Chapter 10
An Overview on Biological Activities of Oxazole, Isoxazoles and 1,2,4-Oxadiazoles Derivatives

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Abbreviations

SRS-A	Slow-Reacting Substance of Anaphylaxis
HIV	Human Immunodeficiency Virus
TTR	Transthyretin
DNA	Deoxyribonucleic Acid
NDM-1	New Delhi metallo-ß-lactamase-1
CYP	Cytochrome P
COX	Cyclooxygenase
CNS	Central Nervous System
ADP	Adenosine di-phosphate
OGTT	Oral Glucose Tolerance Test
PARP	Poly(ADP-ribose)polymerase
RNA	Ribonucleic Acid
SAR	Structure-Activity Relationship
DMT2	Diabetes Mellitus Type 2
PPAR	Peroxisome proliferator-activated receptor
MRSA	Methicillin-resistant Staphylococcus aureus
FATP	Fatty Acid Transport Protein

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P-GP P-glycoprotein
SAC Spindle Assembly Checkpoint

1 Introduction

Oxazole is a heterocycle of the five-membered ring which is composed of oxygen and nitrogen atoms at first and third positions, respectively, whereas for isoxazole oxygen and nitrogen atoms are at 1 and 2 positions. In the last few years, reports of biologically active compounds containing heterocyclic rings have drawn great attention from medicinal chemists. Oxazole is one of the major biologically active scaffolds found so far [1]. Surprisingly, a wide range of biological actions is associated with oxazole containing compounds, including anticancer, antibacterial, anticonvulsant, anti-allergic, anthelmintic, antiviral, antidepressant, analgesic and antioxidant properties [2]. Synthetic derivatives of oxazoles are imperative in the drug research portfolio as a result of good anti-inflammation potential [3], TRPV1 antagonist activity [4], antitubercular [5] and anti-HIV [6] activities. Additionally, oxazoles are also found to be used as fluorescent dyes, agrochemicals, corrosion inhibitors [7, 8] in polymer industries [9–11] and photography [12]. This chapter highlights the modern advancements in the progress of oxazole-based biologically active compounds.

Isoxazoles are also an essential class of heterocycles, which are generally active in the area of therapeutics and pharmaceuticals such as anticancer, insecticidal, antibacterial, antituberculosis, antifungal, antibiotic, antitumour and ulcerogenic. Moreover, marketed anti-inflammatory drugs as well as COX-2 inhibitors contain molecular scaffolds of Isoxazole. Isoxazole derivatives such as oxacillin, sulfamethoxazole, acivicin, cycloserine and sulfisoxazole have been in commercial use for the previous 40 years. In another, Cycloserine is a well-known antibiotic drug that has antibacterial, antitubercular activities, and also in medication of leprosy. Acivicin is an anti-leishmanial, antitumour drug, whilst isoxaflutole is used as an herbicidal drug [13].

Oxadiazole (known as furadiazoles) is one of the important scaffolds having a *N*-heterocyclic five-membered ring consists of two nitrogen and one oxygen atom. Oxadiazoles could arise in four distinct isomeric forms: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole; depends on the position of nitrogen atoms. Amongst the isomers, 1,2,4-oxadiazole, one of the important five-membered *N*-heterocycles, received significant attention due to its excellent bioisosteric properties and the broad spectrum of biological and pharmaceutical applications. The fused and pendant 1,2,4-oxadiazole scaffolds have been traced in several well recognized, commercially accessible drugs. After a few decades since the chemistry of 1,2,4-oxadiazole was invented, the unique potential involved researchers around the globe, giving rise to the recognition of currently available drugs possessing 1,2,4-oxadiazole scaffolds. Nevertheless, the attention in the biological application of 1,2,4-oxadiazoles and their derivatives have been enlarged in the past twenty years [14].

1.1 Biologically Active Oxazole Related Pharmaceutical Drugs

Oxazole compounds [15–17] as the bioisostere of imidazoles [18, 19], thiazoles [18, 19], triazoles [20, 21], benzimidazoles [20, 21] as well as tetrazoles [22], have fascinated progressive consideration. Moreover, several scientists and researchers over the globe have been affording oxazole-based compounds as pharmacophore and conceivably discover novel scaffolds with excellent pharmacokinetic property, low toxicity and a wide spectrum of bioactivity (Fig. 1) [23–25].

