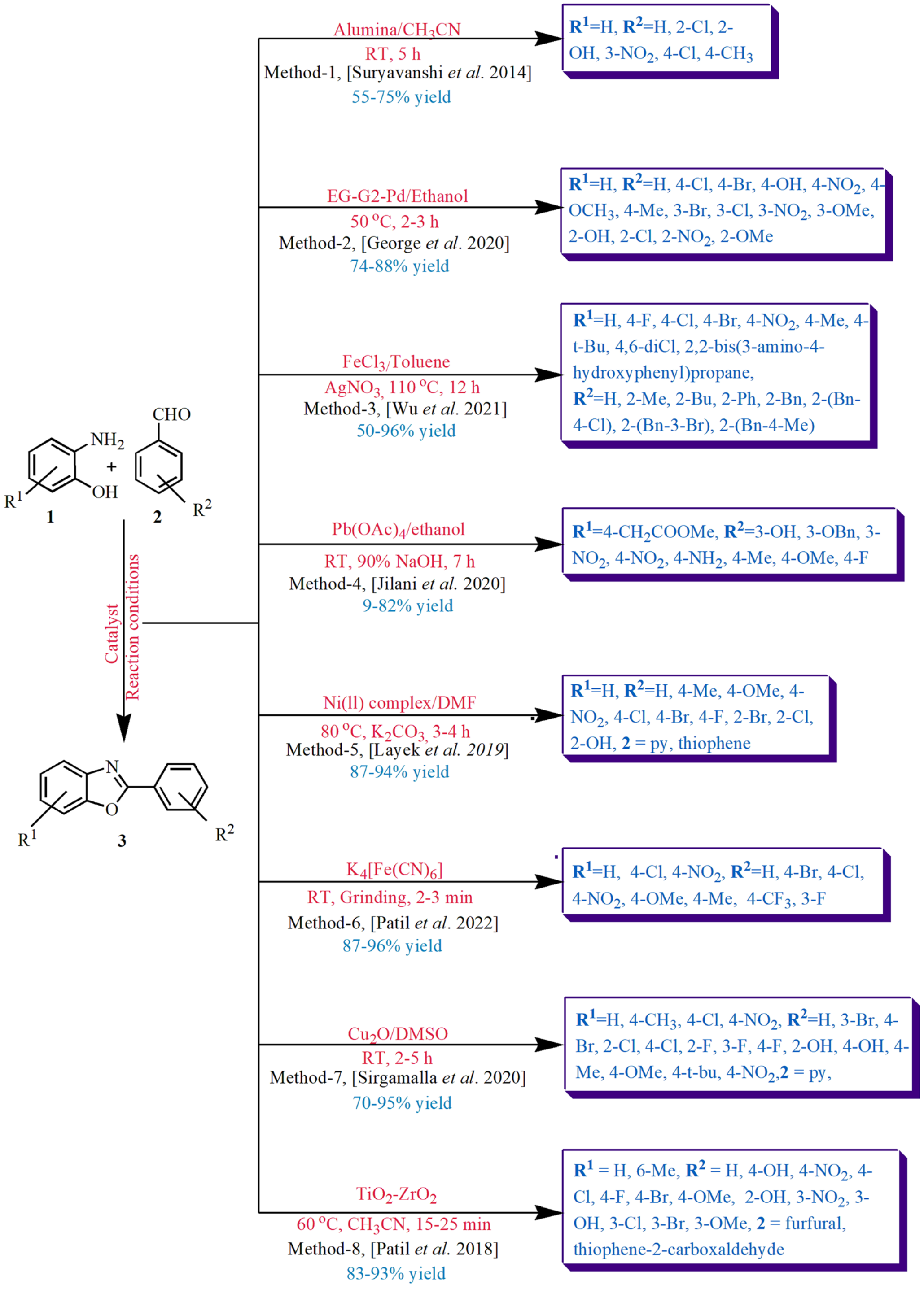
In 2022, Patil *et al.*[56] demonstrated the potassium-ferrocyanide-catalyzed synthesis of benzoxazole derivatives (**3**) with the grinding method using a mortar and pestle under solvent-free conditions from 2-aminophenol (**1**) and aromatic aldehydes (**2**) at RT and found 87–96% yield in less than 2 min. The short reaction time, excellent yield, easy workup, nontoxic catalyst, and solvent-free and modest reaction conditions make this a greener approach (Scheme 4; method 6).

Sirgamalla and colleagues[57] used a Cu_2O catalyst in the reaction of 2-aminophenol (**1**) and substituted aryl aldehydes (**2**) in DMSO (dimethyl sulfoxide) at RT for 2–5 h to obtain a high yield of 2-substituted benzoxazoles (**3**). The authors synthesized 37 derivatives with 70 to 95% yield. The compounds displayed antifungal activity and this activity is similar to the standard drug voriconazole against *Aspergillus niger*. This approach has some benefits, like high yield, ambient reaction conditions, and good atom economy (Scheme 4; method 7).

Patil *et al.*[58] reported the TiO_2–ZrO_2-catalyzed synthesis of 2-aryl benzoxazole derivatives (**3**) from the reaction between 2-aminophenol (**1**) and aromatic aldehyde (**2**) in acetonitrile at 60 °C for 15–25 min and obtained 83–93% yield. This procedure has several significant advantages: *viz.* the use of green catalysts, shorter reaction time, high yield, and environmental friendliness (Scheme 4; method 8).



Scheme 3 Nano-ZnO-catalyzed synthesis of β-carboline scaffolds.



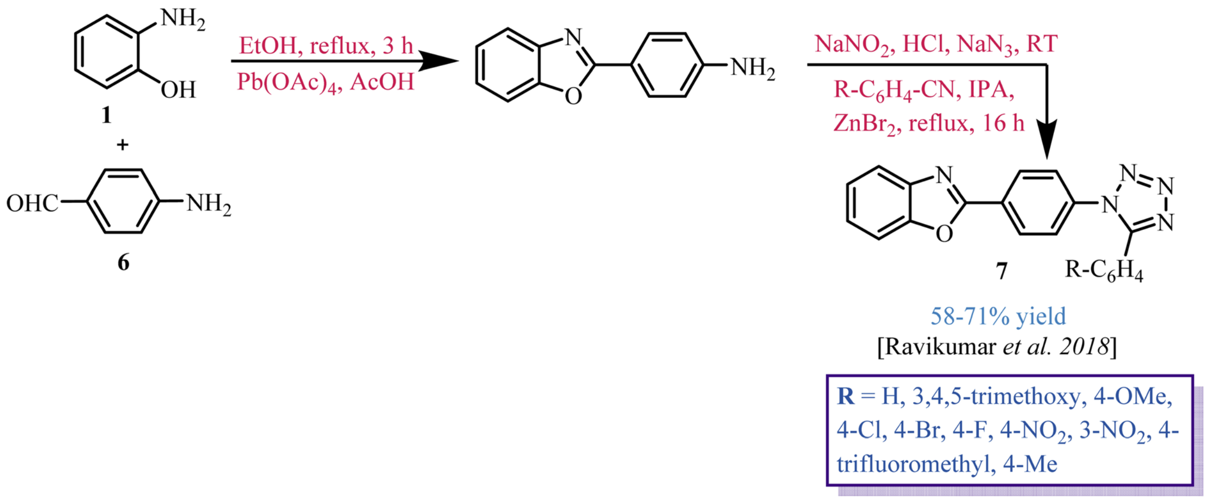
Scheme 4 Metal-catalyzed synthesis of benzoxazole derivatives.

Ravikumar and co-authors[59] synthesized tetrazole fused benzoxazole derivatives (7) and analyzed their cytotoxicity in cancer cell lines. The reaction between 2-aminophenol (**1**) and 4-amino benzaldehyde (**6**) in ethanol using $Pb(OAc)_4$ in acetic acid under reflux conditions, followed by reactions with HCl, $NaNO_2$, and NaN_3, then further reaction with aromatic nitriles in isopropanol and $ZnBr_2$ was used to obtain tetrazole fused benzoxazoles and their anticancer activity was analyzed against cancer cell lines such as MCF-7, KB, Hop62, and A-549 (Scheme 5).

