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Review

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Benzodioxole Scaffold Incorporating Compound with Promising Anti-Fungal Potential: An Overview

This review focuses on the compounds with 1,3-benzodioxole scaffold and their antifungal potential. Different online sources including Google Scholar, Pubchem and Science Direct were used to collect information on benzodioxole containing compounds as antifungal agents from articles published between 2003 and 2022. The health threat posed by fungal infections to humans makes an ongoing search for more different antifungal agents necessary. Diverse heterocyclic moiety proves beneficial in fungal infection, among all of them benzodioxole incorporation into the compound was also found to be effective. The 1,3-benzodioxole or methylenedioxy benzene scaffold is highly adaptable, enabling a range of chemical modifications. The biophoric nature of this scaffold imparts distinctive pharmacological properties, contributing to its broad-spectrum activity. It was shown that the addition of heterocyclic moiety (e.g. primidinone, imidazole, thiazole, etc.), aliphatic linker, amide linker at position 5 and furthermore electron withdrawing group at position 6 enhances the antifungal potential against various phytopathogenic and human pathogenic fungi species. This review highlights the anti-fungal status of benzodioxole scaffold-containing compounds focusing on their efficacy against both phytopathogenic and human pathogenic fungal species. Additionally, the review discusses the structural modification and the future prospects of these compounds in antifungal therapy.

Keywords: Heterocyclic**,** 1,3-benzodioxole, fungal infection, biophoric nature, phytopathogenic, human pathogenic, Pharmacological properties, antifungal therapy.

Content

List of Abbreviations

ATCC — American Type culture collection
BDO — 1,3-benzodioxole
CYP — Cytochrome
DIZ — Diameter of the zone of inhibition
IC50 — Half-maximal inhibitory concentration
MIC — Minimum Inhibitory Concentration
NPBD — Nitropropenyl benzodioxole
NRRL — Northern Regional Research Laboratory

Review Plan

The present review focuses on threats of phytopathogenic and human pathogenic fungal infection and also highlights the benzodioxole incorporating compounds as an antifungal agent and their future prospects. The data presented in the past and recent research publications have been overviewed to provide a clearer understanding of the benzodioxole-containing compound as antifungal surrogates against phytopathogenic and human pathogenic fungal infection.

Various online sources, including Google Scholar, Pubchem, and Science Direct were used to gather information from studies that summarize both phytopathogenic and human pathogenic fungal infection and incorporated benzodioxole against them. This review focuses on the articles published between 2003 to 2022, with studies done before 2003 excluded from our review.

1 Introduction

Fungal infections have increased rapidly over the last several decades, posing a danger to human health and life. The increasing number of immunocompromised patients who are highly vulnerable to invasive fungal infections due to clinical treatment in intensive care units or the use of immunosuppressive therapy, as well as the increasing prevalence of drug-resistant fungi species, is an alarming trend [1]. In addition to invasive fungal infections in humans, the agricultural challenge of providing an adequate and safe food supply for all populations is currently threatened due to the infestation of food crops by virulent pathogens, particularly fungi, and evidence that resistant pathogenic species multiply rapidly once resistance sets in, posing a new challenge to drive the design and synthesis of bioactive chemical agents with high efficiency, more excellent selectivity, biocompatibility, and benign to human health as better alternatives to traditional synthetic fungicides [2, 3]. For decades, imidazole, pyrimidine, and some benzodioxole moieties, etc., have been crucial in and pesticides [4].

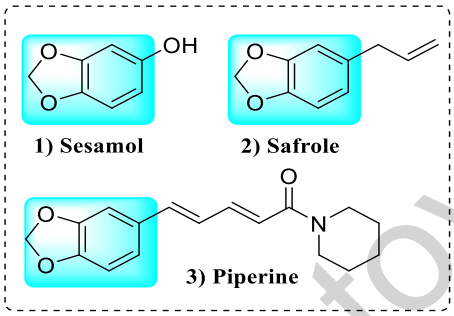


Figure 1. Benzodioxole scaffold containing compounds

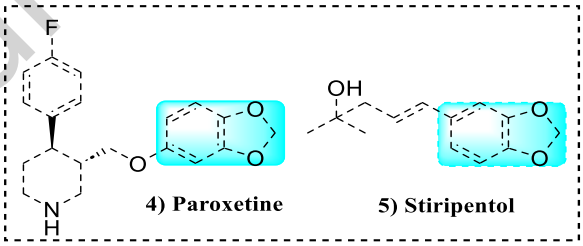


Figure 2 Benzodioxole-containing medicines

The 1,3-benzodioxole nucleus having methylenedioxy unit [5] is an isostere of benzothiazole nucleus [6], also known as BDO [7], and the existence of this pharmacophore confers potential biological activity and demonstrates its diverse character, which can be recognized by different receptors via hydrogen bonding and/or hydrophobic interaction [5, 8]. The key structure of this pharmacophore is present in many natural products (Fig. 1) [9–12] and medicines (Fig. 2) [13, 14]. This nucleus is found in a number of natural plant alkaloids, including Sanguinarine, Liriodenine, and Berberine, which have broad-spectrum action in both medicine and pesticides (Fig. 3) [15].

