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Review Article

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 anthelmintic 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-azole 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 C_7H_5NO, and its molar mass, melting points, and boiling point are 119.12 $gmol^{-1}$, 27–30°C, and 182°C, respectively [4-7].

Benoxazoles have an extensive range of promising biological activities (Fig. 2) such as anticancer [8], antihelmintic [9], cyclooxygenase inhibitory [10], antifungal [11], antitubercular [12], $5HT_3$ receptor antagonists [13], anti-inflammatory, analgesic and cyclin-dependent kinase inhibitory [14], 5-lipoxygenase inhibitory [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 inhibitory [10], antihyperglycemic [25], dopamine D_4 agonists [26], herbicidal [27], amyloidogenesis inhibitors [28,29], rho kinase inhibitors [30], and diarrhea dependent irritable bowel syndrome property [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 report 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

lines. 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 IC_{50} 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 IC_{50} value 24.5 μM. 5-Fluorouracil was used as a positive control in this study [68].

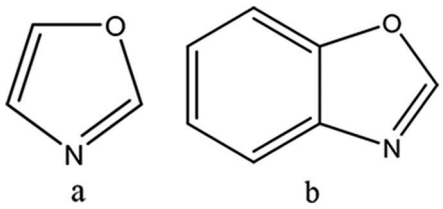


Fig. 1: (a) Oxazole (b) Benzoxazole

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 IC_{50} value against MCF-7 cell lines, respectively >25, 15.47, and 10.86 while IC_{50} 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,

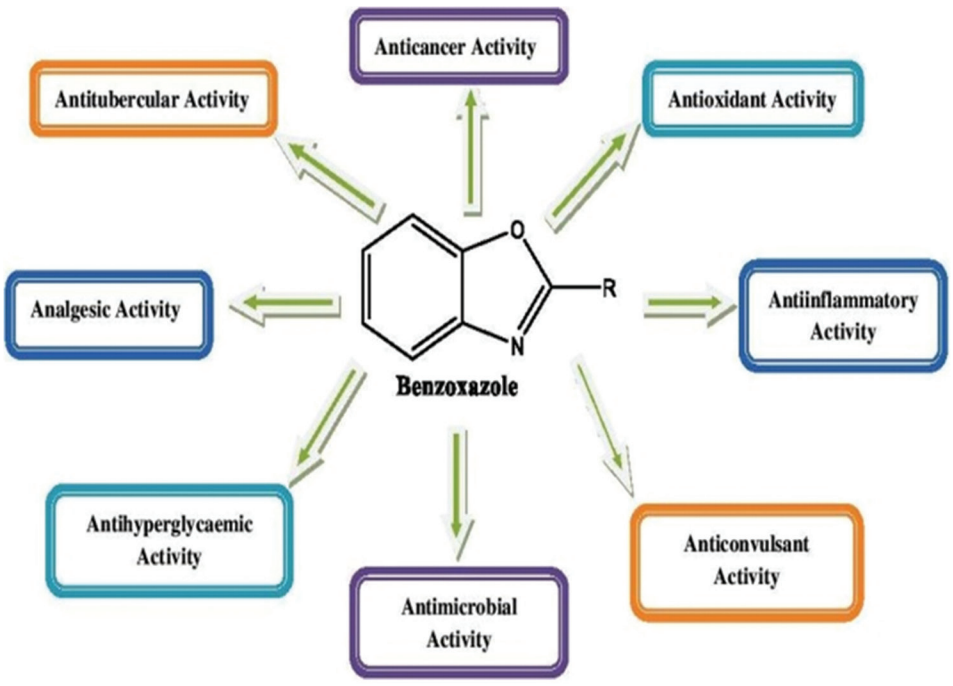


Fig. 2: Biological activities of benzoxazole and its derivatives

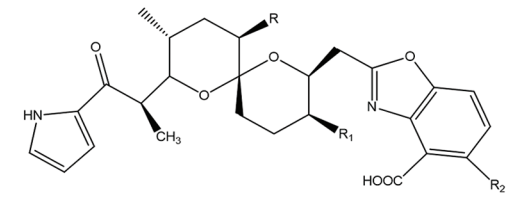
Table 1: Patents of benzoxazole and their derivatives [35-46]