Patil *et al.*'s synthetic strategy for benzoxazole was found to be highly efficient among the described metal-catalyzed protocols.

2.1.3. Ionic-liquid-catalyzed synthesis.

Ionic liquids are compounds that are prepared from ions and work as a soluble support for catalysts. Ionic liquid catalysts have special

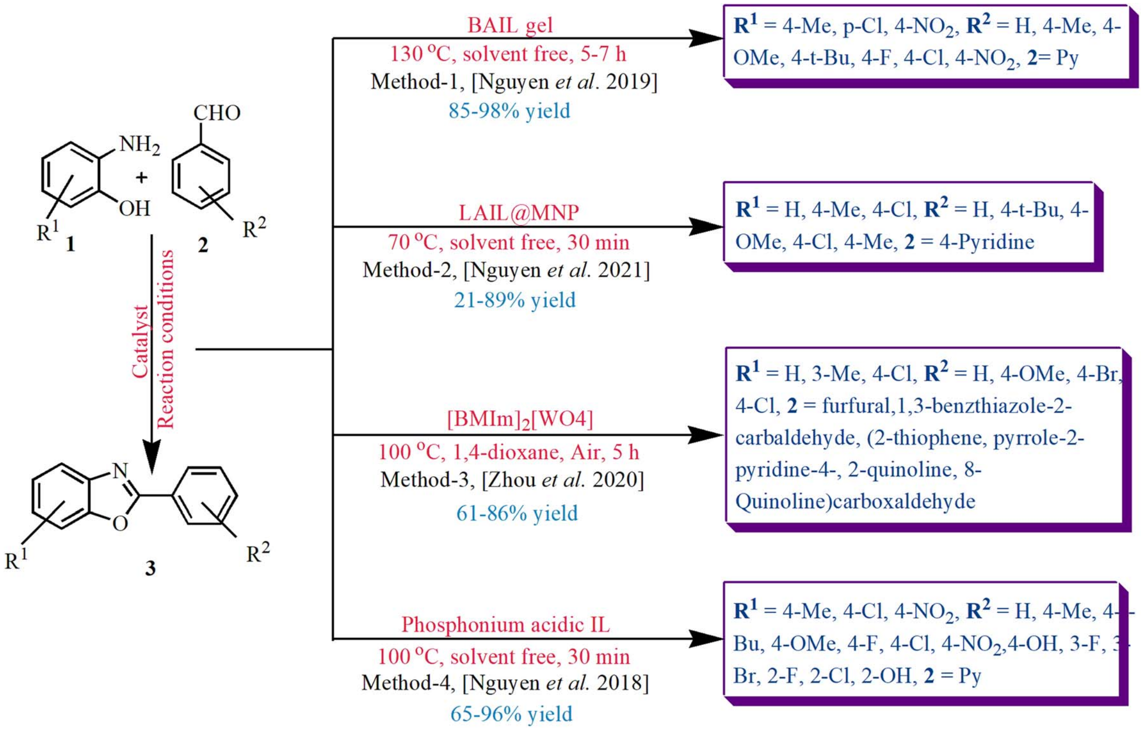


Scheme 5 Method for the synthesis of tetrazole fused benzoxazole derivatives.

characteristics like negligible vapor pressure, unlimited tunability, low melting point, high stability, and good recyclability, and are therefore considered green catalysts. Here, various ionic-liquid-promoted syntheses of benzoxazole scaffolds are illustrated.

In 2019, Nguyen and co-authors[60] reported the synthesis of benzoxazole derivatives (**3**) using a Brønsted acidic ionic liquid gel catalyst in solvent-free conditions for the condensation and aromatization of 2-aminophenol (**1**) and aldehydes (**2**) at 130 °C for 5 h. The authors synthesized 14 derivatives with 85–98% yield. The catalyst was reusable for up to 5 consecutive runs without significant loss in its efficiency. Recoverable green catalysts, high yield, and facile workup are the attractive features of this method. High temperatures and long reactions limit the merits of this method (Scheme 6; method 1).

The synthesis of benzoxazole derivatives (**3**) by a condensation reaction between 2-aminophenol (**1**) and aldehydes (**2**) using a magnetic nanomaterial Fe_3O_4-supported Lewis acidic ionic liquid (LAIL@MNP) was investigated by Nguyen and co-workers.[61] In this study, the reactants were sonicated under solvent-free conditions at 70 °C for 30 min to deliver moderate to high yields. Reusability of the catalyst, easy workup, solvent-



Scheme 6 Ionic-liquid-catalyzed synthesis of benzoxazole derivatives.

free conditions, shorter reaction time, and a green pathway are advantages of this process (Scheme 6; method 2).

Zhou and co-authors[62] prepared an ionic liquid $[BMIm]_2[WO_4]$ catalyst *via* ion exchange using an ion exchange resin, H_2WO_2, and an ethanol solution of [BMIm]OH for 3 h and utilized this catalyst to synthesize various derivatives of benzoxazole (**3**). The reaction between 2-aminophenol (**1**) and aromatic aldehydes (**2**) using 1,4-dioxane as a solvent in the presence of air as an oxidant at 100 °C gave a decent yield. Several major benefits of this method are the use of air as an oxidant, base-free conditions, and catalyst recyclability for up to 5 consecutive runs (Scheme 6; method 3).

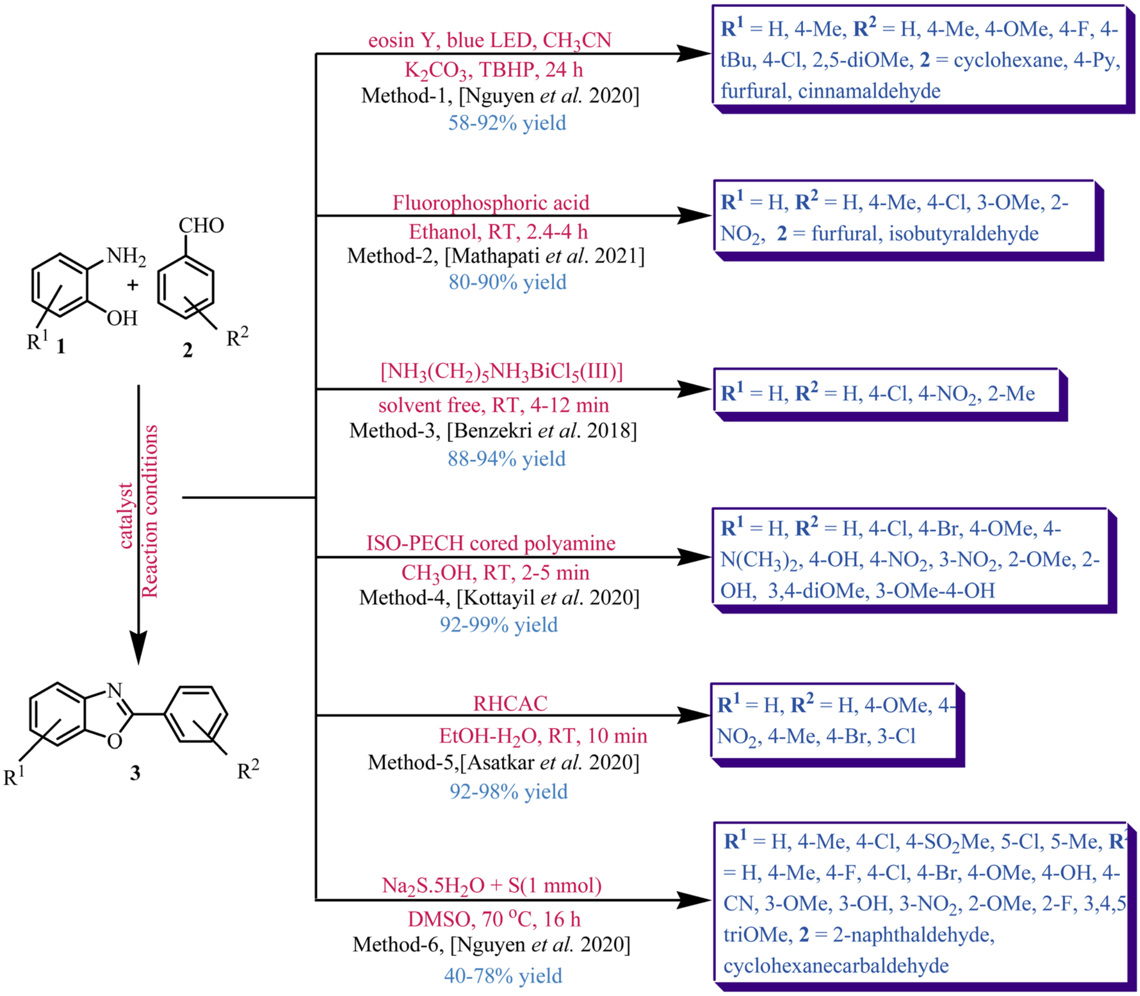
Nguyen *et al.*[63] reported the phosphonium acidic ionic liquid [triphenyl(butyl-3-sulfonyl) phosphonium toluene sulfonate catalyzed synthesis of 2-aryl benzoxazole (**3**) from 2-aminophenol (**1**) and aryl aldehydes (**2**) at 100 °C under solvent-free conditions. The authors prepared 35 derivatives with 65–96% yield. Simple workup, recyclability of the catalyst, and solvent-free synthesis made this a green and efficient protocol (Scheme 6; method 4).