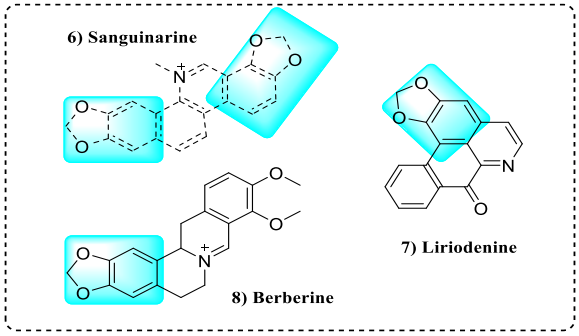


Figure 3. Plant alkaloids containing benzodioxole

1,3-Benzodioxole (BDO) are well-known heterocyclic units in the province of natural and synthetic organic chemistry due to their multiple existences as inhibitors of mono-oxygenase B enzymes [16, 17], antidepressant [14], anticonvulsant [18], pesticides [19], herbicides [20], antioxidant [21], antimicrobials [22–25], in addition, it also *possesses* antitumor [26], antihelminthic [27], antifungals [28–35], and antibacterial [6], anti-inflammatory and analgesic activity [36], anticancer [37], antiepileptic [38], antihypertensive [39], hepatoprotective and hypolipaedemic [40], immunomodulatory [41], antidiabetic [42] as shown in Figure 4. No cytotoxic effects of 1,3-benzodioxole derivatives were observed at a concentration of 10^{-4} M. The relatively low mammalian toxicity, in particular, is of significant interest [26].

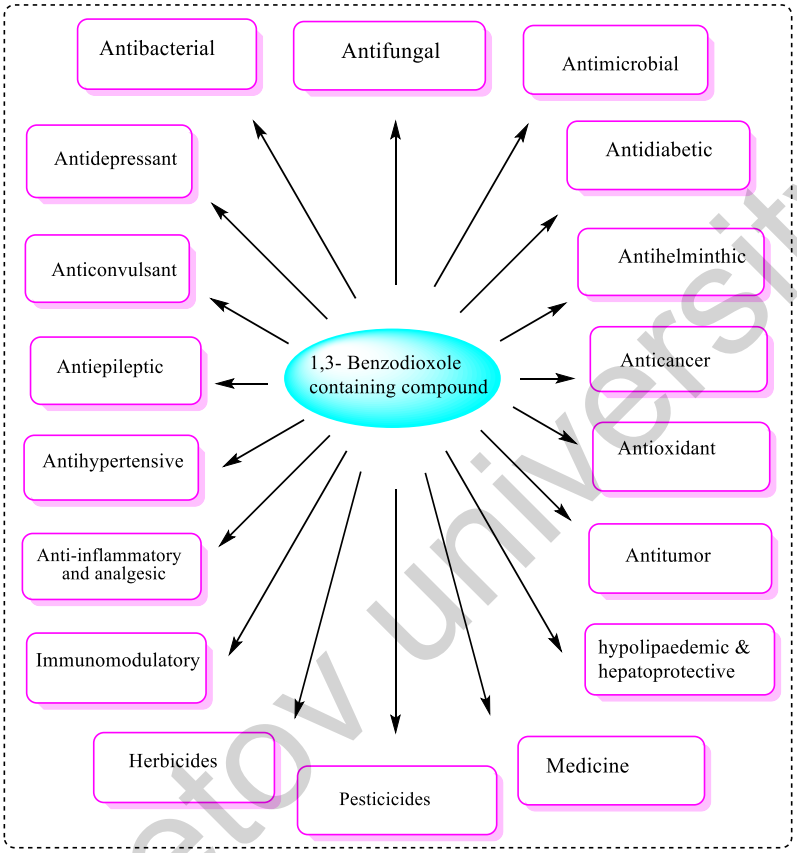


Figure 4. Benzodioxole scaffold containing compound with multiple pharmacological activities

2 The Anti-Fungal Activity Status of Benzodioxole Containing Compounds

2.1 Implication against Human Pathogenic Isolates

A brand-new pyrimidinone derivative incorporating 1,3-Benzodioxole moiety namely, 6-(1,3-benzodioxole-5-ylmethyl)-5-ethyl-2-{[2-(morpholin-4yl)ethyl]sulfanyl}pyrimidin-4(3H)-one was created by Attia et al. (Fig. 5) [22]. The diameter of the inhibition zone (DIZ) assay and the minimum inhibitory concentration (MIC) assay were carried out on agar to assess the target compound's antimicrobial potential against gram-positive bacteria (*Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* NRRL 4219, and *Bacillus cereus*), as well as pathogenic fungi (*Candida albicans* ATCC 10231 and *Aspergillus niger* NRRL). The outcomes were contrasted with Ampicillin trihydra, an antibacterial reference standard, and Clotrimazole, an anti-fungal reference standard. They confirmed the target compound's structure using single X-ray crystallography, particularly its S-alkylation., and they also emphasized its molecular packing, which is maintained by a weak intermolecular interaction. Additionally, they claimed that the targeted chemical was effective only against gram-positive bacteria (MIC value = 0.0619 towards *Staphylococcus aureus*) and some fungus species (MIC value = 0.1859 towards both *Candida albicans* and *Aspergillus niger*) [22].