Several oxazole-embellished natural products are known to be isolated from numerous microorganisms and marine invertebrates [26–28], which assist as core structural motifs for several pharmaceuticals that exhibit various biological activities such as antifungal, antibacterial, antiproliferative [29–33], analgesic, antileukemic, antiviral, anticancer and enzyme inhibitory activities [34–43]. The phenomenal

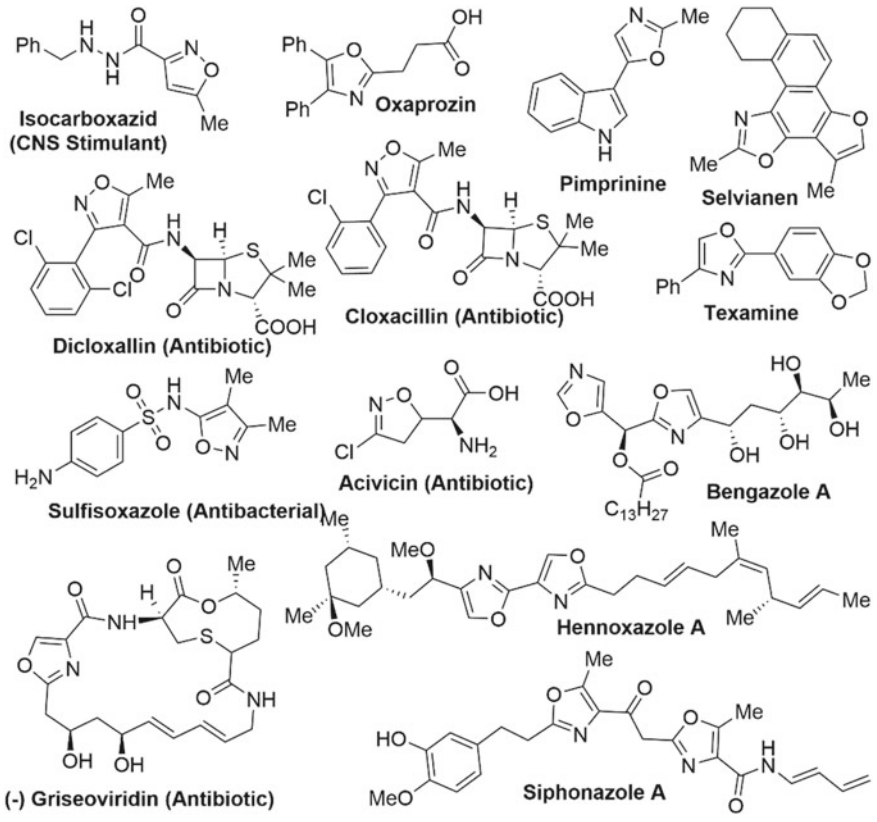
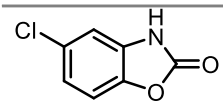
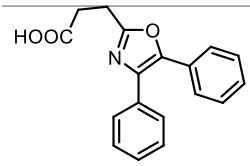
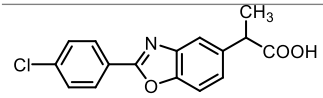


Fig. 1 Biologically active oxazole related pharmaceutical drugs [15–25]

biological functions and ubiquity of oxazoles in synthetic drugs and natural products have generated remarkable attention in the synthesis and biological evolution of functionalized cyclic oxazole scaffold.

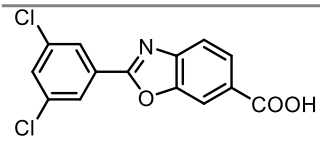
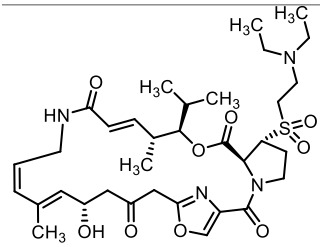
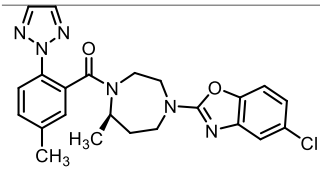
Few of the FDA-approved oxazole containing drugs are listed in Table 1 [43].