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.	Benzothiazole or benzoxazole compounds as SUMO activators	WO2014036242 A3	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.	Benzothiazole, thiazolopyridine, benzoxazole, and oxazolopyridine derivatives as antidiabetic compounds	JP4708474B2	JP2008500088A	June 22, 2011	Wolfgang *et al.*
7.	Benzazoles: Benzoxazole, benzthiazole, and benzimidazole derivatives	CA2338048A1	PCT/GB1999/002377	Jan 12, 2010	Mathews *et al.*
8.	6-O-Substituted benzoxazole and benzothiazole compounds 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/GB2003/004991	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.	Cezomycin	Calcimycin analog	Antimicrobial	[49-52]
4.	UK-1	Mycelial cake of an actinomycete strain	Anticancer (B16, HeLa, and P338 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.	Secopseudopteroxazole (marine diterpenoid alkaloid)	*Pseudopterogorgia elisabethae* (Indian gorgonian coral)	Antitubercular	[60]
14.	Camptothecin	*Camptotheca acuminata* (bark and steam)	Anticancer and traditional Chinese medicine	[64]

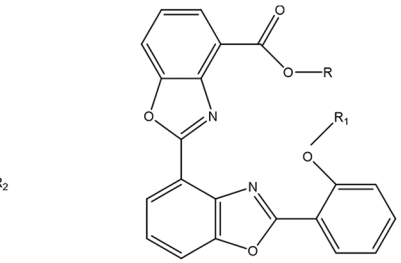
respectively. The results of this study revealed that compound 2-[1-(2,4-difluorobenzyl)-4-(4methoxyphenyl)-1H-1,2,3-triazol-5-yl]-5-methyl-1,3-benzoxazole **28** reported significant anticancer activity toward all three cell lines [73].



1. R=CH_3, R_1=CH_3, R_2=$NHCH_3$

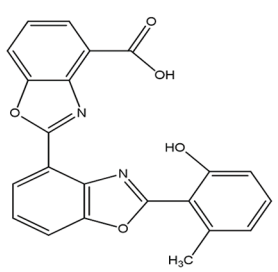
2. R=CH_3, R_1=CH_3, R_2=H

3. R=H, R_1=H, R_2=OH



(4-6)

4. R=CH_3, R_1=H; **5.** R=CH_3, R_1=CH_3; **6.** R=H, R_1=H



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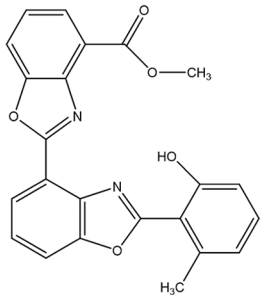

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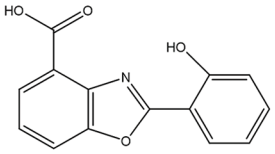

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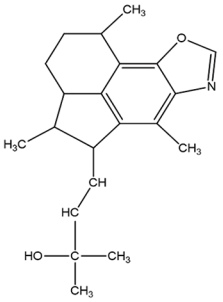

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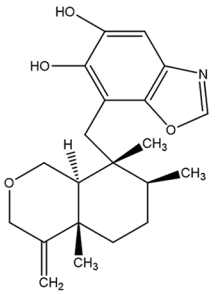

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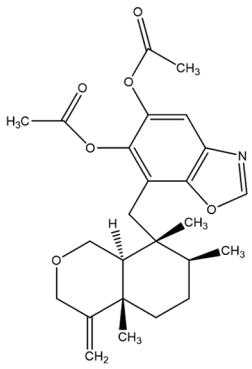

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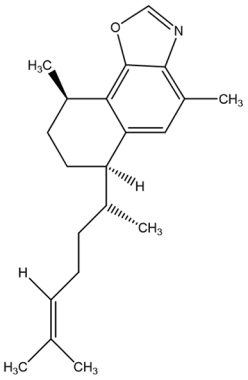