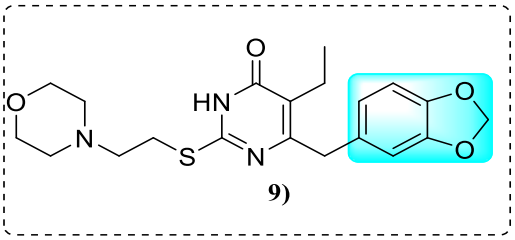


Figure 5. Novel primidinone derivative incorporating 1,3-benzodioxole moiety, namely,6-(1,3-5-ylmethyl)-5-ethyl-2-{[2-(morpholin-4-yl) ethyl]sulfanyl}pyrimidine-4(3H)-one

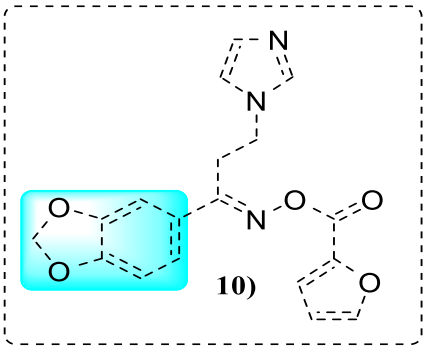


Figure 6. ({[(1E)-1-(1,3-Benzodioxole-5-yl)-3-(1H-imidazole-1-yl) propylidene]amino}oxy)-(furan-2-yl)methanone

New bioactive anti-fungal candidate ({[(1E)-1-(1,3-Benzodioxol-5-yl)-3-(1H-imidazol-1-yl)propylidene]-amino}oxy)(furan-2-yl) methanone was synthesized by Wabli and co-workers (Fig. 6) [28]. Their E-configuration identification of the imine fragment of the title compound was determined via single X-ray crystallography. The reported Natural bond analysis interpreted the chemical hyper-conjugative interactions and electron density transfer and also demonstrated the formation of intramolecular hydrogen bond interaction between n1(N9) and *(C23-H39) anti-bonding orbital with a stabilization energy of 0.65 kcal/mol, respectively, along with Natural population analysis to depict electron distribution and collectively provided the System with stability. The targeted chemical's Hirschfeld surface examination, frontier molecular orbital analysis, and molecular docking investigations were also completed. The optimization of the title compound's molecular structure was approximated using DFT theory at the B3LYP/6-311+G basis level set with the Gaussian 09 software program. The investigated conformation of the target molecule revealed its non-planarity due to steric hindrance. The computed wavenumbers were compared to the FT-Raman and FT-IR wavenumbers obtained experimentally. In the broth microdilution experiment, the title compound has shown equipotent action against *Candida albicans* and *Candida parapsilosis* with a MIC value of 0.724 mol/ mL and compared results with reference anti-fungal [28].

To combat various bacteria and fungi, Shahavar Sultana et al. [25] synthesized a novel series of 20 compounds of thiophene and benzodioxole-linked thiazolyl-pyrazolines (Fig. 7). The findings showed that the majority of the synthesized compounds exhibited antimicrobial activities against 8 bacteria*; Salmonella typhimurium, Klebsiella pneumonia, Proteus vulgaris, Shigela flexneri, Micrococcus luteus, Enterobacter aerogens, Staphylococcus aureus and staphylococcus aureus (MRSA-methicillin resistant)*; 2 fungi: *Candida albicans* and *Malassesia pachydermatis*. To compare results, streptomycin, Gentamicin (antibacterial), Ketoconazole, and fluconazole (anti-fungal) were taken as reference drugs. Gram-positive and Gram-negative bacteria and fungi were found to have significant MIC values. Comparing compounds 11e, 11o, 11r, and 11t to other studied compounds, they showed highly excellent antibacterial activity. When tested against the identified micro-organisms, compound 11o outperformed all other compounds with a MIC value of 31.25 μg/mL [25].

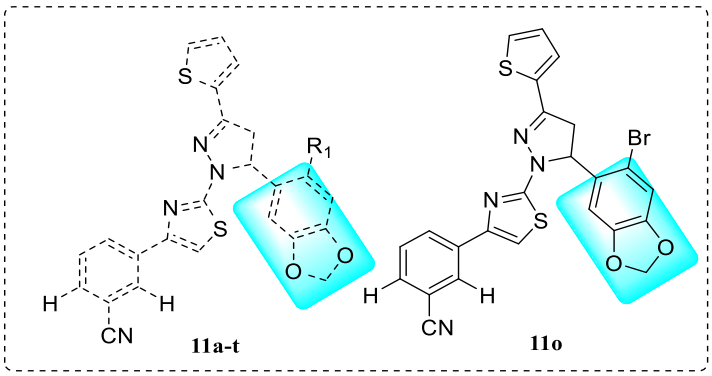


Figure 7. Some thiophene and benzodioxole-linked thiazolyl-pyrazolines derivatives

