BIOLOGICAL POTENTIAL OF BENZOXAZOLE DERIVATIVES: AN UPDATED REVIEW

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ABSTRACT

Heterocycles exhibited an extensive role in the medicinal chemistry for the development of pharmaceutically active molecules. A heterocyclic scaffold is responsible for the therapeutic potential of majority of synthesized drug molecules. Therapeutic changes in the drug molecules related to the slight changes in the heterocyclic moiety. Benzoxazole and its derivatives showed potent and significant pharmacological activities. The main objective of our study is to impart updated information about synthesized benzoxazole derivatives and their biological potential against numerous diseases. A literature search was directed on the databases namely in MDPI, Science direct, PubMed, Springer, Taylor and Francis by searching different keywords “Benzoxazole”, antimicrobial activity, anticancer activity, antitubercular, anti-inflammatory, analgesic, and antihelminthic activity. This review may radiate the path of researchers that are working to synthesized novel benzoxazole derivatives in the prospects of effectiveness and safety. Nonetheless, further in-vivo and clinical studies are warranted on the potential derivatives of benzoxazole.

Keywords: Benzoxazole, Anticancer, Heterocyclic, Antibacterial.

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INTRODUCTION

History of heterocyclic compounds begins with mid-19th century alongside the advancement of organic chemistry. Heterocyclic compounds are a significant piece of the chemical and life sciences. In the pharmaceutical industries, more than 75% of the best 200 medications are from heterocyclic family [1]. A progression of simple and subordinates of heterocyclic bearing nitrogen, oxygen, and oxazole moieties establishes the core structure of numerous biologically active compounds. Most of the pharmaceuticals and naturally active agrochemicals are heterocyclics [2,3]. The compounds derived from the heterocyclic moiety assume a significant role in the advanced medication disclosure, which is wide, applied in the field of restorative science, on account of their various biological activities such as antiviral, anticancer, antimicrobial, antitubercular, antimalarial, and antioxidant [4].

Benzoxazole (1-Oxa-3-aza-1H-indene) is a heterocyclic compound with a benzene fused oxazole ring structure. Oxazole (Fig. 1a) is a 1-3-ylene having an oxygen atom and a pyridine-type nitrogen atom at the 3-position in a five-membered ring. Hantzsch first introduced this compound in 1887. The molecular formula of benzoxazole (Fig. 1b) is C7H6NO3, and its molar mass, melting points, and boiling point are 119.12 g/mol, 27–30°C, and 182°C, respectively [4-7].

Benzoxazoles have an extensive range of promising biological activities (Fig. 2) such as anticancer [8], antihelminthic [9], cyclooxygenase inhibitor [10], antifungal [11], antitubercular [12], SHT, receptor antagonists [13], anti-inflammatory, analgesic and cyclin-dependent kinase inhibitor [14], 5-lipoxygenase inhibitor [15], melatonin receptor agonist [16], anticancer [17], antibacterial [18], anti-HIV-1 [19], anticonvulsant [20], antiviral [21], antiparasitic [22], antiallergic [23], antipyretic [24], COX-2 inhibitor [10], antihyperglycemic [25], dopaminergic D2 agonists [26], herbicidal [27], amyloido genesis inhibitors [28,29], rhino kinase inhibitors [30], and diarrhea dependent irritable bowel syndrome [31].

In addition to their use in medicinal chemistry, benzoxazoles are documented as considerable scaffold in fluorescent probes such as anion and metal cation sensors [32-34]. Many patents on this benzoxazole moiety have been published which highlight its importance, some of which are presented in Table 1.

Plentiful researches were carried out during the past decades on synthesis and biological potential of benzoxazole derivatives, but the available review imparting only scattered information exploring their activity is accessible. Besides, earlier reports did not provide the depth information about the synthesis of benzoxazole derivatives. Considering this, the present review is an attempt to provide a comprehensive review on natural and synthesized benzoxazole derivatives and their biological potentials and also enlighten about the future prospects.

METHODOLOGY

A depth literature review was performed by probing biological potential, natural, and synthesized derivatives of benzoxazole. Published information from several articles and cross-references were collected. Several resources searched, including technical reports, conference proceedings, and web-based scientific databases such as American Chemical Society, PubMed, Bentham Science, Science Direct, Springer, Google Scholar, BMC, MEDLINE, and SCOPEMED, other allied databases covering fields of pharmacology, pharmaceutical chemistry, medicinal chemistry, and biomedicine were rationally reviewed and taken into the study for the report. The publication with available abstract or full text was reviewed for this study along with few existing reviews. This review encompassed the available literature from January 1947 to March 2020.