2.1.4. Miscellaneous. In this section, different types of catalyst are studied for the synthesis of benzoxazole derivatives, including photocatalysts, organocatalysts, and acid catalysts.

In 2020, Nguyen and co-authors[64] introduced eosin Y as an effective photocatalyst to prepare benzoxazole derivatives (**3**). The reaction between 2-aminophenol (**1**) and aldehyde (**2**) in methyl cyanide or DMSO solvent using K_2CO_3 as a base and TBHP (*tert*-butyl-hydroperoxide) oxidant was exposed to radiation under argon with a blue LED (3 W) for 24 h. The authors prepared 18 derivatives with 58–92% yield. The advantages associated with this method are avoidance of the use of pre-synthesized catalysts and the traditional heating process (Scheme 7; method 1).

Mathapati *et al.*[65] used fluorophosphoric acid as a highly effective acid catalyst for the synthesis of benzoxazole derivatives (**3**) by the reaction of 2-aminophenol (**1**) and aromatic/aliphatic aldehyde (**2**) in ethanol under stirring at room temperature for 2.4 h. The advantages of this protocol are the use of inexpensive and stable catalysts with shorter reaction time and ambient conditions (Scheme 7; method 2).

A condensation reaction between 2-aminophenol (**1**) and aldehydes (**2**) to produce 2-aryl benzoxazole derivatives (**3**) in good yield using a pent-ethylene diammonium pentachloro bismuth $[NH_3(CH_2)_5NH_3BiCl_5(\text{III})]$ catalyst at RT under solvent-free conditions was reported by Benzekri *et al.*[66] in 2018.



Scheme 7 Various methods for benzoxazole synthesis using miscellaneous catalysts.

Recyclability of the catalyst for up to 6 cycles, and solvent-free conditions make this a green and sustainable approach. However, less substrate scope is the demerit of this protocol (Scheme 7; method 3).

Kottayil *et al.*[67] developed a method for the synthesis of benzoxazole derivatives (**3**) catalyzed by a homogenous ISO-PECH (isosorbide-initiated poly epichlorohydrin-cored) polyamine organocatalyst. The condensation reaction of 2-aminophenol (**1**) and aromatic aldehydes (**2**) in methanol at RT for 2–5 min gave a 92–99% yield. Economical and reusable catalysts, high yield, short reaction time, and easy workup are the special merits of this method (Scheme 7; method 4).

The facile and elementary synthesis of benzoxazole derivatives (**3**) using an RHCAC (rice husk derived chemically activated carbon) catalyst *via* the reaction of 2-aminophenol (**1**) and aldehydes (**2**) in ethanol and water (1 : 2) was reported by Asatkar *et al.*[68] who obtained excellent yields. Biodegradable and reusable catalysts, high yield, and easy workup are the main features of this protocol (Scheme 7; method 5).

Nguyen *et al.* (2020)[69] suggested the use of elemental sulfur as an oxidant for the synthesis of benzoxazole (**3**). The oxidative coupling of 2-aminophenol (**1**) and aldehyde (**2**) occurred in the presence of hydrated sodium sulfide ($Na_2S\cdot5H_2O$) and DMSO additive at 70 °C for 16 h to give 40–78% yield. Using elemental sulfur rather than oxygen as an oxidant is feasible in organic synthesis, as elemental oxygen suffers a great risk of explosion of flammable organic substrates, and in the gaseous state, its stoichiometric control is not readily possible. On the other hand, sulfur is highly desirable and possesses unique properties like being inexpensive and user-friendly, and it can be used under ambient reaction conditions. With this method, benzoxazole can be simply synthesized while avoiding high-pressure equipment for a larger scale (10–50 mmol) (Scheme 7; method 6).

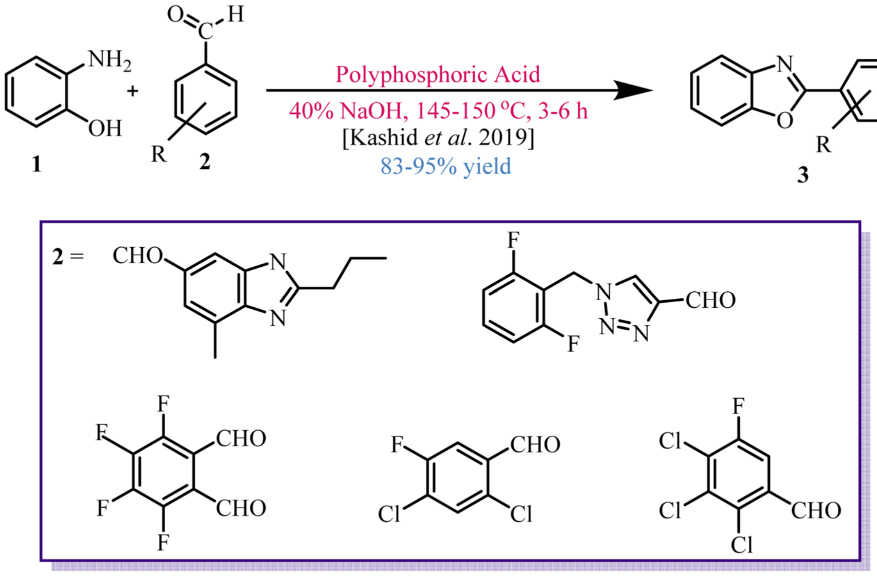
Kashid *et al.*[70] exemplified the use of PPA (polyphosphoric acid) as a catalyst as well as a solvent for the synthesis of benzoxazole derivatives (**3**) and analyzed their antioxidant and antimicrobial activity. The reaction between 2-aminophenol (**1**) and aromatic aldehydes (**2**) in 40% aq. NaOH solution to adjust the pH to 5–6, at 145–150 °C for 3–6 h gave good to excellent yield. Cost-effectiveness, eco-friendliness, and high yield are the benefits of this protocol while the use of high temperature is a drawback of this procedure (Scheme 8).