The cellular target of the studied compound was identified as Sec14p by Pries et al. [32], who also reported the existence of picolinamide and benzamide chemotypes with anti-fungal activities (Fig. 8). Sec14p is a key player in the pathogenicity and virulence of pathogenic fungi. According to the guidelines of the Clinical Laboratory Standards Institute, the inhibitory effect of compounds 2 and 3 were assessed in vitro against four different and clinically significant pathogens: two dimorphic fungi from the Candida genus (*C. albicans* and *C. glabrata*), one filamentous fungus (*Aspergillus brasiliensis*), and the yeast *Cryptococcus neoformans* as a representative of the Basidiomycota. A triazole chemical called posconazole was utilized as a positive control [32].

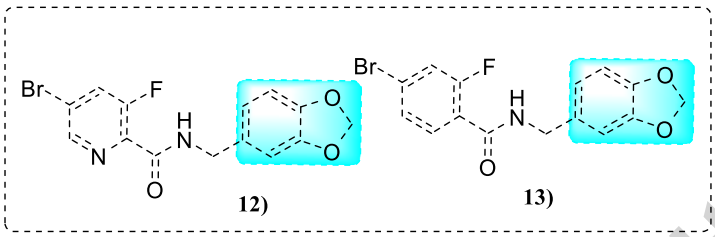


Figure 8. A few picolinamide and benzamide chemotypes with anti-fungal potential

The phenotypic effects of NPBD (Nitropropenyl benzodioxole) on saprophytic, commensal, and parasitic fungal species were studied by Nicoletti and White (Fig. 9) [31]. They examined the variety of distribution and function of cysteine-based enzymes and redox-active thiol compounds, as well as how to select pathogens of interest with desirable properties for an anti-fungal medication candidate. Nitropropenyl benzodioxole was shown to have more potent antibacterial and anti-fungal action than nitroethenyl compounds. Except for parasitic dermatophytes, NPBD demonstrated wide, robust, and rather homogeneous anti-fungal efficacy against 27 saprophytic, commensal, and parasitic species from three orders and twelve families. Hyphae may have a higher MIC and Minimum Fungicidal Concentration (MFC) titre than micro-conidial inocula. In vitro efficacy of NPBD against hyphal forms of thermally dimorphic *fonsecaea*, *Hortaea*, *Phialophora*, *S. apiospermum*, and *C. neoformans*, *Blastomyces dermatitis*, *Histoplasma capsulatem*, *Coccidiodes* species (MIC_{90}: 0.25–2 mg/L), *Cryptococcus gatti* (2mg/L), *Candida glabrata* (0.5–2 mg/L). In the literature, they advocated that NPBD be developed as a therapy for mucocutaneous opportunistic fungal infections [31].

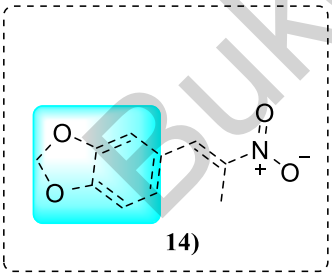


Figure 9. Nitropropenyl Benzodioxole

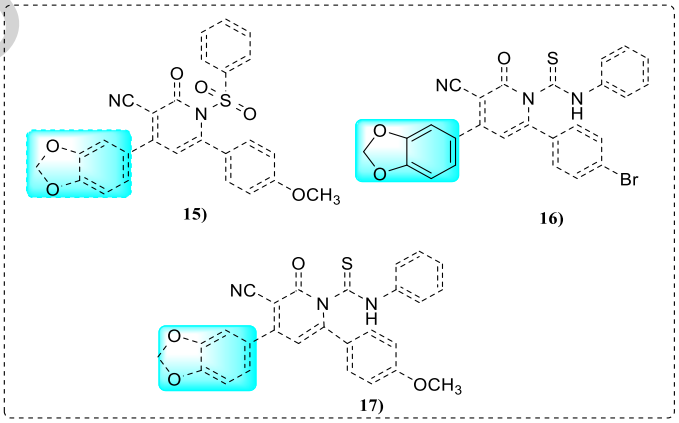


Figure 10. 1,4,6-trisubstituted-2-oxo-1,2-dihydropyridine-3-carbonitriles containing benzodioxole functionalities

A series of 35 unique 1,4,6-trisubstituted-2-oxo-1,2-dihydropyridine-3-carbonitriles were synthesized by Faidallah et al. [23] with some functionalities claimed to have substantial chemotherapeutic potential (Fig. 10). The antimicrobial activity was assessed using an agar cup diffusion technique and a two-fold serial dilution method against Gram-positive bacteria *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6633), & *Micrococcus luteus* (ATCC 21881), Gram-negative bacteria *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853). The cytotoxic activity against three cell lines was also reported, and ampicillin, Clotrimazole, and doxorubicin were used as standard reference drugs for comparing the activity with the synthesized compound. According to the literature, 17 analogs showed antimicrobial

activity, whereas 13 analogs had cytotoxic potential against three human tumor cell lines. In a series of 35 compounds, compound 15 was shown to be the most potent cytotoxic agent and antimicrobial agent, making compounds 15, 16, and 17 attractive dual antimicrobial-anticancer possibilities [23].