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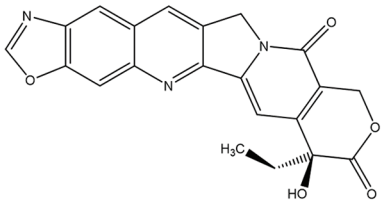

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Fig. 3: Naturally occurring benzoxazole derivatives

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, and12. 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-

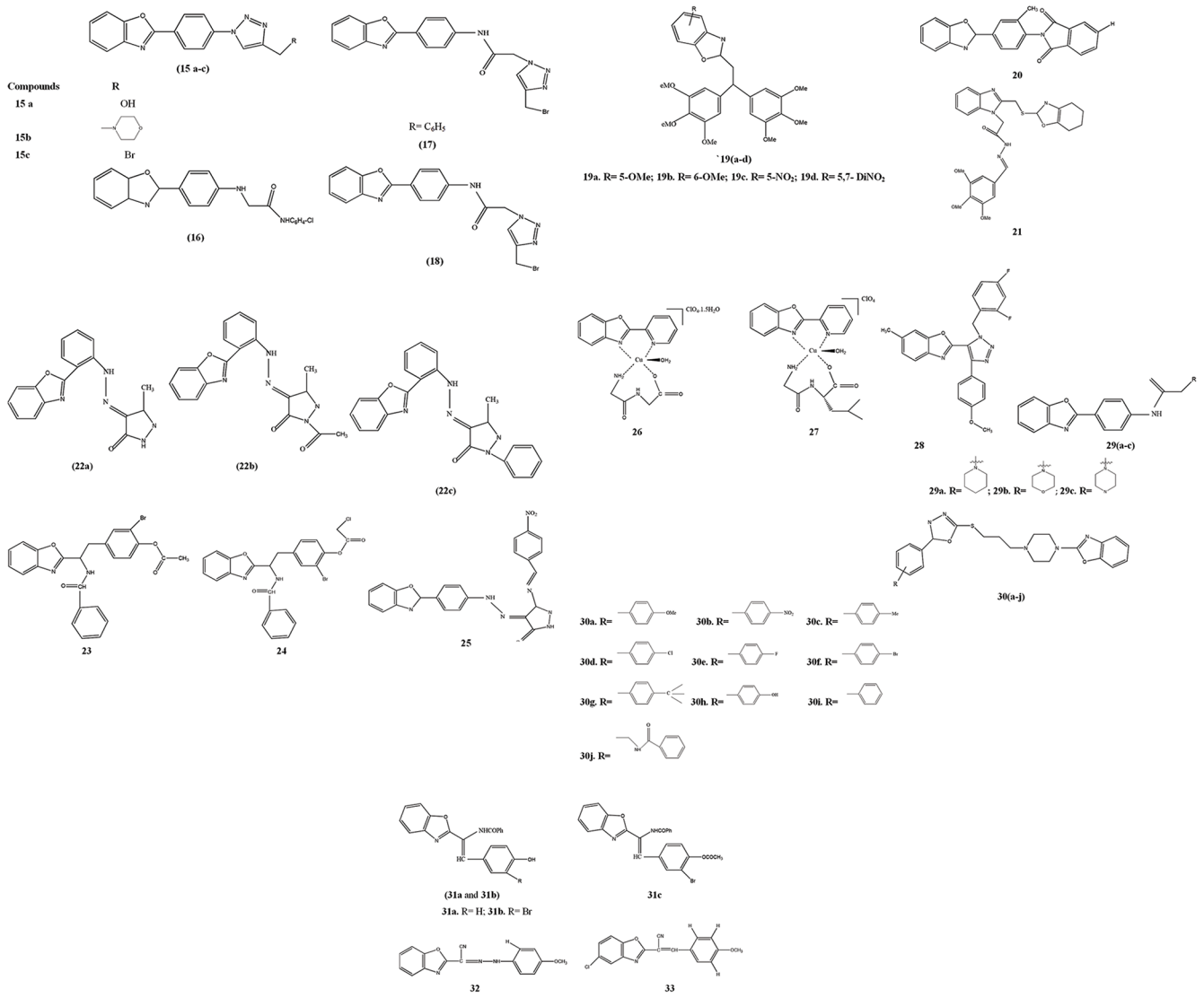


Fig. 4: Benzoxazole derivatives with anticancer potential

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 IC_{50} 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 pneumoniae*, and *Salmonella typhi*) 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