Table 1 FDA-approved oxazole-containing drugs [43]

Structure of the drug name of the drug (Drug bank id)	Category/Indication	Mechanism of action
 Chlorzoxazone	It is recommended for the reliever of pain related to acute painful musculoskeletal conditions	Inhibits degranulation of mast cells, eventually suppressing the liberation of histamine and anaphylaxis (SRS-A), a slow reacting substance, acts as type-I allergic reactions regulator
 Oxaprozin	Recommended for edoema, inflammation, joint discomfort and stiffness which arises from osteoarthritis and rheumatoid arthritis	Anti-inflammatory activities of oxaprozin referred to the suppression of cyclooxygenase within the platelets which results towards the hindrance in the synthesis of prostaglandin. Shows antipyretic activities which is associated to the reactivity on the hypothalamus, leading towards enhanced peripheral blood flow, vasodilation, as well as consequent heat dissipation
 Benoxaprofen	Withdrawn application	Withdrawn application

(continued)

Table 1 (continued)

Structure of the drug name of the drug (Drug bank id)	Category/Indication	Mechanism of action
 Tafamidis	STreatment for stage-1 symptomatic polyneuropathy, which may result to postpone peripheral neurologic impairment in Europe and cardiomyopathy in wild type or hereditary transthyretin-mediated amyloidosis	the specific stabilizer of TTR, and its inhibition of TTR tetramer dissociation forms the rationale for its use as a treatment to slow - but not cure - the disease progression of TTR-FAP
 Dalfopristin	For the treatment of bacterial infections (usually in combination with quinupristin)	Inhibits the early phase of protein synthesis
 Suvorexantore	Approved for the treatment of insomnia	A dual antagonist of orexin receptors OX1R and OX2R that indorses sleep by dipping wakefulness and arousal

1.2 SAR (Structure–Activity Relationship) of 1,2,4-Oxadiazole Compounds

The 1,2,4-oxadiazoles showcased various essential pharmacokinetic characteristics and share decent activity in murine models of Methicillin-resistant Staphylococcus aureus (MRSA) infection (Fig. 2) [44, 45]. They are usually embrace of four cyclic ring system, assigned as A, B, C and D. The subsequent structure–activity relationship (SAR) recognized some significant explanations:

- The H-bond donor of the ring A is important, whereas for antibacterial activity, H-bond acceptors at ring A are unfavoured.
- Structural distinctions on ring C are recognized for the biological activity.

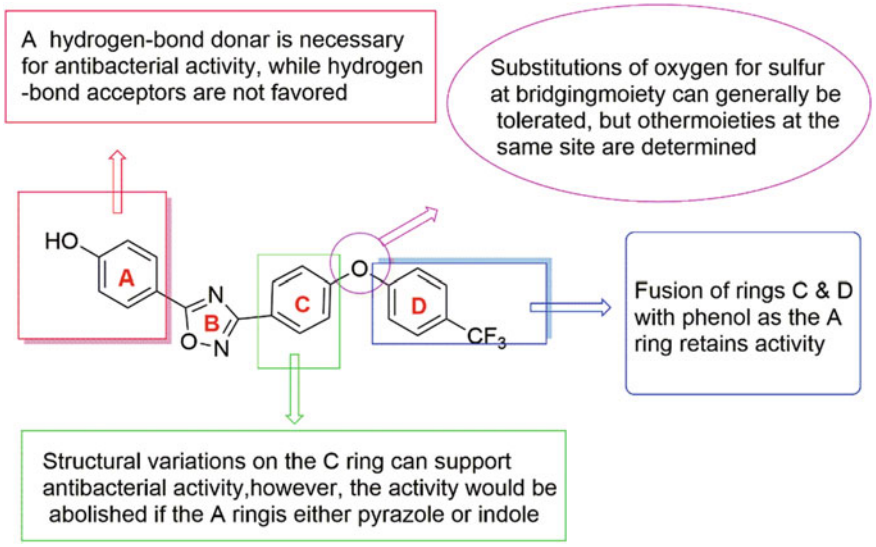


Fig. 2 SAR studies of oxadiazole compounds [44, 45]

- When other moieties are present, substitution of an oxygen atom by a sulphur atom at the connecting moiety between rings C and D can ordinarily be reinforced; but, when other moieties are present, it is unfavourable.
- Ring C and D fusions with phenol are permitted.

The structural differences on the ring C can exhibit bioactivity but, whilst the A ring is either indole or pyrazole, and the activity would be overturned (Fig. 2).

2 Antibacterial Activity of Oxazole Derivatives

The appearance of carbapenemase forming bacteria, particularly New Delhi Metallo-β-lactamase known as NDM-1 and its alternates, has elevated a major worry to the human health. NDM-1 and its variants hydrolyze a broad variety of β-lactam antibiotics, as well as carbapenemase. In this context, methyl oxazole amide, compound **1** was a comparatively potent inhibitor against NDM-1 [46–52]. The amide and thiol-groups are also essential for correlating to the active site of the NDM-1 protein [47]. In addition, Benzamide-based oxazole moieties **2** (**a**–**d**) displayed decent activity against *Staphylococcus aureus* ATCC (Fig. 3).