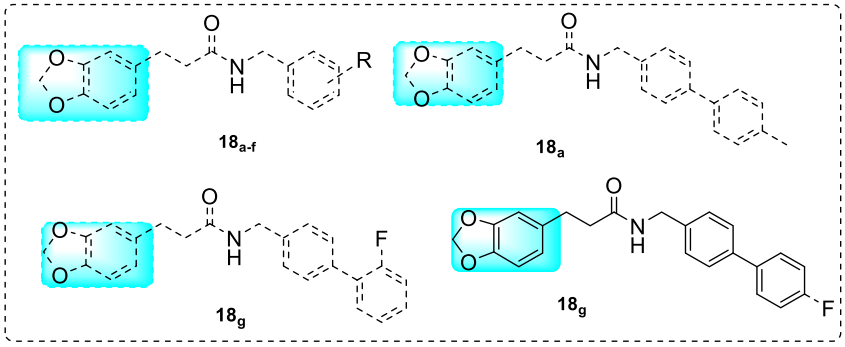


Figure 11. Some 3-(benzo [1,3] dioxol-5yl)-N-(substitutedbenzyl0-propanamides derivatives are arranged

In vitro testing and synthesis of fluconazole-synergistic 3-(benzo[d][1,3]-dioxol-5yl)-N-(substituted benzyl)-propanamide was performed by Cai et al. (Fig. 11) [29]. The lead compound 7d's amide moiety was swapped out for a retro-amide moiety to create the series 18a-f, and compounds 18a, 18e, and 18g showed more potent compounds to boost fluconazole's anti-fungal activity against the most prevalent fungal pathogen, *Candida albicans*, and reported that while they did not individually have anti-fungal activity when combined, they increased fluconazole's susceptibility to fluconazole-resistant *Candida albicans* [29].

2.2 Implication against Phytopathogenic Fungi

In 2020, based on a piperine scaffold, a series of 21 novel compounds (19–21a-g) were designed and synthesized by Wang et al. [35], which were derived from naturally occurring phenolic compounds found in essential oils (Fig. 12). They then tested the compound's potential anti-fungal activity using mycelial growth rate against six phytopathogenic species, including *Gloeosporium thea-sinensis*, *Fusarium graminearum,* and *Phomopsis adianti*. Among 21 essential oil derivatives, some target compounds showed good inhibitory action, some had more decisive inhibitory action, and some had more vigorous inhibitory activity than the original piperine and carbendazim against the tested fungus. They carried out the preliminary assay value and IC_{50} value determination steps in the primary screening and secondary screening. They claimed that compound 20b had broad-spectrum fungicidal and broad-spectrum bacteriostatic activity [35].

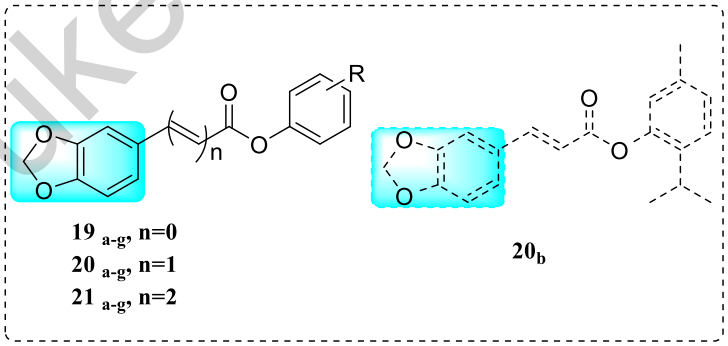


Figure 12. Piperine based essential oil derivatives;
18b: -(2-Isopropyl-5-methylphenyl 3-(benzo[d] [1,3] dioxol-5-yl)acrylate

The series of lactam analogs containing 1,3-benzodioxole, 21(a-o), and the 2(5H)- furanone derivatives, 21(p-s) were designed and synthesized by Song et al. (Figure 13) [34]. Their anti-fungal activities were assessed against four serious crop-threatening agricultural fungi, including *Rhizoctonia solani*, *Alternaria tenuis Nees*, *Gloesporium theae-sinensis*, and *Fusarium graminearum* and carbendazim and piperine were used as a standard reference drug. Against particular phytopathogenic fungi, some of the compounds demonstrated strong anti-fungal efficacy. Compound 7b demonstrated the best anti-fungal activity in vitro against *Gloeosporium theae-sinensis* and *Fusarium graminearum*, with +IC_{50} values of 64.47 and 113.47 mg/L, respec-

tively. Compounds 21a, 21b, and 21i, which emerged as a novel lead compound, showed stronger inhibitory effects against Alternaria tenuis Nees than the widely used fungicide carbendazim. In addition, 1,3-benzodioxole was found to enhance the activity [34].