BIOLOGICAL POTENTIAL OF BENZOXAZOLE DERIVATIVES

Literature review revealed that fourteen benzoxazole derivatives were isolated from the natural sources and their biological potential against cancer, microbial infection (Gram positive, Gram negative, fungi, and yeast), and tuberculosis were studied. These naturally active benzoxazole compounds, their sources, and reported biological activities are tabulated in Table 2 and their structures are shown in Fig. 3.

Anticancer activity

Earlier studies suggested that 39 benzoxazole derivatives were synthesized and tested for anticancer potential toward numerous cell
The structures of these synthesized compounds are presented in Fig. 4.

Omer et al. synthesized 2-substituted benzoxazole derivatives and evaluated their in vitro proliferative potential against MCF-7 and MDA-MB-231 cell lines. Compounds (15a), (15b), and (16) exhibited higher cytotoxic potential toward MCF-7 cell line while compounds (15c), (17), and (18) showed potential cytotoxic activity against MDA-MB-231 cell lines [65].

Kumar et al. synthesized 14 derivatives of benzoxazole linked combretastatin and evaluated their anticancer potential against three human cancer lines, namely, MCF-7 (breast), A549 (lungs), and A375 (melanoma). The study revealed that out of these 14 derivatives, four derivatives (19a-19d) showed potent anticancer activity, doxorubicin was used as standard drug under this study [66].

Philoppes and Lamiet synthesized benzoxazole derivatives with phthalamide core and screened their anticancer activity toward HepG2 and MCF-7 cell lines. Researchers concluded that compound (20) exhibited higher anticancer potential toward both cancer cell lines with IC₅₀ values 0.011 and 0.006 μM, respectively [67].

Kakkar et al. synthesized benzoxazole derivatives and performed their anticancer activity against human HCT-116 cancer cell line using sulforhodamine-B (SRB) assay. The result of this study revealed that compound 21 was found to be a potential anticancer effect on cancer cell line with IC₅₀ value 24.5 μM. 5-Fluorouracil was used as a positive control in this study [68].

Abdelgawad et al. prepared benzoxazole substituted pyrazole derivatives and evaluated their antiproliferative potential against MCF-7 and A549 cancer lines using the MTT assay. Results of this study revealed that benzoxazole derivatives (22a), (22b), and (22c) showed IC₅₀ value against MCF-7 cell lines, respectively >25, 15.47, and 10.86 while IC₅₀ value against A549 cell lines, respectively, >25, 15.08, and 11.32. Doxorubicin was used as positive control in this study [69].

El-Hady et al. synthesized benzoxazole derivatives and evaluated their antitumor potential toward two cancer cell lines, MCF-7 and HePG2. The finding of this study suggested that synthesized compound 4-{2-(1,3-benzoxazol-2-yl)-2[(phenylcarbonyl)amino]ethyl}-2-bromophenyl acetate 23 showed potent activity toward MCF-7 and the compound 4-{2-(1,3benzoxazol-2-yl)-2-[(phenylcarbonyl)amino]ethyl}-2-bromophenyl chloroacetate 24 exhibited higher antitumor potential towards HePG2 with IC50= 6.7 lg/ml to 6.9 lg/ml, respectively [70].

Belal and Abdelgawed synthesized 10 benzoxazole-pyrazole hybrids and screened their anticancer potential against three human cell lines, namely, A549, MCF-7, and HeP3B. Compound 25 showed higher anticancer potential against A549 [71].

Gan et al. prepared two novel mononuclear copper (II)-Dipeptide complexes of 2-(2′-Pyridyl) benzoxazole and studied their anticancer potential against A549, PC-3, and HeLa cancer cell lines. Compound 26 exhibited higher anticancer potential than compound 27. Cisplatin was used as positive control in this study [72].