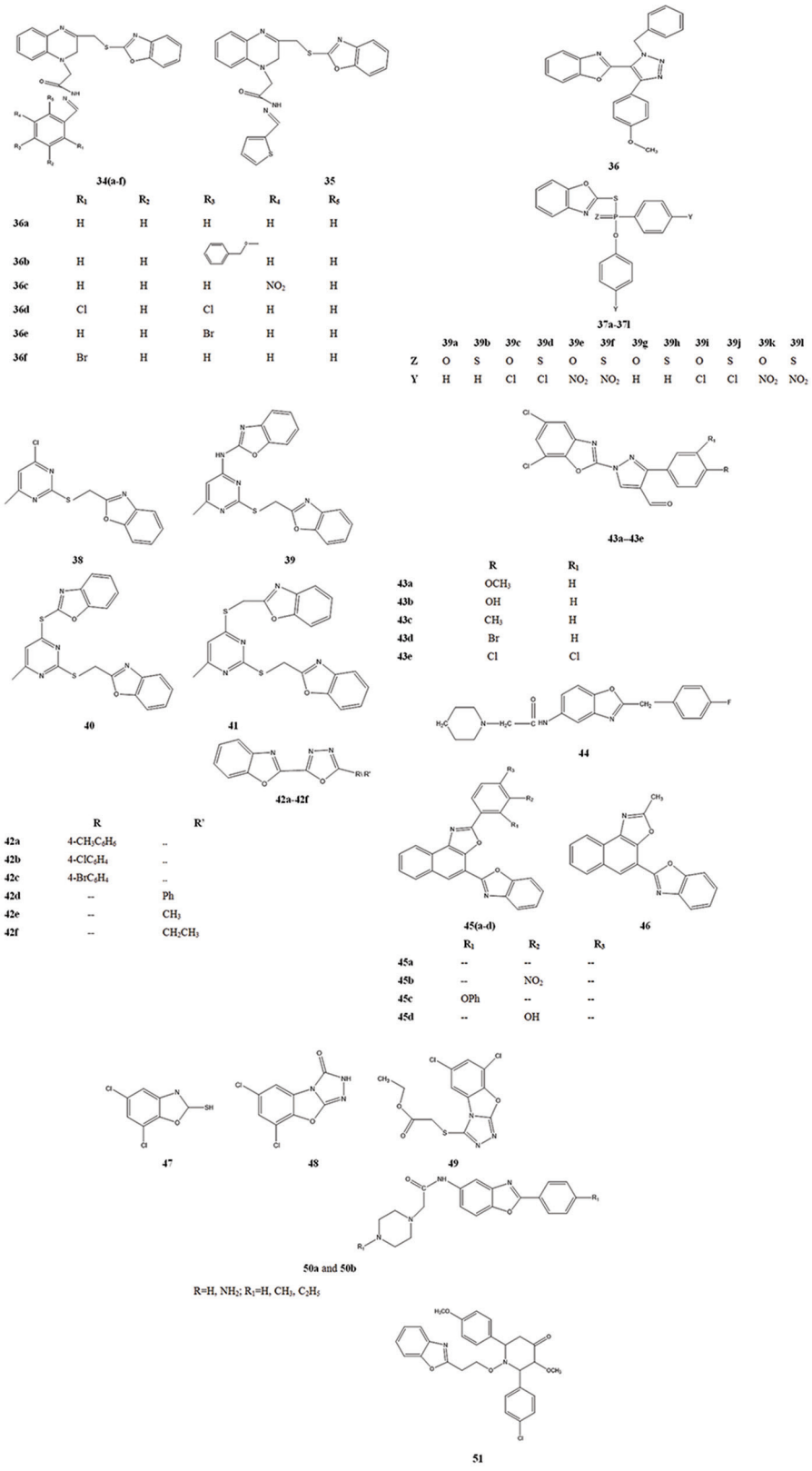


Fig. 5: Benzoxazole derivatives with antimicrobial potential

(*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-pyrimidinylsulfanylmethyl 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)-benzoxazoles 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. fumigates*) 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 reflected 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-carbaldehyde derivatives **43a–43e** and evaluated their antimicrobial potential against two Gram-positive (*S. aureus* and *B. subtilis*) two Gram-negative (*E. coli* and *S. typhi*) bacterial strains and two fungal strains (*A. niger* and *C. albicans*) in 10–50 μg concentrations. Ciprofloxacin and fluconazole were used as positive control in this study. Compound **43b** displayed higher antimicrobial potential against all tested bacterial and fungal trains [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 25923, 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 [82].

Phatangare *et al*. synthesized five derivatives **45(a-d)** and **46** of 4-(1,3-benzoxazol-2-yl)-2-phenylnaphtho[1,2-*d*][1,3]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].

Arpaci *et al*. synthesized five-[2-(morpholin-4-yl) acetamido] and 5-[2-(4-substituted piperazine-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 ethoxypiperidones **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 Cu^{+2} 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.

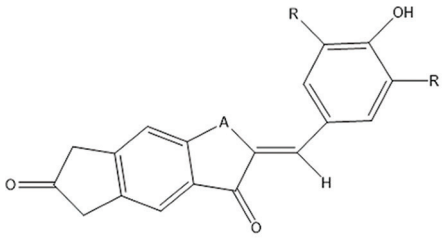