Moreover, compound **2c** was more potent than clinical Linezolid or Vancomycin. Additionally, Coumarin-based isoxazole **3**, isoxazole moiety bearing -Cl substitution at *-o* and *-p* positions of aromatic ring showed higher activity against *Pseudomonas aeruginosa* and *Bacillus cereus*. It is might specify that coumarin scaffold with isoxazoles is obviously important for the medicinal implication [48]. In

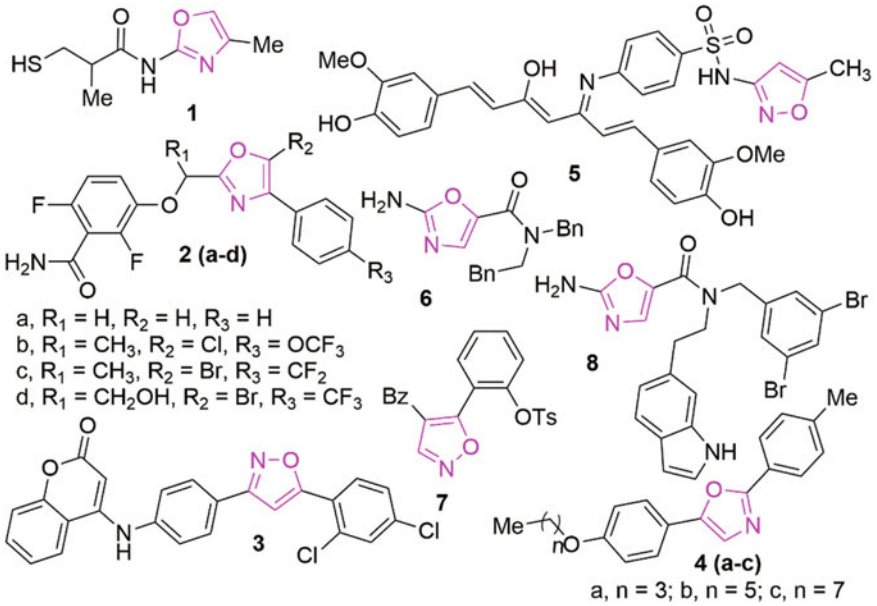


Fig. 3 Oxazole and Isoxazole as antibacterial compounds [46–52]

continuation, bisbenzyl substituted oxazoles **4** (**a**-**c**) were studied for antibacterial activity and compound **4c** displayed supreme antibacterial activity against *P. aeruginosa* as well as compounds **4a** and **4c** displayed comparable inhibition against *E. coli* [49]. In addition, the carbonyl group of curcumin, attached with isoxazole sulfonamide which provided compound **5** and displayed robust antibacterial activity. Again, when both carbonyl groups were involved with two isoxazole sulfonamide molecules, the activity would decline faintly [50]. In another, Enterococci are the significant pathogens for resistance, and mainly Enterococcus faecium, associated with the group of "ESKAPE" pathogens which presently originate from nosocomial infections. In continuation, D-aspartate ligase from E. faecium (Aslfm) as a prominent object for advancement of narrow-spectrum antibacterial agents which is active against multi-drug-resistant *E. faecium*. In addition, amino oxazole **6** resulting from the bacterial biotin-dependent carboxylase inhibitors exhibited little micro molar activity, and specifically, compound **8** prevents Aslfm with good activity [51]. In addition, isoxazole **7** bearing tosyloxy phenyl group was screened by the agar cup plate process for antibacterial activity, utilizing Ampicillin as a classic drug, the compound shown potential anti-*P. Aeruginosa* activity [52].

The 2-amino oxazole/4-substituted-phenyl oxazole was synthesized and assessed for antibacterial and antifungal potency. Some of the molecules have shown greater activity, i.e. zone of inhibition of 18 mm to 22 mm in Gram-positive bacteria, 16 mm to 18 mm in Gram-negative bacteria, and 16 mm to 19 mm in Fungi. It indicates that the oxazole moieties exhibit a strong antibacterial and antifungal activity [53].

Various substituted oxazoles were synthesized and assessed for antibacterial activity for various strains like *S. aureus, E. coli, P. vulgaris, K. pneumonia* and

compared with the various standards like Ampicillin and Ciprofloxacin. Some of the compounds have shown more potent activity than Ampicillin. The zone of inhibition of the new compounds was found to be 25 mm, whereas Ampicillin is 20 mm in *S. aureus*. One compound exhibited a 21 mm inhibition zone, whereas Ampicillin was 22 mm in E. coli which indicates comparable activity. The third compound exhibited an inhibition zone of 22 mm, whereas Ampicillin was 20 mm in *P. vulgaris* and others exhibited 23 mm, whereas Ampicillin was 21 mm in *K. pneumonia.* But all the newly synthesized compounds have not exhibited comparable activity with Ampicillin. They exhibited good to moderate antibacterial activity [54].