Srivastava et al. synthesized benzoxazole derivative by 1,3-dipolar cycloaddition reaction and screened their anticancer property against three cancer cell line HeLa, SKBr3, and HepG2.
Table 1: Patents of benzoxazole and their derivatives [35-46]

| S. No. | Title of patent | Patent no. | Application/publication no. | Patent date       | Inventor                  |
|--------|-----------------|------------|-----------------------------|-------------------|---------------------------|
| 1.     | Synthesis method of benzoxazole compound | CN104327008A | CN103554050A | Feb. 2, 2015 | Zhou et al.               |
| 2.     | Benzothiazole and benzoxazole derivatives and methods of use | US8580968B2 | US13/410,206 | Nov. 12, 2013 | Black et al.              |
| 3.     | Benzoxazole or benzoxazole compounds as SUMO activators | WO2014036242A3 | PCT/US2013/057264 | Aug 29, 2013 | Russell Dahl et al.       |
| 4.     | Organic compound, benzoxazole derivative, and a light-emitting element, light-emitting device, and electronic device using benzoxazole derivative | US8450485B2 | US13/427,119 | May 28, 2013 | Hiroshi Kadoma et al.     |
| 5.     | Benzoxazole, oxazolopyridine, benzothiazole, and thiazolopyridine derivatives | AU2006286573B2 | AU2006286573A | May 31, 2012 | Alfred Binggeli et al.    |
| 6.     | Benzoxazole, thiazolopyridine, benzothiazole, and oxazolopyridine derivatives as antidiabetic compounds | JP4708474B2 | JP2008500888A | June 22, 2011 | Wolfgang et al.           |
| 7.     | Benzoxazoles: Benzoxazole, benzthiazole, and benzimidazole derivatives | CA2338048A1 | PCT/GB1999/002377 | Jan 12, 2010 | Mathews et al.            |
| 8.     | 6-O-Substituted benzoxazoles and benzothiazoles and methods of inhibiting CSF-1R signaling | US7553854B2 | US 11/737,069 | Jun 30, 2009 | Sutton                    |
| 9.     | Benzimidazole, benzthiazole, and benzoxazole derivatives and their use as lta4h modulators | EP1660491B1 | EP04779219A | Aug 6, 2008 | Axe et al.                |
| 10.    | Benzoxazole derivatives and their use as adenosine receptor ligand | WO2004063177A1 | PCT/EP2004/000053 | July 29, 2004 | Norcross                  |
| 11.    | Benzoxazole, benzthiazole, and benzimidazole acid derivatives and their use as heparanase inhibitors | WO2004046122A3 | PCT/GB2003/04991 | June 3, 2004 | Courtney et al.           |
| 12.    | Benzoxazole derivatives as novel melatonergic agents | US6737431B2 | US10/383,131 | May 18, 2004 | Takaki et al.             |

Table 2: Naturally occurring benzoxazole derivatives and their biological activities

| S. No. | Name of compounds | Source | Biological activities | References |
|--------|-------------------|--------|-----------------------|------------|
| 1.     | Calcimycin (A23187) | Streptomyces chartreusis NRRL 3882 | Antimicrobial | [47,48]     |
| 2.     | Routiennocin | Calcimycin analog | Antimicrobial | [49-52]     |
| 3.     | Gezomyacin | Calcimycin analog | Antimicrobial | [49-52]     |
| 4.     | UK-1 | Mycelial cake of an actinomycete strain | Anticancer (B16, HeLa, and P388 cell lines) | [53-56] |
| 5.     | MUK-1 | Methyl derivative of UK-1 | Antimicrobial | [55]        |
| 6.     | DMUK-1 | Dimethyl derivative of UK-1 | Antibacterial | [55]        |
| 7.     | AJI9561 | Streptomyces species (mycelium extract) | Anticancer (Jurkat and P388 cell lines) | [54-57] |
| 8.     | Nataxazole | Streptomyces species (strain Tü 6176) | Anticancer (AGS, MCF7 and HepG2 cell lines) | [58] |
| 9.     | Caboxamycin | Streptomyces species NTK 937 (marine strain) | Antimicrobial, anticancer (AGS, HepG2, and MCF-7 cell lines), and antitubercular | [59-61] |
| 10.    | IleBethoxazole | Pseudopterogorgia elisabethae | Antitubercular | [60-62] |
| 11.    | Nakijinol B (Sesquiterpene benzoxazole) | Methanol extract Dactylospongia elegans (marine sponge) | Anticancer (SF-268, H460, MCF-7, and HT-29 cell lines) | [63] |
| 12.    | Nakijinol B diacetate | Acetylated derivative of Nakijinol B | Anticancer (SF-268, H460, MCF-7, and HT-29 cell lines) | [63] |
| 13.    | Secospseudopteroxazole (marine diterpenoid alkaloid) | Pseudopterogorgia elisabethae (Indian gorgonian coral) | Antitubercular | [60] |
| 14.    | Camptothecin | Camptotheca acuminata (bark and steam) | Anticancer and traditional Chinese medicine | [64] |