2.2. Reaction of 2-aminophenol with acids and their derivatives

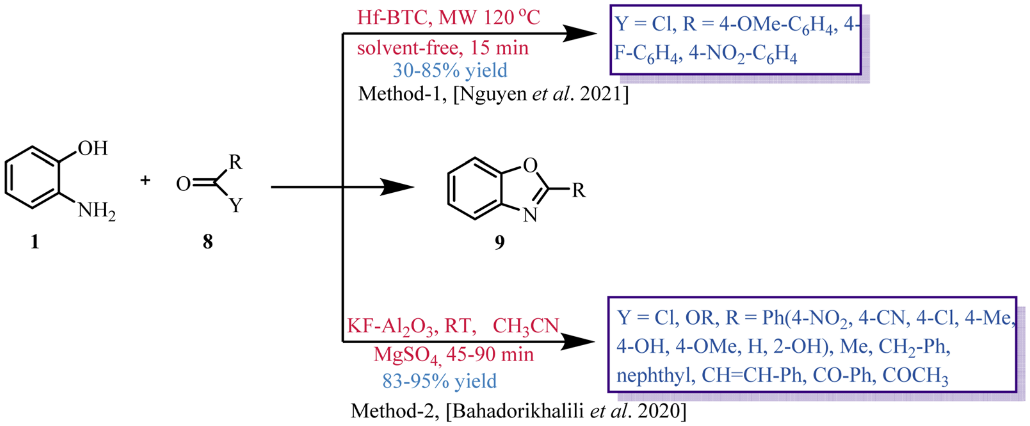
An eco-friendly protocol was disclosed by Nguyen and co-authors[71] using a Brønsted and Lewis dual acidic (Hf-BTC) catalyst to synthesize 2-phenyl benzoxazole derivatives (**9**) *via* a condensation reaction between 2-aminophenol (**1**) and benzoyl chloride (**8**) at 120 °C under microwave irradiation and solvent-free conditions for 15 min, which gave 30–85% yield. The reusability of the catalyst was examined and it showed catalytic activity up to 5 runs without significant loss in its activity (Scheme 9; method 1).

An efficient and facile heterogeneous base-catalyzed ($KF-Al_2O_3$) synthesis of 2-substituted benzoxazole (**9**) was reported by Bahadorikhalili and Sardarian.[72] The reaction between 2-aminophenol (**1**) and acid derivatives (**8**) in acetonitrile and anhydrous $MgSO_4$ at room temperature for 45–90 min gave 83–95% yields. No significant decrease was found in catalytic efficiency for 10 consecutive runs. High yield, wide substrate scope, no by-product generation, and operational simplicity are the remarkable merits of the protocol (Scheme 9; method 2).

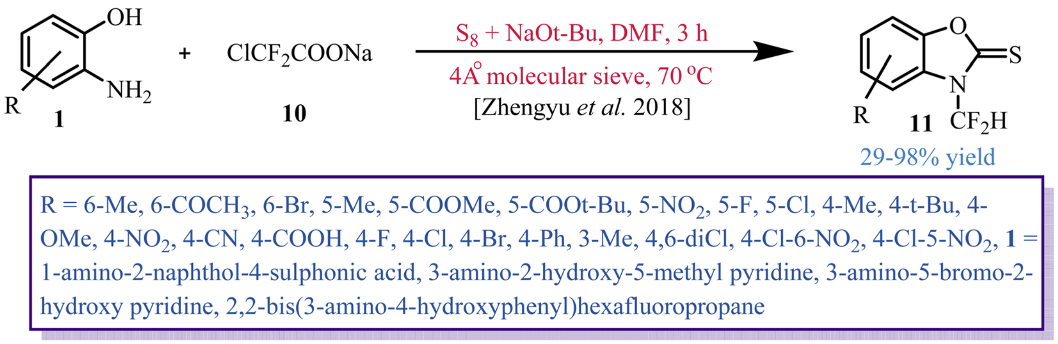
Zhengyu *et al.*[73] investigated a novel and efficient one-pot synthesis of 3-difluoromethyl benzoxazole-2-thiones (**11**) using an NaO*t*-Bu (sodium *tert*-butoxide) base and elemental sulfur and evaluated their insecticidal activities against *Plutella xylostella*. This methodology took place *via* cyclization and *N*-difluoromethylation of 2-aminophenol (**1**) and sodium chloro-



Scheme 8 Synthesis of biologically active benzoxazole derivatives using PPA.



Scheme 9 Methods for the synthesis of benzoxazole using acids and their derivatives.



Scheme 10 Synthesis of benzoxazole derivatives using an NaO*t*-Bu catalyst.

difluoro-acetate (**10**) in DMF and a 4Å-type molecular sieve as an additive at 70 °C. Operational simplicity, high yield, broad substrate scope, and easily available reactants are the special features of this method (Scheme 10).

Park *et al.*[74] demonstrated a proficient synthesis of nocarbenzoxazoles and their derivatives (**14**) in high yield by cyclodehydration, demethylation, and reduction reactions and analyzed their anti-inflammatory activity in LPS-induced raw cells (264.7) *via* a nitric oxide inhibitory effect. The reaction was performed with ethyl ester substituted benzoic acid (**12**), substituted benzoyl chloride (**13**), and $POCl_3$ in 1,4-dioxane at 90 °C for 15 h, further reaction with $BBr_3/CHCl_3/AlCl_3$ in CH_2Cl_2 at −78 °C to RT, and a further reduction reaction using $LiAlH_4$ in THF at 0 °C to RT for 30 min, to give 91–97% product yield (Scheme 11; method 1).

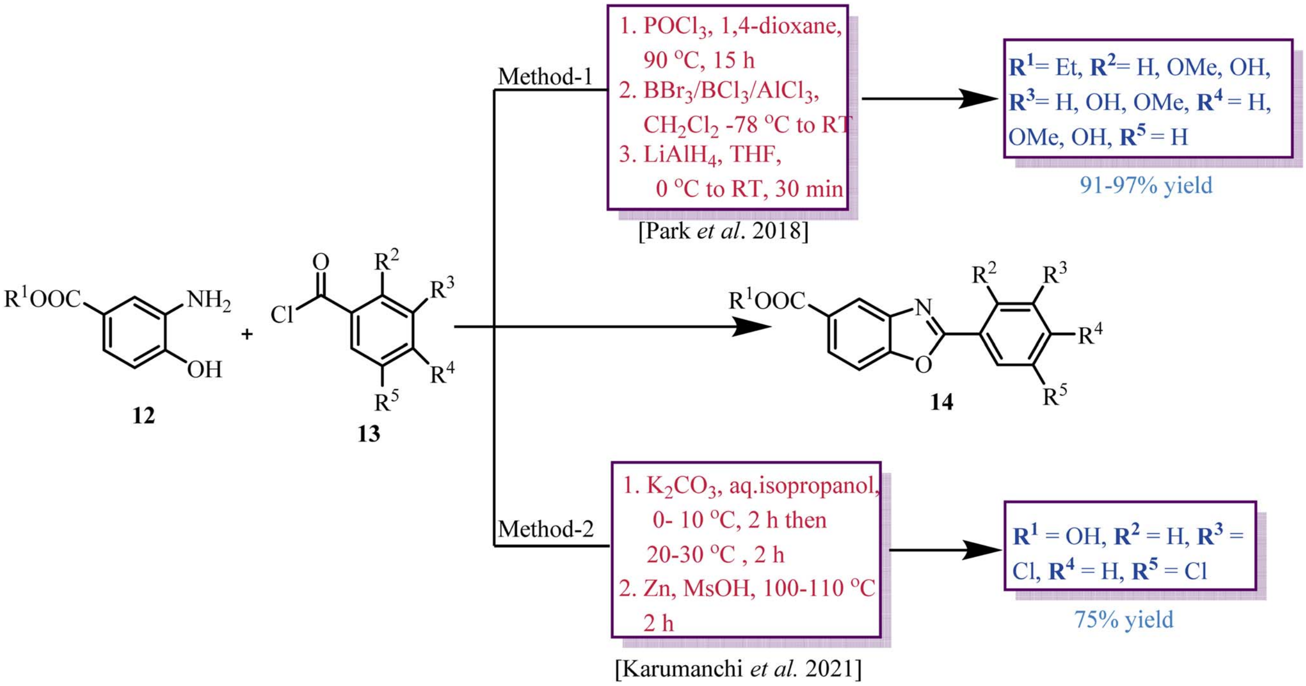
Karumanchi and colleagues[75] reported the synthesis of tafamidis (**14**), a benzoxazole derivative *via* a two-step synthesis. In the first step, *o*-benzoylation of 3-hydroxy-4-nitrobenzoic acid (**12**) was undertaken using 3,5-dichlorobenzoyl chloride (**13**) and K_2CO_3 in aq. isopropanol at 0–10 °C for 2 h then at 20–30 °C for 2 h. In the second step, reductive cyclization took place by Zn in MsOH at 100–110 °C for 2 h and a moderate yield of the desired product was obtained. Ease of operation and mild reaction conditions are the merits of this protocol (Scheme 11; method 2).