Angajala and Subashini synthesized 2-substituted benzoxazole derivatives and evaluated their anti0inflammatory property using membrane stabilization and proteinase inhibitory methods. The results of this study revealed that compounds **53**, **54,** and **55** exhibited good anti-inflammatory potential 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].

Ayaz *et al*. synthesized bis(5-fluorobenzo[*d*]oxazole-2-yl) derivatives **56a**-**56d**. Synthesized compounds exhibited immunomodulatory property by a decrease in TNF-α, IL1-β, 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)-benzoxazole-5-yl)benzamide derivatives (3a–3n). *In vivo* anti-inflammatory activity of these six compounds **(57a-57f)** was assessed by carrageenan-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

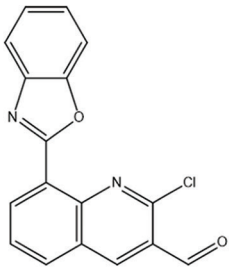
Praveen *et al*. developed benzoxazole derivative by cyclocondensation reaction and performed their analgesic property using the tail immersion method. The results of this study revealed that **58**, **59**, **60**, **61**, and **62** showed the least analgesic potency, respectively, 50.6%, 50.9%, 51.3%, 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



52

A- $CH(CH_3)$, R- t-C_4H_9

Fig. 6: Benzoxazole derivative with antioxidant potential



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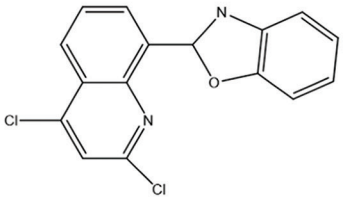

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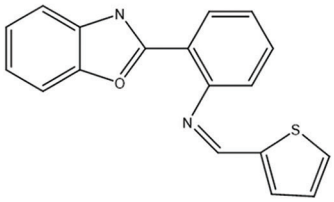

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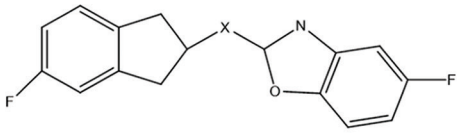
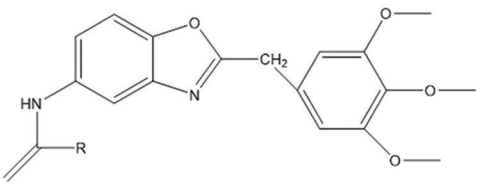


56a-56d

X	
56a.	$-CH_2-$
56b.	$-C_2H_4-$
56c.	$-C_3H_6-$
56d.	$-CH_2-S-CH_2$



57a-57f

R= 57a. 4-chlorophenyl; 57b. 2-chlorophenyl; 57c. 4-methylphenyl; 57d. 4-ethylphenyl; 57e. 4-nitrophenyl; 57f. 2-chloro-4-nitrophenyl.