respectively. The results of this study revealed that compound 2-[1-(2,4-difluorobenzyl)-4-(4methoxyphenyl)-1H-1,2,3-triazol-5-yl]-5-methyl-1,3-benzoxazole 28 reported significant anticancer activity toward all three cell lines [73].
Abdelgawad et al. synthesized benzoxazole derivative using 4-benzoxazol-2-yl-phenylamine as starting material and evaluated their anticancer potential against human MCF-7 and MDA-231 cell lines using MTT assay. Results of this study revealed that benzoxazole derivatives (29a), (29b), and (29c) showed IC_{50} value against MDA-231 cell lines, respectively, 42, 37, and 17 while IC_{50} value against MCF-7 cell lines, respectively, 30, 31, and 12. Doxorubicin was used as a positive control in this study [74].

Murty et al. synthesized piperazinyl benzoxazole derivatives (30a-30j) coupled with 1,3,4-oxadiazole-2-thiol and screened their anticancer potential against five different human cancer cell lines, namely, MCF-
Fig 4: Benzoxazole derivatives with anticancer potential

7, HeLa, HepG2, A431, and A549 using MTT assay. Compounds 30a, 30e, and 30j showed higher anticancer activity as compared to other synthesized compounds (30b and 30c) [75].

Hady and Abubshait prepared benzoxazole derivatives (31a-31c) and studied their anticancer potential against MCF-7 and HepG2 cancer cell lines. Compounds 31a and 31c exhibited higher anticancer potential against the HepG2 cell line with IC50 values 6.7 μg/ml and 6.9 μg/ml, respectively. Vinblastine was used as positive control in this study [76].

Jauhari et al. synthesized 2-substituted benzoxazole derivatives and studied their anticancer activity against the HeLa, WiDr, HepG2, and MCF-7 human cancer cell lines. This study results revealed that compounds 32 and 33 exhibited higher antioxidant activity against all four cancer lines [77].

Antimicrobial activity

The previous literature revealed that 45 benzoxazole derivatives were synthesized and screened their potential toward number Gram-positive and Gram-negative bacterial species as well as fungal strains. The structures of these synthesized compounds are shown in Fig. 5.

Kakkar et al. synthesized benzoxazole compounds and screened their in vitro antimicrobial action toward one Gram-positive (Bacillus subtilis) and four Gram-negative (Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonias, and Salmonella typh) bacterial strains and two fungal strains (Candida albicans and Aspergillus niger) using tube dilution technique. The study revealed that compounds (34a-34f) and 35 had potential antimicrobial activity. Ofloxacin and fluconazole were used as a positive control in this study [68].

Srivastava et al. synthesized benzoxazole derivative 2-[1-benzyl-4-[4-methoxyphenyl]-1H-1, 2, 3- triazol-5-yl]-1,3-benzoxazole (36) and screened their antibacterial potential against Gram-negative bacteria (S. aureus and E. coli). The results of this study indicated that this compound exhibited potent antibacterial activity against both Gram-positive and Gram-negative bacterial strains [73].

Jain et al. synthesized 2-substituted benzoxazole organophosphates and investigated their antibacterial potential against one Gram-positive (Staphylococcus aureus) and one Gram-negative (Escherichia coli) bacterial strains. Researchers also synthesized 2-substituted benzoxazole phenoxy derivatives and studied their antifungal potential against two fungal strains (Aspergillus niger and Fusarium oxysporum). The compounds 37a-37l were found to moderate antibacterial and antifungal activity [78].