3 Oxazoles and Their Clinical Drugs

Plenty of medicinal drugs containing oxazole-containing scaffolds have been widely used in the clinic, for example; Sulfisoxazole **9**, Furazolidone **10**, Toloxatone **11** and Linezolid **13** (Fig. 4) [55].

4 Antifungal Activity of Oxazole Derivatives

The installation of the oxazole motif into the indole frame, compound **15**, exhibited good activity against *Alternaria brassicicola.* Nevertheless, compound **14** comprising the oxadiazolyl group comparatively gave faint inhibitory action [56]. Streptochlorin **18** was originally synthesized from lipophilic extracts of Streptomyces sp. mycelium and a series of improved streptochlorin analogues such as **16**, **17**, **19** and **21** were tested for potency against seven phytopathogenic fungi. All of the compounds, on the other hand, demonstrated reasonable activity [57]. Additionally, 2-(4-ethyl-2-pyridyl)-1*H*-imidazole based 1,3,4-oxadiazole scaffolds (compounds **21**, **22**, **23,** and **24**) were verified against several fungal strains and compounds **22**, **23**

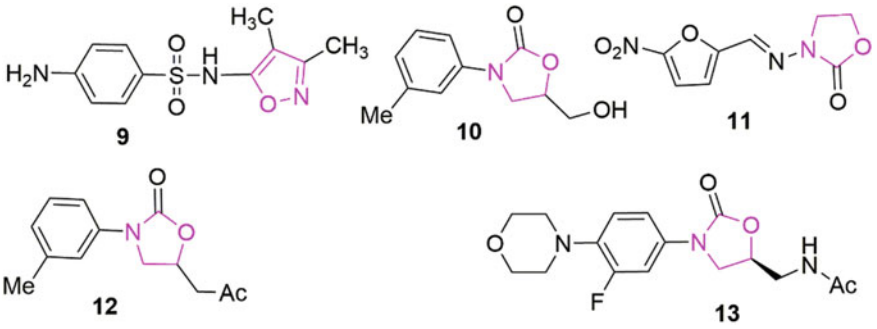


Fig. 4 Clinical oxazole drugs [55]

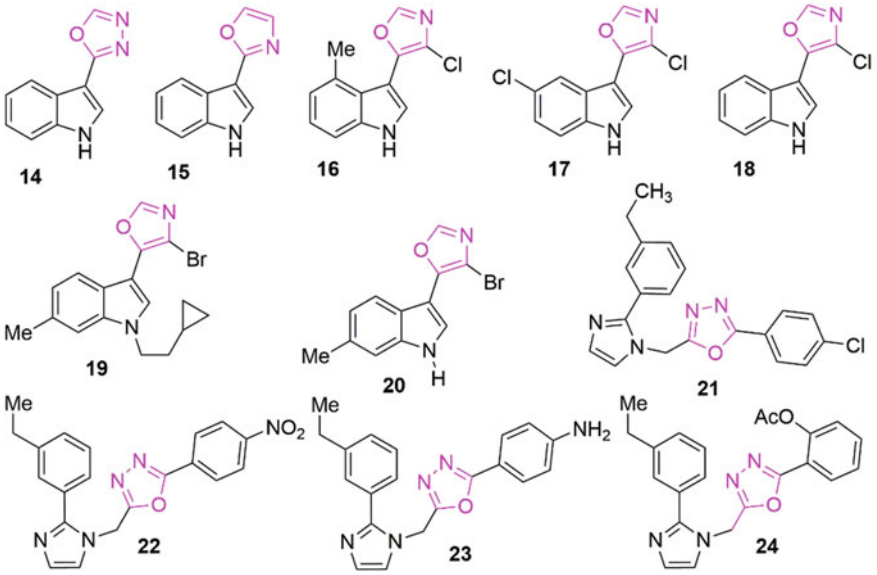


Fig. 5 Oxazole related antifungal agents [56-58]

and **24** showcased respectable antifungal activity in contrast with fluconazole (Fig. 5) [58].