Fig. 7: Benzoxazole derivatives with anti-inflammatory 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 H37RVwith 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- amyloglucosidase inhibitory activity. Compounds **70b** and **71b** showed potent IC_{50} 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-amyloglucosidase with IC_{50} 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** shown the potent anthelmintic properties. The researcher also performed molecular docking studies and concluded that the inhibition of b-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 antihelmintic 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 IC_{50} 57 ± 4.2 µM [95]. Structures of these synthesized compounds with antileishmanial property are presented in Fig. 12.

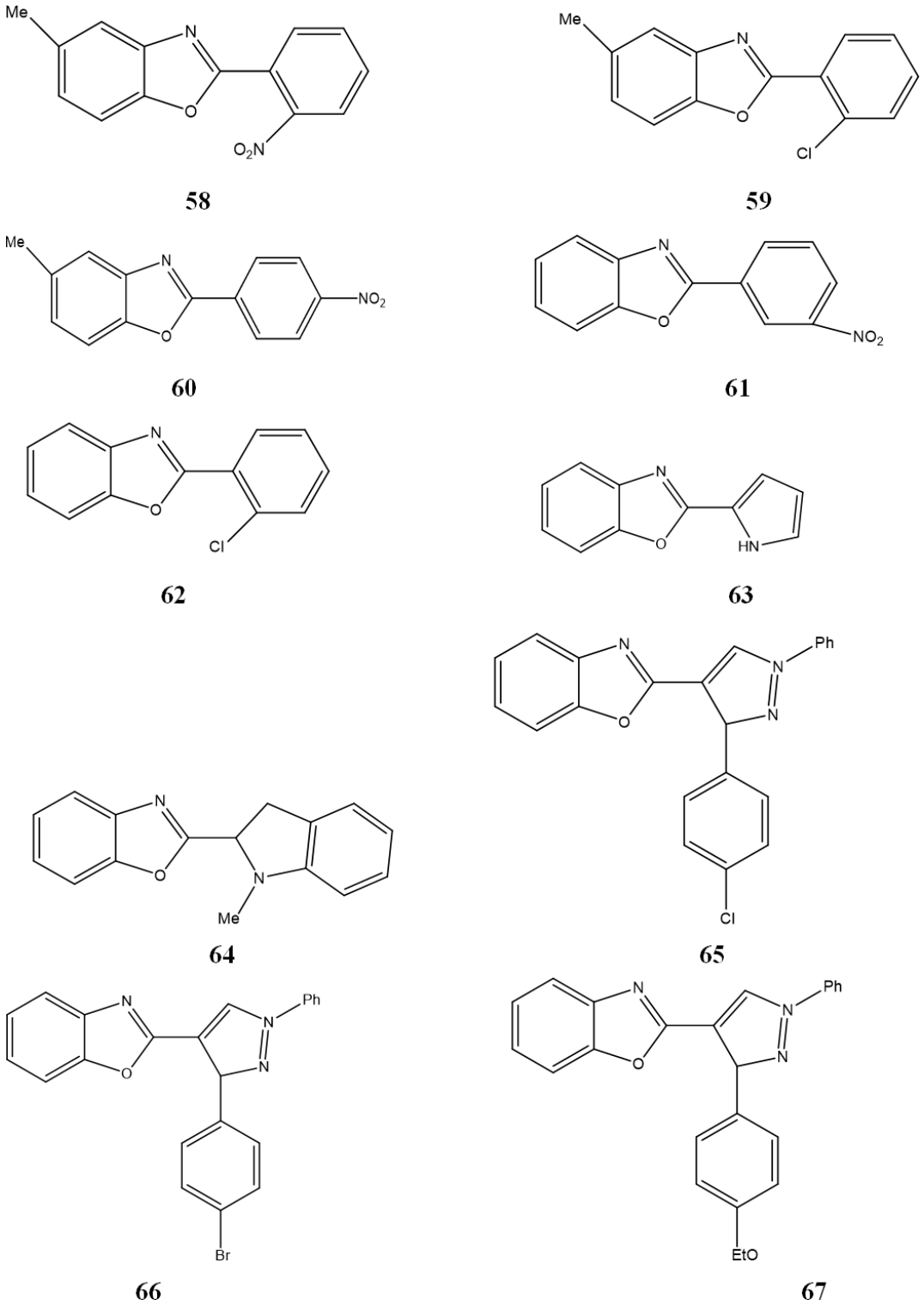


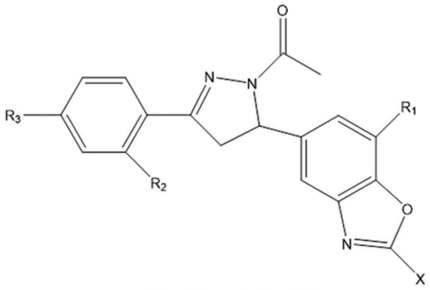
Fig. 8: Benzoxazole derivatives with analgesic potential

Enzymes inhibitory activity

Arpaci *et al*. developed 2-[4-(4-substitutedbenzamido/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

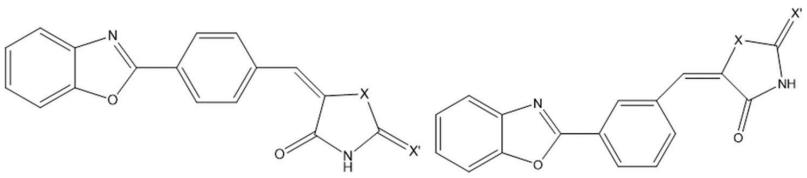