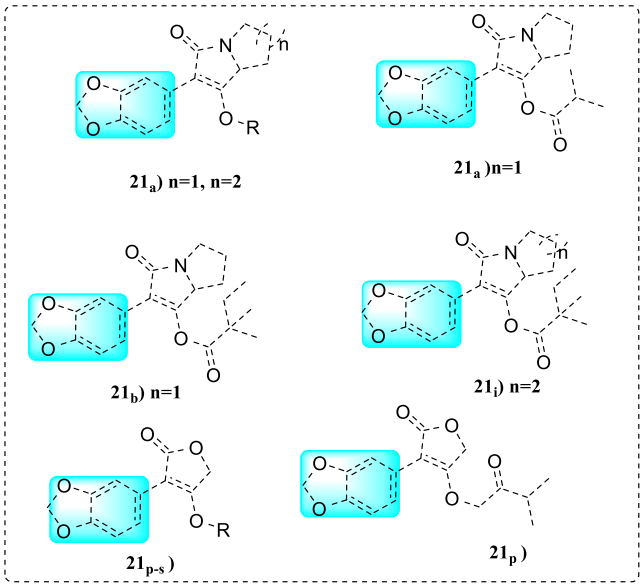


Figure 13. Lactam analog (21a-o) and furanone analog (21p-s) derivatives containing benzodioxole

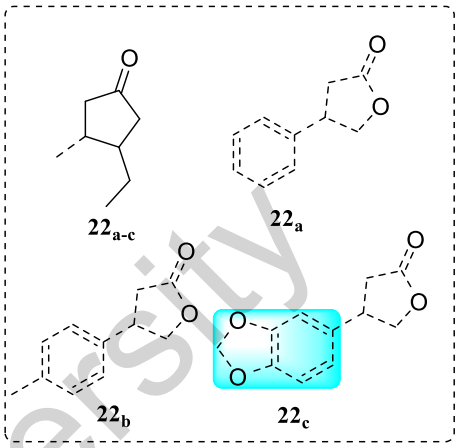


Figure 14. Some β-aryl-γ-lactone derivative/benzodioxole containing lactone derivative

Eighteen derivatives of racemic β-aryl-γ-lactones through chemical synthesis were prepared, characterized, and tested for their antifeedant and fungistatic activity by Skrobiszewski et al. (Fig. 14) [33]. The aromatic substituent structure was the most important element in anti-fungal action. The lactones with benzo[d][1,3]dioxole ring (22c etc.) were the most active whereas those with an unsubstituted benzene ring had a little action. Didecyldimethylammonium chloride (DDAC) was utilized as a reference compound. Eight lactones were shown to be effective against *Tribolium confusum, Trogoderma granarium, SitophilusGranaries,* and four species of *fusarium* species. The highest inhibition was observed for lactone 22c, which inhibited the growth of *F.oxysporum* AM13 in 70 %, F. avenaceum AM 11 and *F. solani* AM 203 in 66 %, and F. culmorum AM 9 in 55 %.The highest activities were found in the group of trans-γ-ethyl-γ-lactones (22a-c): lactone 22a and 22b were strong antifeedants, whereas lactone 22c exhibited the highest anti-fungal activity [33].

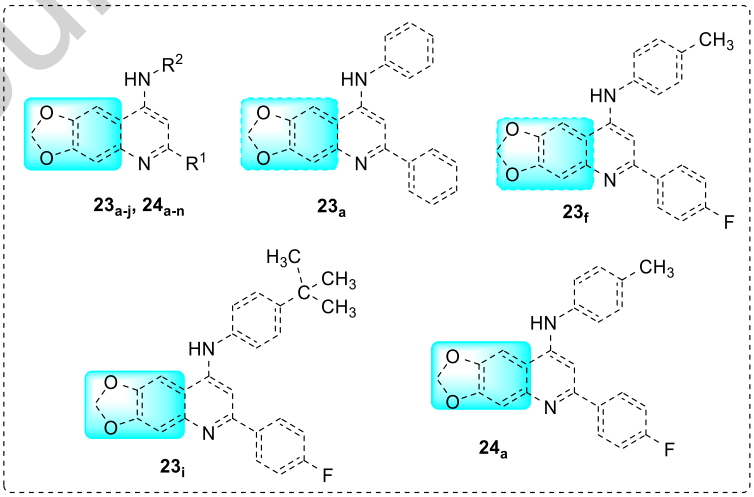


Figure 15. Some of the 4-aminoquinoline derivative containing 1,3-benzodioxole moiety