The suppressors of the dual-specificity protein phosphatase CDC25C were discovered to be benzo[*d*]oxazsole-4,7-diones. Antifungal action of these moieties must be evaluated. Presence of arylamino, arylthio, or halogen groups will improve the antifungal activity. So, 5-arylamin-6-bromo-2-ethylbenzo[*d*]oxazole-4,7-diones and other compounds by several substituent were considered and evaluated for the antifungal activity. Two compounds were found to be more effective when associated with the standard drug, 5-Fluorocytosine. The MIC of two compounds was found to be 1.6 μg/ml and 0.8 μg/ml in Candida albicans Berkhout KCCM 50,235, 3.2 μg/ml and 3.2 μg/ml in Candida tropicalis Berkout KCCM 50,662, 3.2 μg/ml and 3.2 μg/ml in Candida krusei Berkhout KCCM 11,655, 1.6 μg/ml and1.6 μg/ml in Cryptococcus neoformans KCCM 50,564, 1.6 μg/ml and 0.8 μg/ml in Aspergillus niger KCTC 1231, 3.2 μg/ml and 1.6 μg/ml in Aspergillus flavus KCCM 11,899, whereas 5-Fluorocytosine was found to be 3.2 μg/ml, 3.2 μg/ml, 3.2 μg/ml, 3.2 μg/ml, 1.6 μg/ml and 1.6 μg/ml, respectively. This indicates that the Benzoxazole derivatives are highly potent antifungal agents [59].

Phenyl thiazole moiety is an insecticide. It contains phenyl thiazole in its structure. Replacement of this with its biosphere like oxazole/thiazole ring enhances the activity of the drug transforming the insecticide into fungicide. This indicates the role of oxazole in the antifungal activity exhibiting compounds [60].

5 Anticancer Activity of Oxazole Derivatives

Cytochrome P-450 enzymes (CYPs) were the major catalysts for the development of target-selective suppressor due to the wide homology range of common heme–iron scaffolds. Moreover, adrenal and intra tumoural androgen biosynthesis was found to be reduced by the orally active CYP17A1 inhibitor abiraterone acetate. Thus, it is found to be an active molecule for the treatment of prostate cancer. In continuation, oxazole 255 well-found satisfactory lyase effectiveness in inhibiting Rat CYP17 lyase activity and showed adequate inhibitory activity against human CYP3A4 [61]. In addition, several 2,4-diphenyloxazole derivatives (compounds **26**, **27** and **28**) were appraised for their anticancer affectivity and as the results displayed that compounds **26** and **27** exhibited auspicious activity on the HepG2 cell line. Whereas compound **28** showed noteworthy growth inhibition on HeLa cells. Researchers found that substituted phenyl ring at the second position was positive for the anticancer potency of scaffold [62]. Compounds **29**, **30** and **32** which replaced the phenolic hydroxyl group with naphthalene, pyridine, or quinoline moieties, demonstrated strong inhibitory effect against three cell lines: A549 (Human lung carcinoma), MCF-7 (Human breast carcinoma) and Hela (Human cervical carcinoma). Compound **29** exhibited exceptional inhibitory movement over MCF-7 (Human breast carcinoma) cell lines. Furthermore, structure–activity relationships (SAR) revealed that the C-5 position of the oxazole ring is linked to naphthalen-2-yl and quinolin-3-yl, which is important for 5-aryl-2-methyloxazole potency and selectivity [63]. In another, mono-substituted oxazole **33** afforded reduced activity in contrast with furan derivatives of transcription in transfected PC-3 cells, whereas 3,5-bis(trifluoromethyl)benzoyl aniline substituted compound **34** showed better activity (Fig. 6) [64].

In addition, MPS1 (protein kinase monopolar spindle 1) is a critical component of the spindle assembly checkpoint (SAC) signal, which is improperly expressed in a variety of human malignancies. Moreover, MPS1 is the topmost 25 genes which are over-expressed in tumours with chromosomal uncertainty. PTEN-deficient breast tumour cells are mainly reliant on MPS1 for survival, which makes it the remarkable target in oncology. In addition, the 1*H*-pyrrolo[3, 2-c]-pyridine moiety-based oxazoles (compounds **35** and **36**) verified potent as well as ligand-efficient binding to MPS1. The crystal structures of MPS1 with oxazoles **35** and **36** further revealed that the oxazole scaffold maintained connection with the active site Lys553 side chain [65]. In addition, a new 2,5-disubstituted oxazole **37** was isolated from Aspongopus chinensis (an insect from the Pentatomidae family) and exhibited noteworthy activity against various tumour cell lines. Multidrug resistance (MDR) is a complicated abnormality caused by the overexpression of transmembrane proteins from the ATP binding holder transporter family. P-glycoprotein (P-GP), one of these transporters, is frequently intertwined with MDR. In another, substituted naphthalenyl oxazole derivatives (compounds **31**, **38**, **39**, **40** and **41**) were measured as P-glycoprotein (P-GP) substrate as it encouraged ATP cell reduction. The SAR studies has shown that existence of F, H or OH substituents were encouraging for bioactivity, whereas Br was found to be contrary in the ATPase assay (Fig. 6) [66].