Luisa *et al*. synthesized 2-amino-6-(trifluoromethoxy)benzoxazole derivatives **(76-80)** and studied their neuroprotective potential toward amyotrophic lateral sclerosis. All the synthesized compounds were tested for voltage-dependent Na^+ current blocking activity using the patch clamp technique in 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



(68a-68h and 69a-69h)

Compound No.	R_1	R_2	R_3	X
68a	$-OCH_3$	H	H	$-NH_2$
68b	$-OCH_3$	Cl	Cl	$-NH_2$
68c	$-OCH_3$	H	F	$-NH_2$
68d	$-OCH_3$	Br	H	$-NH_2$
68e	–H	–H	–H	$-NH_2$
68f	–H	–Br	–H	$-NH_2$
68g	–Cl	–H	–H	$-NH_2$
68h	–Cl	–Br	–H	$-NH_2$
69a	$-OCH_3$	H	H	–SH
69b	$-OCH_3$	Cl	Cl	–SH
69c	$-OCH_3$	H	F	–SH
69d	$-OCH_3$	Br	H	–SH
69e	–H	–H	–H	–SH
69f	–H	–Br	–H	–SH
69g	–Cl	–H	–H	–SH
69h	–Cl	–Br	–H	–SH

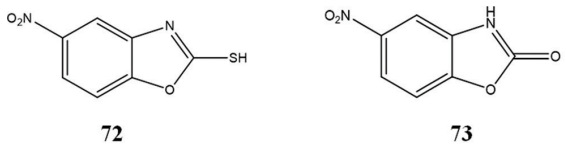
Fig. 9: Benzoxazole derivatives with antitubercular potential



70a-70d 71a-71d

Compounds	X	X'
70a and 71a	S	O
70b and 70c	S	S
70c and 71c	NH	O
70d and 71d	NH	S

Fig. 10: Benzoxazole derivatives with antihyperglycemic potential



72 73

Fig. 11: Benzoxazole derivatives with anthelmintic potential

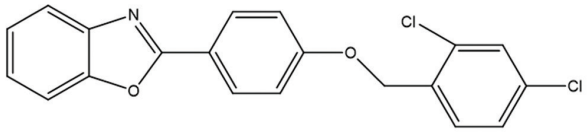


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Fig. 12: Benzoxazole derivative with antileishmanial potential

78, 79, and 82 demonstrated 50–70% of current reduction [97]. Structures of these synthesized compounds with neuroprotective potential toward amyotrophic lateral sclerosis are presented in Fig. 14.