Seenaiah et al. synthesized eight pyrimidinyl benzoxazoles derivatives and evaluated their antibacterial potential toward Gram-positive
Fig. 5: Benzoxazole derivatives with antimicrobial potential

(*Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacterial strains and two fungal strains (*Aspergillus niger* and *Penicillium chrysogenum*) at three different concentrations 25, 50, and 100 mg/well, respectively. Out of these eight synthesized compounds, four compounds were tested for their antibacterial activity by agar well diffusion assay. Compound **38** (4-chloro-pyrinidylsulfanylmethyl benzoxazole) showed the least activity. The amino linked heterocycles **39** showed slightly higher activity than those having thio group **40**. While pyrimidinyl bis methylthio benzoxazole **41** displayed greater activities toward *S. aureus*.
and *P. chrysogenum* both gram negative bacterial strains. Compound 41 also displayed good antifungal potential than other three compounds. Ciprofloxacin and ketoconazole were used as standard drug under this study [79].

Vodela et al. synthesized 2-(5-substituted-[1,3,4]oxadiazol-2-yl)-benzoxazole derivatives and investigated their antimicrobial activity toward four Gram-positive (*S. aureus, S. albus, S. faecalis*, and *K. pneumoniae*) and four Gram-negative (*E. coli, P. aeruginosa, P. mirabilis*, and *S. typhi*) bacterial strains and two fungal (*C. albicans* and *A. fumigatus*) strains by disk diffusion method. The results of this study revealed that compound 42a was good active only against *S. faecalis* and almost inactive toward *E. coli*. This compound exhibited moderate antimicrobial potential against the rest of the organisms. Compound 42b exhibited mild-to-moderate activity against the tested Gram-positive and Gram-negative organisms. In contrast, surprisingly, the compound 42c with ethyl substituent is compared with other molecules that were found to be inactive against *E. coli*. The higher antimicrobial property was seen in the compound 42d with para nitro phenyl derivative against *S. aureus, S. albus, S. faecalis, K. pneumoniae*, and *P. aeruginosa* as compared to the standard drug amikacin, but shows only moderate activity against *E. coli* and *P. mirabilis*. This compound also performed high activity against two fungal organisms with marked activity index. This study suggested an introduction of a nitro group reflect better activity against different organisms. Both compounds 42e and 42f with relative substituents exhibit the highest antifungal activity against *C. albicans* and *A. fumigatus* as compared to the standard drug fluconazole [80].

Jayanna et al. synthesized (5,7-dichloro-1,3-benzoxazol-2-yl)-3-phenyl-1H-pyrazole-4-carboxaldehyde derivatives 43a-43e and evaluated their antimicrobial potential against two Gram-positive (*Klebsiella pneumoniae* RSHM 574, *Pseudomonas aeruginosa* ATCC 25853, *Staphylococcus aureus* ATCC 29213, and *Bacillus subtilis* ATCC 6633), one Gram-negative (*Escherichia coli* ATCC 25922) bacterial strains and two fungal strains (*Candida albicans* ATCC 10231 and *Candida krusei* ATCC 6258). Compound 44 displayed potent MIC value against all tested bacterial and fungal strains [81].

Arisoy et al. 2,5-disubstituted benzoxazoles and screened their antimicrobial potential toward four Gram-positive (*Klebsiella pneumoniae* RSHM 574, *Pseudomonas aeruginosa* ATCC 25853, *Staphylococcus aureus* ATCC 29213, and *Bacillus subtilis* ATCC 6633), one Gram-negative (*Escherichia coli* ATCC 25922) bacterial strains and two fungal strains (*C. albicans* and *A. niger*). Streptomycin and fluconazole were used as a positive control in this study. Compound 43b displayed higher antimicrobial potential against all tested bacterial and fungal trains [81].

Phatangare et al. synthesized five derivatives 45(a-d) and 46 of CH,CH,CH_2OCH_2CH_2N=CHCO_2H [1,3,4]oxazole and studied their antimicrobial activity against two Gram-negative (*E. coli* and *S. aureus*) bacterial strains and two fungal strains (*C. albicans* and *A. niger*). Streptomycin and fluconazole were used as a positive control in this study [83].

Rangadhol et al. synthesized 5,7-Dichloro-1,3-benzoxazole-2-thiol and screened their antibacterial activity against two Gram-positive (*B. subtilis* and *S. aureus*) and four Gram-negative (*E. coli, P. aeruginosa, P. vulgaris*, and *S. typhi*) bacterial strains. Compounds 47, 48, and 49 displayed good antibacterial agents without showing any resistance against bacterial strains. Ciprofloxacin was used as a positive control in this study [84].