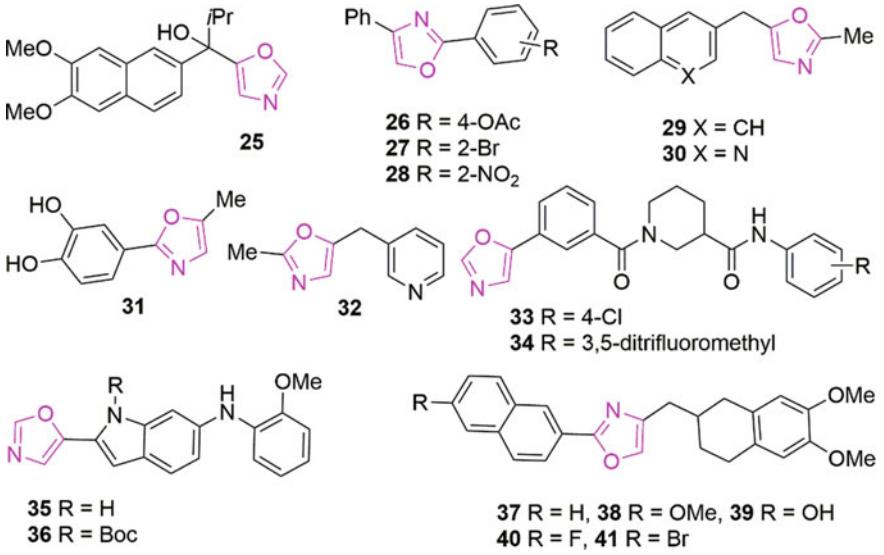


Fig. 6 Mono and bis-substituted oxazoles as anticancer agents [61–64]

Combrestatin A-4 (CA-4) exhibits an effective antitumour activity but the solubility issues limited its use in anticancer therapy. These drawbacks were resolved by the addition of imidazole and oxazole rings. In various cell lines, including human 518A2 melanoma, human HT-29 colon carcinoma and EA. HY926 endothelial hybrid cells, the substitution of a halogen atom on the oxazole ring improved anticancer activity [67]. Oxazole ring plays prominent role in anticancer activity.

Pongamol, a chalcone derivative isolated from *Derris indica,* has many pharmacological activities. One of the activities exhibited by it is the antitumour activity. There is no documented evidence of this traditional medicine. The oxazole ring addition to this natural drug enhances its antitumour activity. So pongamol derivatives of Oxazole and Pyrazole were synthesized and antitumour activity was estimated over three different human cancer cell lines, HeLa, IMR-32 and Jurkat. The oxazole derivative and the pyrazole derivative have shown increased activity compared to the natural drug Pongamol [68].

6 Antitubercular Activity of Oxazole Derivatives

Through the establishment of strains of drug-resistant of *Mycobacterium tuberculosis*, several attempts were made for the improvement of antitubercular agents possessing higher potency, less adverse effects/toxicity and less multi-drug resistances [69, 70]. Fascinated by the aminothiazole compounds showing excellent therapeutic index and dominant activity, amino oxazole compound **42** (Fig. 7) was

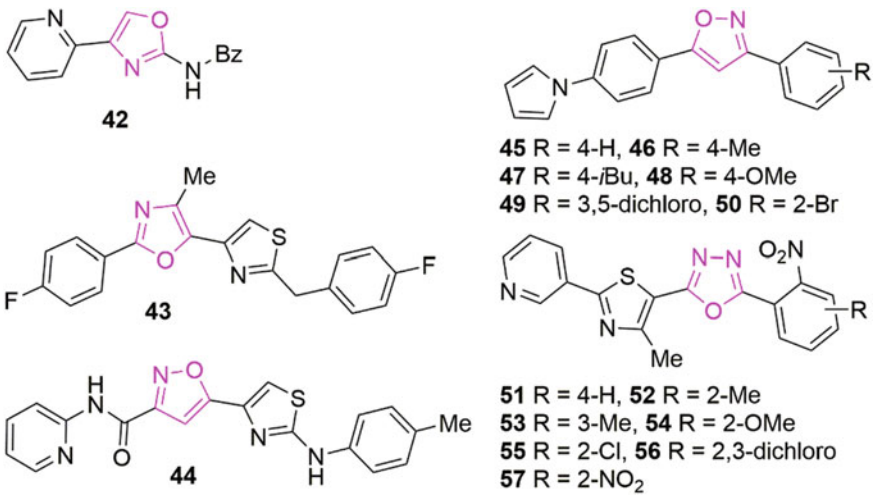


Fig. 7 Oxazoles, isoxazoles and oxadiazoles as antitubercular agents [71–73]