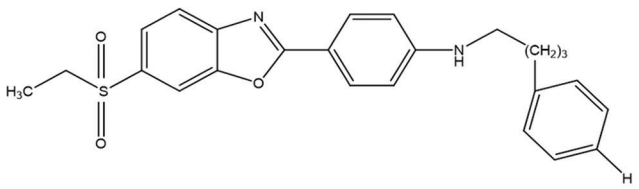

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Fig. 13: Benzoxazole derivative with enzyme inhibitory potential

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

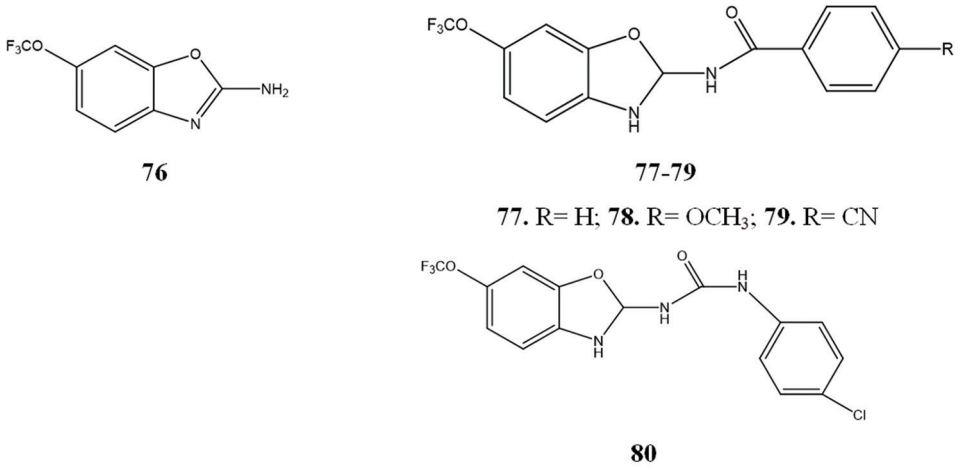

Fig. 14: Benzoxazole derivative with neuroprotective activity

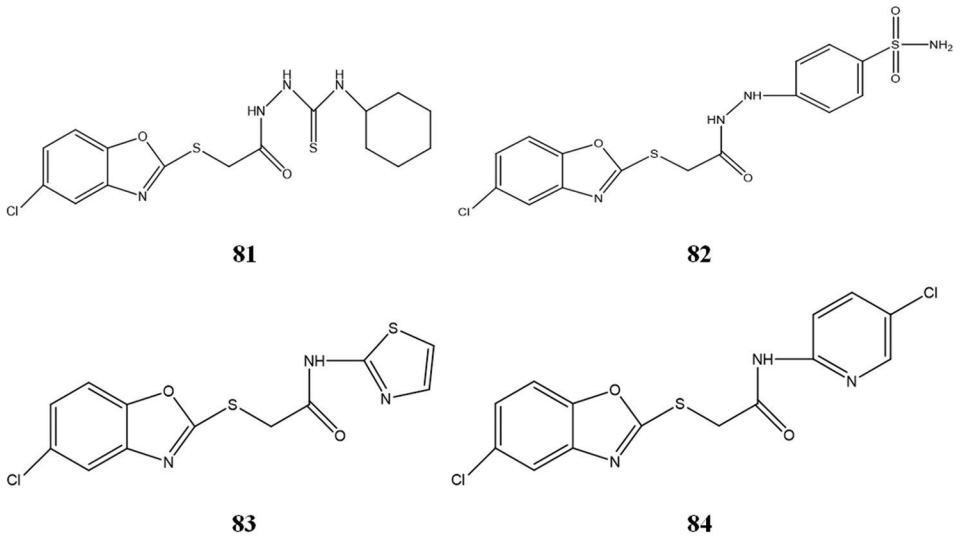

Fig. 15: Benzoxazole derivative with anticonvulsant activity

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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