2.3. Reaction of 2-aminophenol with benzyl alcohols

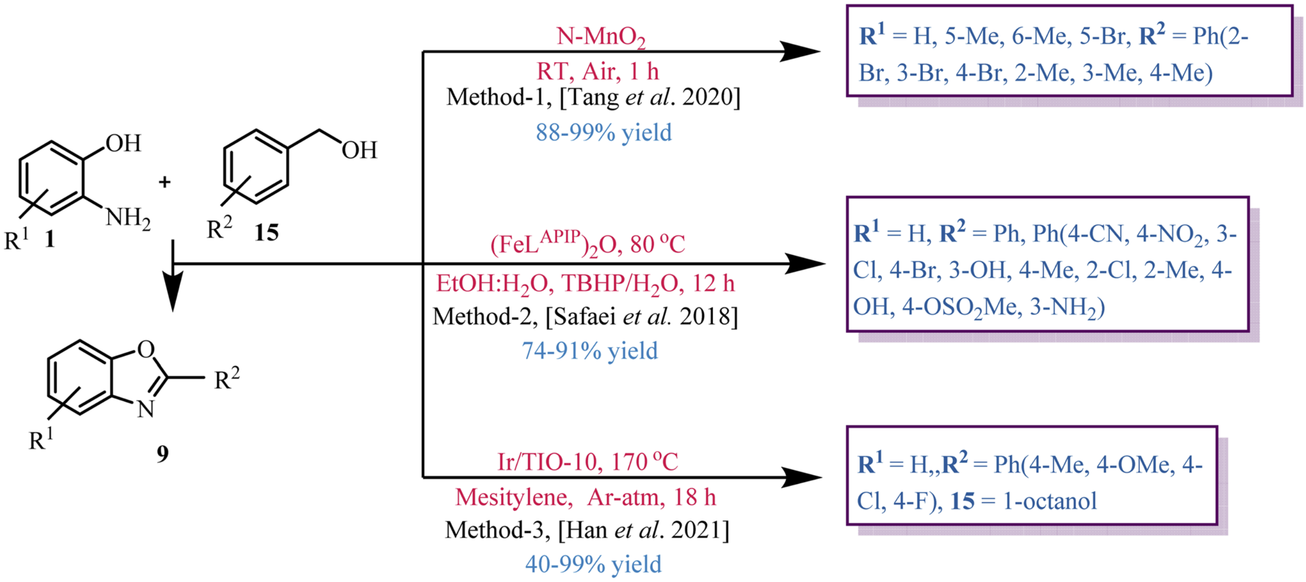
In 2020, Tang *et al.*[76] fabricated a new N–MnO_2 catalyst by a hydrothermal and calcination method using manganese(II) sulfate, acetate tetrahydrate, ethylene glycol, ultrapure water, and urea, and used it to synthesize benzoxazole derivatives (**9**) from the oxidation of benzyl alcohol (**15**) to benzyl aldehyde, and continued the condensation with 2-aminophenol (**1**) at RT for 1 h to give 88–99% yield. This protocol possesses several merits like catalyst recyclability up to 10 consecutive runs, excellent yield, mild reaction conditions, and operational simplicity (Scheme 12; method 1).

Safaei and co-authors[77] prepared a new binuclear oxo-bridged iron(III) complex catalyst and used it for the synthesis of benzoxazole derivatives (**9**) by the reaction between benzyl alcohols (**15**) and 2-aminophenol (**1**) in ethanol–water (1 : 1) solvent and TBHP as an oxidant in water at 80 °C for 12 h in good yield. Moderate reaction conditions, and low catalyst loading, are additional features of the method (Scheme 12; method 2).

Han and co-workers[78] developed a titania-supported iridium catalyst by an impregnation method and used it to prepare 2-substituted benzoxazoles (**9**) *via* acceptor-less dehydrogenative synthesis using 2-aminophenol (**1**) and primary alcohols (**15**) in mesitylene under an argon atmosphere at 80–170 °C for 18 h to give decent yields. This protocol has special properties like an



Scheme 11 Methods for the synthesis of nocarbenzoxazole and tafamidis.



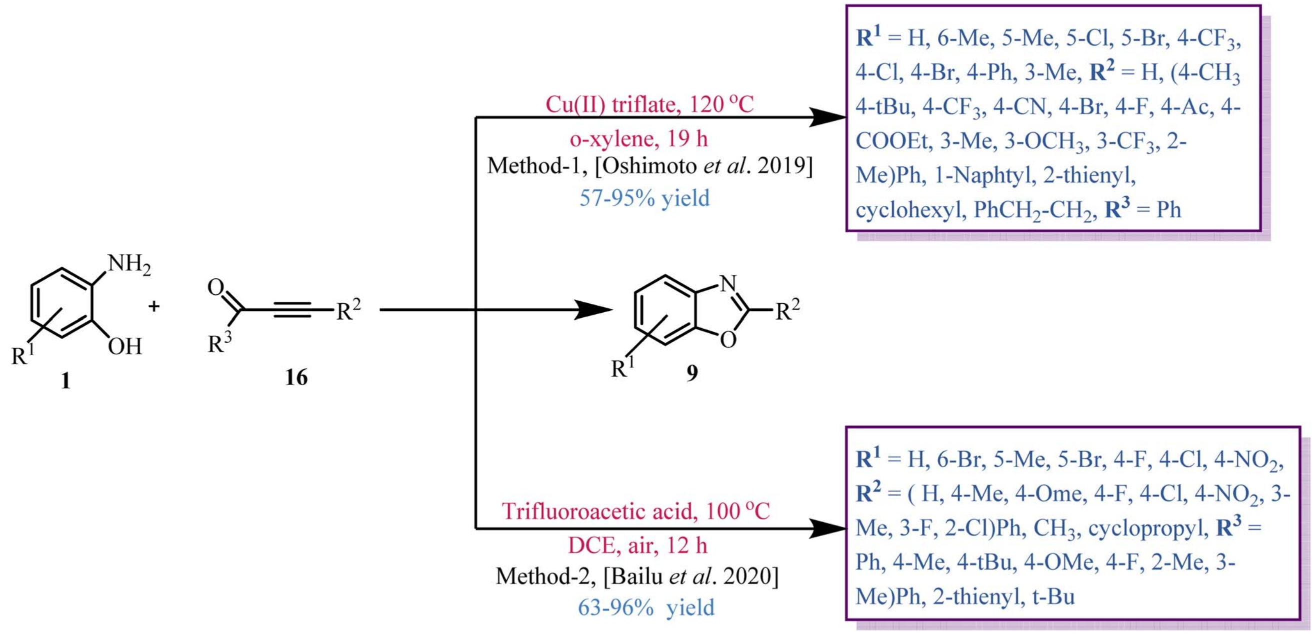
Scheme 12 Synthesis of benzoxazole analogs using benzyl alcohols.

easily recoverable and reusable catalyst with high efficiency, broad substrate scope, high yield, and low waste generation. Longer reaction time and high temperature limit the efficiency of the method (Scheme 12; method 3).

2.4. Reaction of 2-aminophenol with alkynones

Oshimoto *et al.*[79] demonstrated a feasible Cu(II) triflate catalyzed synthesis of benzoxazole derivatives (**9**) by the hydroamination of alkynones (**16**) and 2-aminophenol (**1**) in *o*-xylene at 120 °C for 19 h. Here, the authors investigated 30 derivatives with moderate to high yields. The easily accessible and user-friendly procedure and a wide range of functionalizations are the major benefits of this approach (Scheme 13; method 1).

Bailu and colleagues[80] disclosed a novel and facile one-pot synthesis of benzoxazole derivatives (**9**) promoted by TFA (trifluoroacetic acid) by the cleavage of the C–C double bond of *N*-(2-hydroxylphenyl) enaminones derived from the reaction of 2-aminophenol (**1**) and alkynones or diketones (**16**) in 1,2-



Scheme 13 Different methods for benzoxazole synthesis using alkynones.

dichloroethane (DCE) at 100 °C for 12 h to give 63–96% yield. This pathway provided broad substrate scope, less toxicity, economy, high product yield, and fewer by-products. The use of toxic solvents and a long reaction time are the disadvantages of the protocol (Scheme 13; method 2).