Arpacı et al. synthesized five-[2-{(morpholin-4-yl) acetamido} and 5-[2-{4-substituted piperazino-1-yl]acetamido]-2-(p-substituted phenyl] benzoxazole derivatives [50a and 50b] and screened their Gram-positive and Gram-negative bacteria as well as the yeasts *C. albicans, C. krusei, and C. glabrata*. The study results revealed that synthesized compounds have shown a large spectrum of antimicrobial potential [85].

Ranalingam et al. synthesized benzoxazolyl ethoxypropiononedes [51] and examined their antimicrobial property against three Gram-positive (*S. faecalis, B. subtilis, and S. aureus*) and two Gram-negative (*E. coli and P. aeruginosa*) bacterial strains and three fungal (*C. albicans, A. niger, Candida-51, and *A. flavus*) strains. The compound showed higher antimicrobial potential against all bacterial and fungal strains [86].

**Antioxidant activity**

Aichaoui et al. synthesized 2(3H)-benzoxazolone derivatives and screened their *in vitro* antioxidant potential in 10 μM concentration to prevent human LDL copper-induced oxidation using Cu²⁺ as oxidizing agent. Compound 52 showed higher antioxidant potential and inhibit the initiation and the propagation of copper-mediated LDL oxidation as determined by time- and dose-dependent manner [87]. Structure of synthesized compound is shown in Fig. 6.

**Anti-inflammatory activity**

Earlier researches demonstrated that 13 benzoxazole derivatives with anti-inflammatory potential were synthesized. The structures of these synthesized compounds are shown in Fig. 7.

Angajala and Subashini synthesized 2-substituted benzoxazole derivatives and evaluated their anti-inflammatory property using membrane stabilization and proteinase inhibitory methods. The results of this study revealed that compounds 53, 54, and 55 exhibited good anti-inflammatory potential with percentage inhibition of 74.26 ± 1.04, 80.16 ± 0.24, and 70.24 ± 0.68 for membrane stabilization activity 80.19 ± 0.05, 85.30 ± 1.04, and 75.68 ± 1.28 toward proteinase inhibitory efficacy at a concentration of 100 μg/mL [88].

Ajaz et al. synthesized bis[5-hlorobenzodio]oxazole-2-y1) derivatives 56a-56d. Synthesized compounds exhibited immunomodulatory property by a decrease in TNF-α, IL-1β, and IL6 secretion in 56a-56d plus LPS-treated groups when compared to LPS-treated control group [89].

Kaur et al. synthesized N-(2-[3,4,5-trimethoxybenzyl]-benzamido derivatives (3a-3n). In *vivo* anti-inflammatory activity of these six compounds (57a-57f) was assessed by carrageen-induced rat paw edema method. The compound 57a (79.54%), 57e (75.00%), 57f (72.72%), and 57b (68.18%) exhibited significant anti-inflammatory activity than standard drug ibuprofen (65.90%) [90].

**Analgesic activity**

Praveen et al. developed benzoxazole derivative by cyclocondensation reaction and performed their analgesic property using the tail immersion method. The results of this study revealed that 58, 59, 60, 61, and 62 showed the least analgesic potency, respectively, 50.6%, 50.9%, 51.3%, 51.3%, and 50%. Compounds 63 and 64 exhibited moderate analgesic potential, respectively, 54.5% and 59.6% while compounds 65, 66, and 67 demonstrated higher analgesic potency, respectively, 73.5%, 76.4%, and 74%. Pentazocine was used as a positive control.

**Fig. 6: Benzoxazole derivative with antioxidant potential**
in this experiment [91]. The structures of these synthesized analgesic compounds are presented in Fig. 8.

**Antitubercular activity**

Rana et al. developed benzoxazole derivatives and screened their antitubercular potential towards *Mycobacterium tuberculosis* H37RV and multidrug-resistant TB (MDR-TB) strains. Compounds 68a and 69g exhibited potent activity toward H37RV with MIC values 0.625 and 1.25 μg/ml. Compounds 68c, 68h, and 69h showed moderate activity toward H37RV with MIC values 6.25, 3.25, and 6.25 μg/ml while other derivatives demonstrated the least potential toward *M. tuberculosis* H37RV strain. Compounds 69c and 69f exhibited moderate antitubercular potential against MDR-TB strain with MIC values 6.25 and 6.25 μg/ml while the other compounds exhibited the least potential toward this strain [92]. The structures of these compounds are presented in Fig. 9.