In 2021, a series of aminoquinolines bearing a 1,3-benzodioxole moiety were prepared and characterized by Yang et al. [4]. All of the target compounds (23a-23j and 24a-24n) and the positive control azoxystrobin (a commercial agricultural fungicide) were tested in vitro for anti-fungal activity against five phytopathogenic fungi (*P. piricola, A. brassicae, C. lunata, P. grisea*, and *A. alternate*) at 50g/mL using the mycelium growth rate method (Fig. 15). It was discovered that quinolone compounds with a phenyl substitution at position 2 and an aniline moiety at position 4 were effective anti-fungal possibilities, with the aniline moiety at position 4 playing a significant role in anti-fungal activity. Among compounds 23a-23j, compounds 23f and 23i possessed potent anti-fungal activities against the five tested fungi with an inhibition rate of more than 51.1 %. In most cases, their anti-fungal potencies were superior to the positive control azoxystrobin against the matching fungal strains. Moreover, compound 23a demonstrated anti-fungal solid activity against *C. lunata* and *A. alternative*, with 71.5 % and 63.1 % inhibition rates, respectively. After that, compound 24a–24n was produced by derivatization from compound 23f further to investigate the impact of C-2 substituents on anti-fungal efficacy. Most of the compounds 24a–24n demonstrated good to exceptional anti-fungal activity against the bulk of the fungal strains examined [4].

Anti-fungal activity against *C. lunatus* strain MUCL 38696 (m118), *A. niger* N402 cspA1, and *P. ostreatus* Plo5, Korosec et al. [30] tested 42 selected compounds of cinnamic acid derivatives (Fig. 16). Compound 25 was the most effective *C. lunatus* inhibitor. Additionally, the methyl piperidine in compound 28 anticipated that it would be able to generate Vander Waals and hydrophobic contacts with Ile274. Compound 28 demonstrated broad and robust anti-fungal activity, suppressing fungal growth by 75 % in all three tested species. Compound 25 literature predictions of the interaction between benzodioxole oxygen and heme iron may help to explain why both compounds 25 and 28 have more inhibitory activity than cinnamic acid. They show that the fungus benzoate 4-hydroxylase, CYP53A15, is competitively inhibited by cinnamic acid and four (25, 26, 27, and 28) of the 42 investigated derivatives [30].

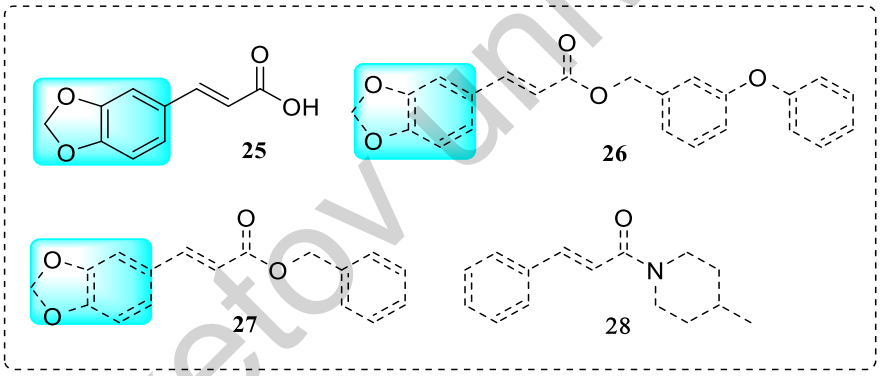


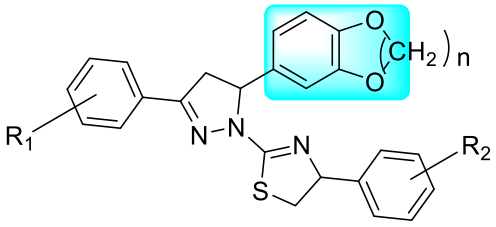
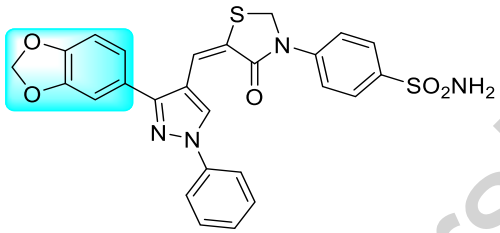
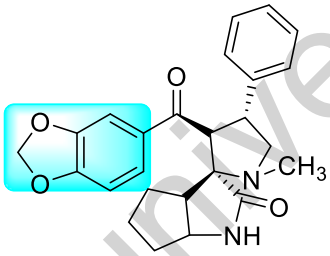
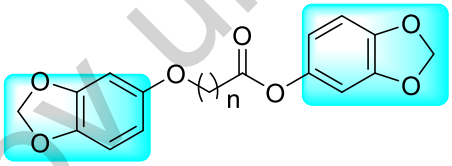
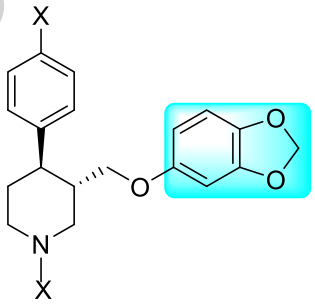
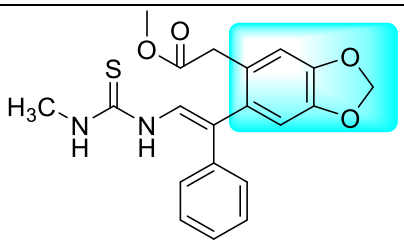
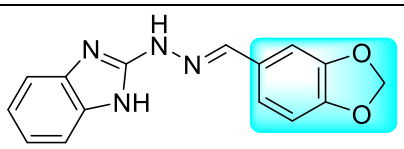
Figure 16. Some of the Cinnamic acid derivatives are 25. (E)-3-(benzo [d][1,3] dioxol-5-yl) acrylic acid, 26. (E)-3-phenoxybenzyl-3-(benzo[d][1,3] dioxol-5-yl)acrylate, 27. (E)-benzyl 3-(benzo[d][1,3]dioxol-5-yl)acrylate, 28. (E)-1-(4-methylpiperidin-1-yl)-3-phenyl prop-2-en-1-one