2.5. Reaction of 2-aminophenol with isothiocyanates

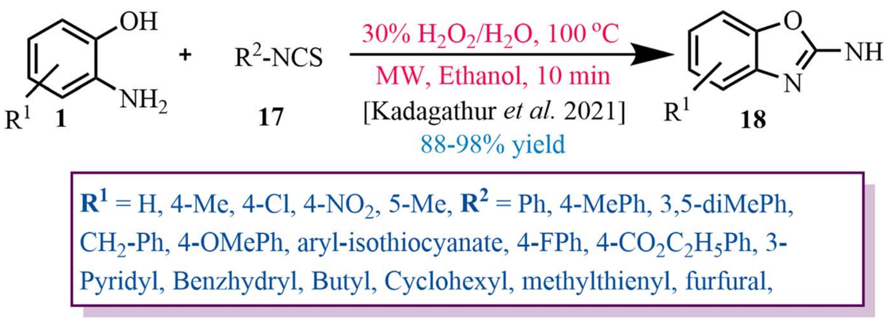
Kadagathur *et al.*[81] designed an easy, greener, and proficient pathway for the synthesis of benzoxazole (**18**) analogs by the cyclo desulfurization reaction of 2-aminophenol (**1**), isothiocyanates (**17**), and 30% H_2O_2 in water as an oxidant in ethanol under microwave irradiation for 10 min at 100 °C. Ease of operation, cleaner reaction profiles, high yield of products (88–98%), short reaction time, and the use of a green solvent made this an eco-benign protocol (Scheme 14).

In 2020, Wu and colleagues[82] disclosed the effective synthesis of glycosyl benzoxazole analogs (**20**) and evaluated their cholinesterase inhibition activity (AChE and BuChE). In this process, desulfurization and cyclization reactions took place using glycosyl isothiocyanate (**19**) and 2-aminophenol (**1**) for 8–10 h, with the later addition of *p*-toluene sulfonyl chloride in THF and pyridine to give the desired product. The presence of 4-methyl and 5-chloro substituents on the benzoxazole ring showed the highest inhibitory activity for AChE and BuChE, respectively. This procedure involved various benefits like ambient conditions, the use of green solvents, and economical and simple operation (Scheme 15).

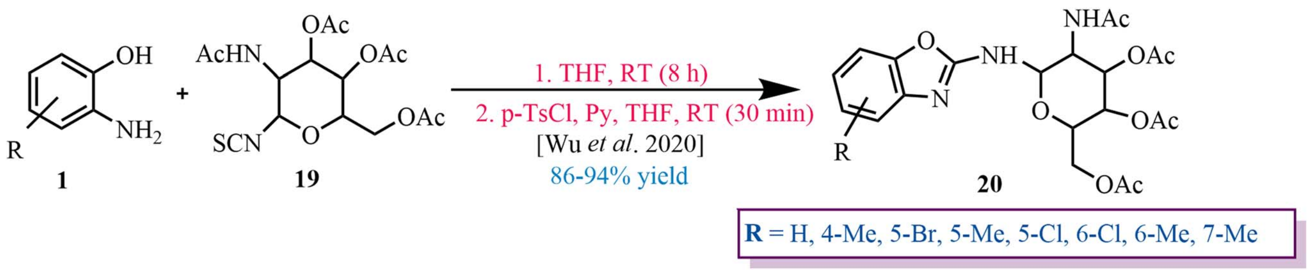
2.6. Reaction of 2-aminophenol with ketones

Kummari and co-authors[83] synthesized benzoxazole derivatives (**9**) using a montmorillonite KSF clay catalyst. The reaction of 1,3-diketones (**21**) and 2-aminophenol (**1**) in CH_3CN at 90 °C for 14 h in air gave an excellent yield of 82–93%. The feasible operation, high product yield, reusability of the catalyst for up to 3 significant runs, and broad substrate range are the salient attributes of this method (Scheme 16).

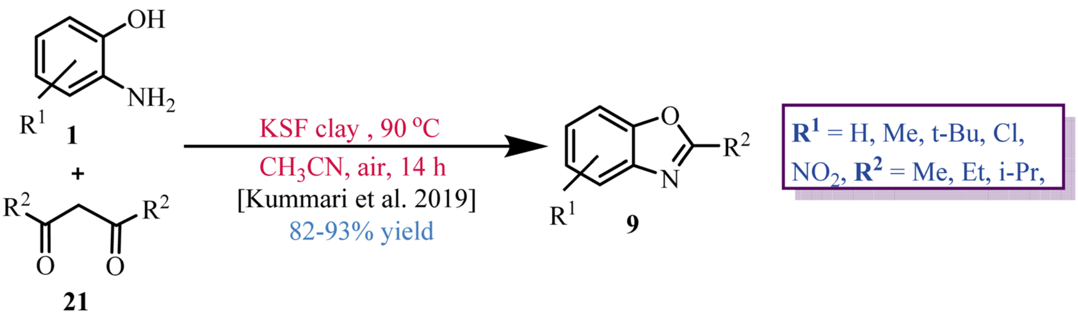
Recently, Nguyen *et al.*[84] proposed a unique and efficient sulfur-promoted synthesis of 2-benzoylbenzoxazoles (**23**) by the



Scheme 14 Synthesis of benzoxazole derivatives using isothiocyanates.

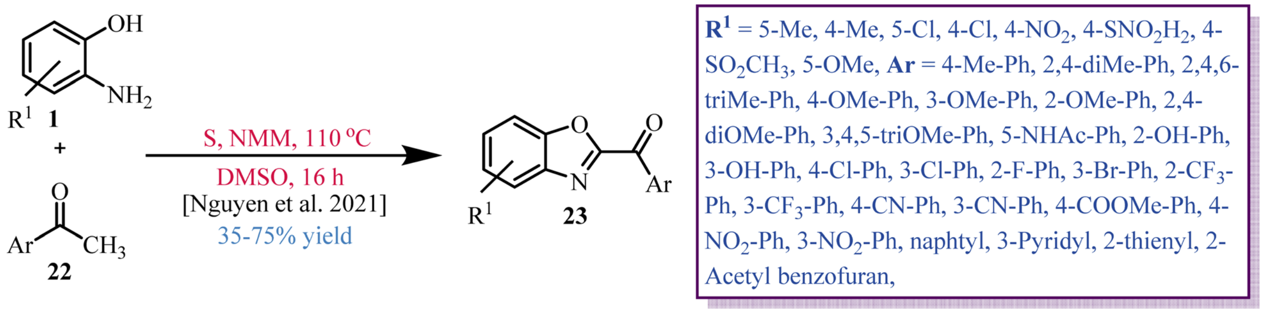


Scheme 15 Synthetic pathway for benzoxazole derivatives using glycosyl-isothiocyanate.

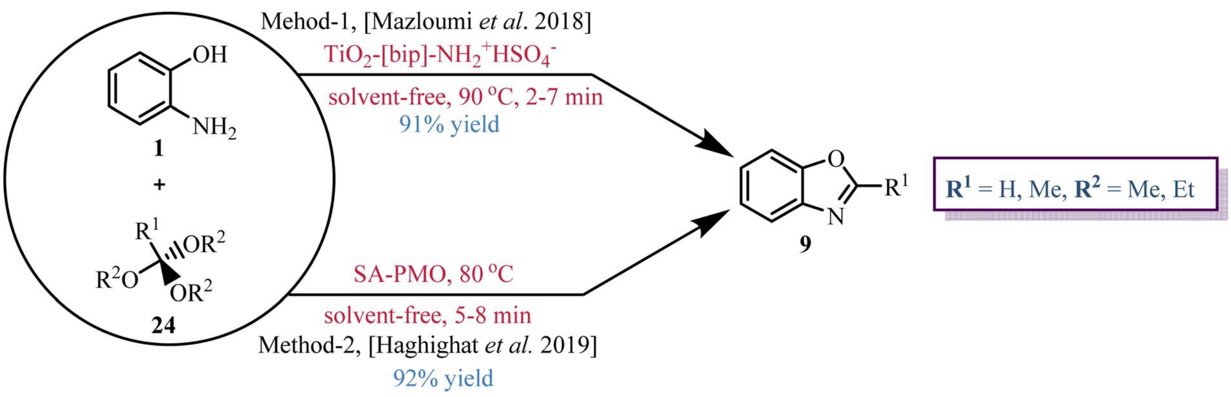


Scheme 16 Synthesis of benzoxazole derivatives using 1,3-diketones.

reaction of 2-aminophenol (**1**) and acetophenones (**22**) using NMM (*N*-methyl morpholine) in DMSO solvent at 110 °C for 16 h. The authors synthesized 35 derivatives in 35–85% yield. Easily available and cost-efficient reagents, operational simplicity, and a variety of substrate scopes are the significant features of this protocol (Scheme 17).