**Antihyperglycemic activity**

Singh et al. synthesized benzoxazole derivatives (70a-70d and 71a-71d) and studied their α-amylglucosidase inhibitory activity. Compounds 70b and 71b showed potent IC₅₀ values in the range of 0.24 ± 0.01–0.94 ± 0.01 μM and compounds 71a and 71c demonstrated least inhibitory activity against α-amylglucosidase with IC₅₀ values 22.00 ± 1.21 and 29.03 ± 1.11 μM while other compounds demonstrated moderate potential. Acarbose was used as a positive control in this experiment [93]. Structures of these synthesized compounds with antihyperglycemic potential are presented in Fig. 10.

**Anthelmintic activity**

Satyendra et al. synthesized 5-nitro-1, 3-benzoxazole derivatives and evaluated their anthelmintic activity. The results of this study demonstrated that compounds 72 and 73 showed the potent anthelmintic properties. The researcher also performed molecular docking studies and concluded that the inhibition of β-tubulin target protein elite to the parasites is the principal mechanism behind the anthelmintic property of these synthesized compounds [94]. Structures of these synthesized compounds with anthelmintic property are presented in Fig. 11.

**Antileishmanial activity**

Kapil et al. synthesized 2-(4-((2,4-dichlorobenzyl) oxy)phenyl)-1H-benzo[d]oxazole (74) and screened its antileishmanial activity towards *Leishmania donovani* using miltefosine as standard. Synthesized compounds showed IC₅₀ 57 ± 4.2 μM [95]. Structures of these synthesized compounds with antileishmanial property are presented in Fig. 12.
Enzymes inhibitory activity

Arpaci et al. developed 2-[4-(4-substituted benzamido/phenylacetamido/butanamido)phenyl]-5-ethylsulphonyl-benzoxazole derivative and studied their tyrosinase, acetylcholinesterase (AChE), and butyrylcholinesterase (BChE) inhibitory activity. The study suggested that compound 75 showed moderate tyrosinase inhibition, but compound did not exhibit inhibitory effect against AChE and BChE [96]. Structures of these synthesized compounds with enzyme inhibitory property are presented in Fig. 13.

Neuroprotective activity

Luisa et al. synthesized 2-amino-6-(trifluoromethoxy)benzoxazole derivatives (76-80) and studied their neuroprotective potential toward amyotrophic lateral sclerosis. All the synthesized compounds were tested for voltage-dependent Na⁺ current blocking activity using the patch clamp technique in primary cultures of cerebellar and cortical neurons. Riluzole was used as positive control in this study. Compounds 80 and 81 exhibited higher voltage-dependent Na⁺ current blocking potential (97±2% and 98±2%) while the compounds...
Structures of these synthesized compounds with neuroprotective potential toward amyotrophic lateral sclerosis are presented in Fig. 14.

Anticonvulsant activity
Ibrahim et al. synthesized 5-chloro-2-substituted sulfanylbenzoxazole and performed their anticonvulsant activity against pentylenetetrazole-induced seizures in mice. Researchers also studied the molecular docking study of synthesized compounds to assess their binding affinities to the KCNQ2 receptor. The result of this study revealed that...
compounds 81, 82, 83, and 84 showed the highest binding affinities toward KCNQ2 receptor along with the highest anticonvulsant potential [98]. Structures of these synthesized compounds with anticonvulsant activity are presented in Fig. 15.

CONCLUSION AND FUTURE PERSPECTIVES
Numerous researches stated that benzoxazole scaffold is versatile multifunctional molecules that exhibited their therapeutically potential cancer and microbial strains. This review may provide a novel arena for medicinal chemistry researchers that are working in the development of novel compounds containing benzoxazole scaffold. Researchers synthesized numerous derivatives with potent biological activity but still, clinical study on these synthesized compounds is warranted.

AUTHORS’ CONTRIBUTIONS
All authors have equally contributed to the drafting, reviewing, and editing of the manuscript.

CONFLICTS OF INTEREST
There are no conflicts of interest.

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