2.3 Miscellaneous Activity of Benzodioxole Incorporating Compounds

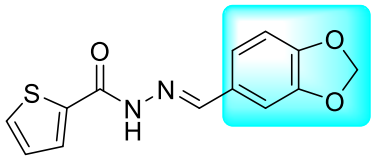
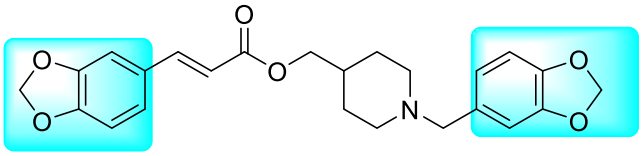
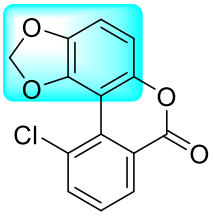
The benzodioxole moiety is a structural feature commonly found in numerous bioactive compounds, particularly in the field of medicinal chemistry. Its versatility allows it to exhibit a wide range of pharmacological activities. Table presents some of the miscellaneous potential associated with benzodioxole nucleus-containing compounds.

T a b l e

Miscellaneous activity of benzodioxole nucleus-containing compounds

S.No.	Biological activity	Chemical compound	Reference
1.	Anticancer activity	 n=1 or 2	(H.H. Wang et al., 2013) [37]thirtythree
2.	Anti-inflammatory and analgesic		(Abd El Razik et al., 2017) [36]
3.	Antidiabetic		(Nivetha et al., 2022) [42]
4.	Hypolipaedemic & hepatoprotective		(Xie et al., 2021) [40]
5.	Antidepressant		(Slack et al., 2019) [14]
6.	Anticonvulsant		(Aboutabl et al., 2020a) [13]
7.	Antihelminthic		(Anichina et al., 2021) [27]

Continuation of Table

S.No.	Biological activity	Chemical compound	Reference
8.	Antihypertensive		(Leal et al., 2012) [39]
9.	Leishmanicidal		(Fernandes et al., 2015) [43]
10.	Antioxidant		(Zhou et al., 2021a) [21]

3 Future Perspectives of 1,3-Benzodioxole as an Antifungal Agent

The substances discussed in this review show promising antifungal activity. It is essential to understand the molecular mechanisms that drive the antifungal effect of these drugs. In order to find ways to increase the efficacy of these compounds, reduce their toxicity and increase their bioavailability, future research could focus on further optimising their structures. It is possible to increase efficacy and lower the likelihood of resistance development by combining antifungal drugs with various modes of action. The compounds containing 1,3-benzodioxole may have synergistic effects with currently available antifungal agents or with one another. It's critical to evaluate the environmental impact of these compounds in light of agricultural applications that were highlighted in the assessment. If these substances demonstrate efficacy in clinical trials and agricultural settings, factors such as large-scale manufacturing, affordability, and regional accessibility will be critical to their practicality.

4 Conclusions

The emergence of resistance to the existing anti-fungal drugs is a threatening condition for agroecosystems apart from a severe threat to human health. Therefore, researchers are motivated to find novel, secure, low-toxicity, low-resistance, high-efficacy anti-fungal compounds because of the progressive rise in the resistance profile and host toxicity of the currently available anti-fungal medications. The 1,3-benzodioxole scaffold in the arena of anti-fungal treatment against several pathogenic fungus species is well explained in this article. The material gathered from multiple reliable papers briefly explains that attachment of heterocycle moiety (e.g., primidinone, imidazole, thiazole, etc), aliphatic linker, amide linker at position 5, and in addition electron-withdrawing group (e.g., Br_2, etc.) at position 6 enhances the antifungal potential against various phytopathogenic and human pathogenic fungus species. The review may facilitate the creation of novel anti-fungal lead candidates and be very helpful to researchers and readers in medicinal chemistry.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Amita Joshi Rana, Sanjana Bisht, Kumud Upadhyaya** — conceptualization, data curation, investigation, methodology, validation, visualization, writing-review and editing; **Pawan Singh, Mahendra Rana, Shweta Singh** — data curation, formal analysis; **Sanjana Bisht, Pawan Singh** — conceptualization, data curation, resources, supervision, writing — original draft, writing — review and editing.

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Conflict of interest

The authors declare no conflict of interest.

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