Scheme 17 Pathway for the synthesis of benzoxazole derivatives using acetophenones.



Scheme 18 Methods for the synthesis of benzoxazole using *ortho*-esters.

2.7. Reaction of aminophenols with *ortho*-esters

Mazloumi *et al.*[85] prepared a (trimethoxysilylpropyl) ammonium hydrogen sulfate catalyst by nano-TiO_2 with bis-3-(trimethoxysilylpropyl) amine and used it in the solvent-free synthesis of benzoxazole derivatives (**9**) from the reaction between 2-aminophenol (**1**) and *ortho*-esters (**24**) at 90 °C in excellent yields. Reuse of the catalyst for up to 8 runs without significant loss in efficiency, high product yield, and green synthesis under mild reaction conditions are the attractive features of this method (Scheme 18; method 1).

In 2019, Haghighat and co-workers[86] synthesized an efficient and eco-benign periodic mesoporous organo-silica with bridged *N*-sulfonic acid groups (SA-PMO) catalyst and assessed its catalytic activity for the solvent-free synthesis of benzoxazoles (**9**) from 2-aminophenol (**1**) and *ortho*-esters (**24**) at 80 °C for 5–8 min. Simple workup, short reaction time, enriched yields, reuse of the catalyst for up to 5 runs with less change in yield, and solvent-free condition made this a green pathway (Scheme 18; method 2).

2.8. Miscellaneous

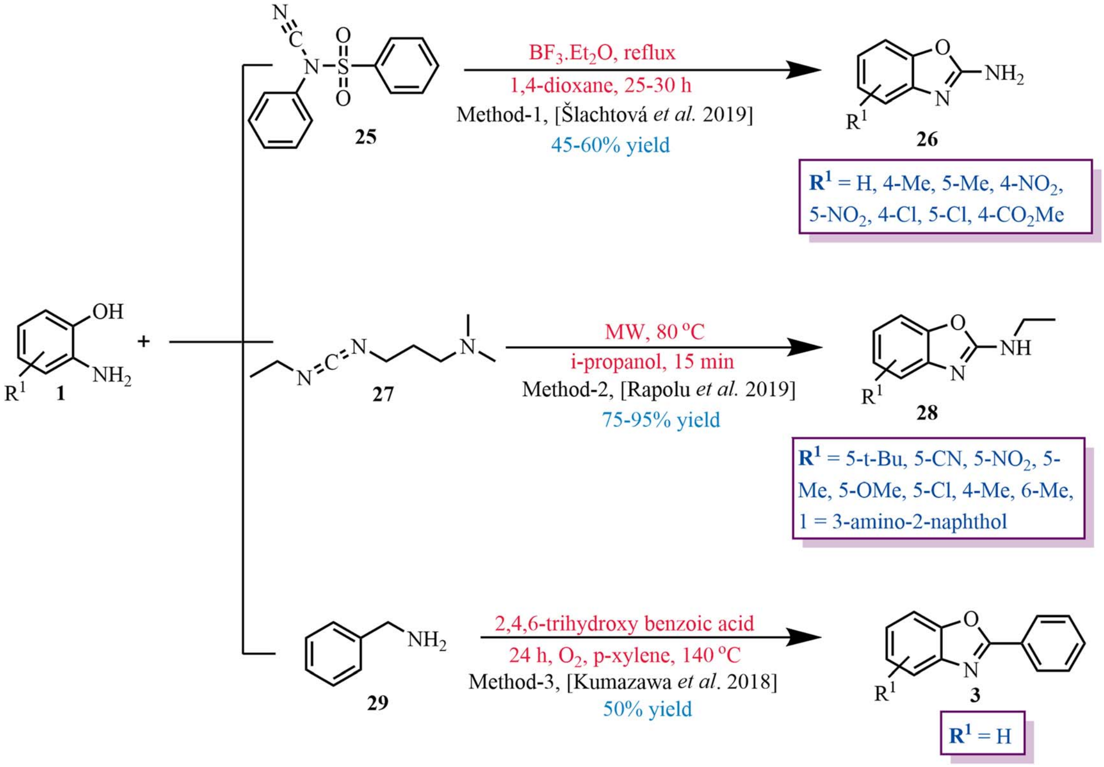
Šlachtová *et al.*[87] reported a facile synthesis of 2-amino benzoxazole (**26**) by a cyclization reaction between 2-aminophenol (**1**) and *N*-cyano-*N*-phenyl-*p*-toluene sulfonamide (NCTS) (**25**) using a $BF_3 \cdot Et_2O$ catalyst and 1,4-dioxane as a solvent at reflux to acquire a 45–60% yield. Ease of operation, good yield, and nontoxic and easily available reagents are the notable advantages of this method (Scheme 19; method 1).

Rapolu *et al.*[88] illustrated a facile simple one-pot reaction for the synthesis of benzoxazole derivatives (**28**) under microwave irradiation at 80 °C from 2-aminophenol (**1**) and EDC·HCl (**27**) in isopropanol. This pathway provided some merits like a one-step reaction, simple operation, shorter reaction time, and the use of MW irradiation (Scheme 19; method 2).

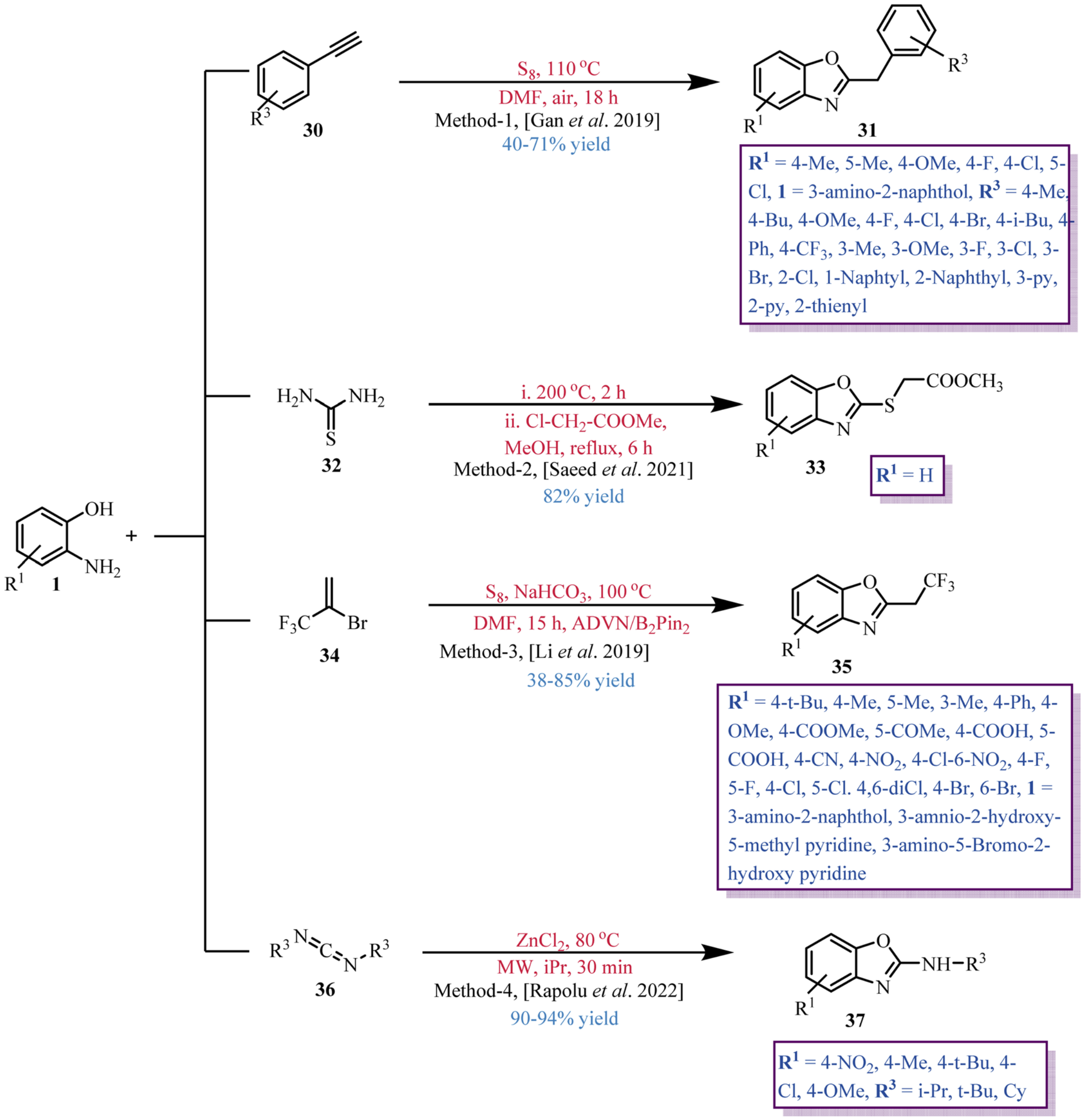
The 2,4,6-trihydroxy benzoic acid-catalyzed synthesis of 2-phenyl benzoxazole (**3**) from the oxidative coupling of 2-aminophenol (**1**) and benzylamine (**29**) under an O_2 atmosphere was explained by Kumazawa and colleagues.[89] The authors employed this reaction in four different solvents, ethyl acetate, acetonitrile, toluene, and *p*-xylene, at 70 °C–140 °C. Among the solvents, *p*-xylene proved the best solvent at a temperature of 140 °C (Scheme 19; method 3).

Gan *et al.*[90] investigated a practical, convenient, and well-organized pathway for benzoxazole synthesis (**31**) by the cyclization of 2-aminophenol (**1**) and aryl acetylenes (**30**) in dimethyl formamide (DMF) using sulfur as an oxidant at 110 °C. A broad range of aryl acetylenes with electron withdrawing and donating groups was examined and gave low to moderate (40–71%) yield. A clean reaction profile, operational simplicity, and easily available starting materials are the plus points of this approach (Scheme 20; method 1).

With this method, Saeed and co-authors[91] demonstrated an effective and facile synthesis of benzoxazole methyl ester (**33**). The reaction between 2-aminophenol (**1**) and thiourea (**32**) at 200 °C for 2 h produced benzoxazole-2-thiol which was further reacted with methyl chloroacetate in methanol for 6 h at reflux. The authors further studied Hirshfeld surface analysis *via*



Scheme 19 Various pathways for the synthesis of benzoxazole using 2-aminophenol and different substrates.



Scheme 20 Various pathways for benzoxazole synthesis using 2-aminophenol with different substrates.

crystal packing interactions in which H–H interaction was found to make the biggest contribution (33.2%) to the entire crystal packing (Scheme 20; method 2).

In this procedure, efficacious elemental sulfur promoting the synthesis of benzoxazole derivatives (**35**) was introduced by Zhengyu and colleagues.[92] The reaction of 2-aminophenol (**1**) and 2-bromo-3,3,3-trifluoropropene (**34**), $NaHCO_3$ base, and 2,2′-azobis-(2,4-dimethylvaleronitrile) or bis(pinacolato) diboron ($ADVN/B_2Pin_2$) additive was conducted under a nitrogen atmosphere in DMF solvent at 100 °C for 15 h to obtain the desired product. A variety of derivatives was investigated in 38–85% yield by changing the substituents with different EWG and EDG at the aryl ring of the amino phenol. A simple workup process, a broad scope of functionalization, high yield, and cost-effectiveness are the highlights of this methodology with a long reaction time as its demerit (Scheme 20; method 3).

Rapolu *et al.*[93] developed an eco-friendly and microwave-irradiated one-pot synthesis of the analog of 2-substituted benzoxazole (**37**) from 2-aminophenol (**1**) and carbodiimides (**36**) in $ZnCl_2$ catalyst and isopropanol solvent at 80 °C for 30 min and found excellent yields (90–94%). This pathway is employed as an atom economic method with scaled-down toxicity, amount of solvent, and reaction time (Scheme 20; method 4).

3. Conclusion

Benzoxazole derivatives have evolved as an essential motif in organic chemistry with applications in medicinal, pharmaceutical, and industrial areas. This review article outlined recent synthetic methodologies of benzoxazole derivatives using 2-aminophenol with various other substrates like aldehydes, ketones, acids and acid derivatives, isothiocyanates, *ortho*-

esters, benzyl alcohol, alkynones, *etc.* with different solvents and catalysts like nanocatalysts, ionic liquid catalysts, and metal catalysts, amongst others. Most of the cited protocols are nurtured with simple, economical, and ecological approaches giving high yields, vast functionalization, and easy workup with less hazardous reagents, and reusable catalysts under mild reaction conditions. However, some methodologies have used hazardous solvents and harsh reaction conditions, which can hurt the environment. These reactions contribute to environmental concerns and call for the development of more environmentally friendly and sustainable methodologies in the field. This review will help researchers with new challenges to develop facile, cost-effective, and green approaches to synthesize benzoxazole derivatives to serve mankind.

Conflicts of interest

The authors confirmed that this article has no conflict of interest.

Abbreviations

TTIP	Titanium tetraisopropoxide
MTAMO	Mesoporous titania–alumina mixed oxide
H_2O_2	Hydrogen peroxide
K_2CO_3	Potassium carbonate
DMF	Dimethylformamide
$SrCO_3$	Strontium carbonate
ZnO	Zinc oxide
$FeCl_3$	Ferric chloride
$AgNO_3$	Silver nitrate
NaOH	Sodium hydroxide
MCF-7	Michigan Cancer Foundation-7
HCT-116	*Homo sapiens* colon carcinoma 116
Cu_2O	Copper oxide
DMSO	Dimethyl sulfoxide
$Pb(OAc)_4$	Lead tetraacetate
HCl	Hydrogen chloride
$NaNO_2$	Sodium nitrite
NaN_3	Sodium azide
$ZnBr_2$	Zinc bromide
KB	HeLa (Henrietta Lacks) KB
Hop62	Hopkins 62
A-549	Human adenocarcinomic alveolar basal epithelial cell line
Fe_3O_4	Iron(II,III) oxide
TBHP	*tert*-Butyl hydroperoxide
LED	Light emitting device
PPA	Polyphosphoric acid
pH	Potential of hydrogen
RHCAC	Rice-husk derived chemically activated carbon
Na_2S	Sodium sulfide
$MgSO_4$	Magnesium sulfate
NaO*t*-Bu	Sodium *tert*-butoxide
$POCl_3$	Phosphoryl chloride
BBr_3	Boron tribromide
$CHCl_3$	Chloroform
$AlCl_3$	Aluminium chloride
CH_2Cl_2	Dichloromethane
$LiAlH_4$	Lithium aluminium hydride
THF	Tetrahydrofuran
MsOH	Methane sulfonic acid
TFA	Trifluoroacetic acid
DCE	1,2-Dichloroethane
AChE	Acetylcholinesterase
BuChE	Butyrylcholinesterase
CH_3CN	Acetonitrile
NCTS	*N*-Cyano-*N*-phenyl-*p*-toluene sulfonamide
EDC·HCl	3-Ethylcarbodimide hydrochloride
MW	Microwave
$NaHCO_3$	Sodium bicarbonate
ADVN	2,2-Azobis-(2,4-dimethylvaleronitrile)
B_2Pin_2	Bis(pinacolato)diboron
EWG	Electron withdrawing group
EDG	Electron donating group
$ZnCl_2$	Zinc chloride
NMM	*N*-Methyl morpholine

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