screened for biological evolution and found that compound **42** exhibited reasonable potency against *Mycobacterium tuberculosis* H37Rv. The replacement of oxazole scaffold through oxadiazole might lead into a 2-to-fourfold recovery in strength comparative to oxazole **42** [71]. In addition, the tri-substituted oxazole **43** with a thiazole ring was used, and equivalent action against inert Mycobacterium TB H37Ra and Mycobacterium bovis BCG strains was observed when compared to the conventional antibiotic Rifampicin. Additionally, Isoxazole **44** containing pyridine and thiazole rings was initiate to own high-inhibitory potency against vulnerable strains of *M. tuberculosis*. In another, Phenylisoxazoles (compounds **45**, **46**, **47**, **48**, **49** and **50**) bearing pyrrole rings were screened. The antitubercular action of these moieties displayed that compound **47** with electron-rich isopropyl group exhibited the notable potency for *M. tuberculosis* H37Rv strain, whereas moieties containing methyl & methoxy (compounds **46** & **48)** provided comparatively abridged activity. Nevertheless, unsubstituted compound **45** and electron-poor group substituted ones **49** and **50** displayed minimum bioactivity. Precisely, the most potent compound **47** exhibited a good safety profile against the A549 cell line [72].

2-Pyridinyl functionalized thiazolyl-5-aryl-1,3,4-oxadiazoles (compounds **51-57**) were evaluated in the search for more safe and effective anti-tubercular medicines. In addition, 2-phenyl substituted compounds **52**, **54**, **55** and **57** showed auspicious activity against Mycobacterium bovis BCG, and additionally, these compounds also exhibited little cytotoxicity over four human cancer cell lines (THP-1, HeLa, PANC-1, HCT116). Nevertheless, compound **51** with no substitution and other position substituted compounds **53** and **56** gave extremely reduced antitubercular activity [73].

Mycobacterial infections are the most common infectious disease globally. Furthermore, tuberculosis (TB) is witnessed amongst the top ten reasons of death

worldwide. This is also the dominating fact of death from a single-infectious agent. The emergence of drug-resistant mycobacterial strains, which need the use of more toxic and less effective medications as well as therapy prolonging, is a source of particular concern. However, 4-methyl-2-aryl-5-(2-aryl/benzyl thiazol-4-yl) oxazole was synthesized and antitubercular activity was evaluated against various strains of M. tuberculosis HA37Ra (MTB, ATCC 25,177) and *M. bovi* s BCG (BCG, ATCC 35,743) in liquid medium using Rifampicin as a standard drug. In these series of compounds, five active compounds were found. It has been found that 3-Cl and 4-F substituted benzyl rings increased the antitubercular potency and some compounds exhibited comparable activity with Rifampicin. One of the molecules possess excellent antibacterial activity [69].

Oxazoles with carboxylic group substituents exhibit antitumour activity against *Mycobacterium tuberculosis* with low toxicity. One of the compounds exhibited anti-TB activity showing MIC of 0.07 & 0.14 mM against *Mycobacterium tuberculosis* and multi-drug-resistant *Mycobacterium tuberculosis* [74].

7 Anti-inflammatory and Analgesic Activity of Oxazole Derivatives

There is growing interest in the progress of specific inhibitors for FAAH (fatty acid amide hydrolase) that point to the cytosolic port Cys269 in medication for inflammatory, pain, or sleep disorders, due to the therapeutic potency of specific inhibitors for FAAH (fatty acid amide hydrolase) that point to the cytosolic port Cys269 in medication for inflammatory, pain, or sleep disorders. Oxazole bromide **58** (Fig. 8) showed noteworthy potency in inhibition of FAAH, whereas the compound **59** having nitrile gave slightly weak activity [75–83]. The irretrievable inhibitors of FAAH exhibited that predictable compassion to the position of the electrophile starter, but those were successfully showed amazing drifts in specious sensitivity towards Cys269 that would not be simply projected [76]. In continuation, tri-substituted oxazole compound **60** displayed excellent efficiency in frequent preclinical models together with the spinal nerve ligation (SNL) pain models and complete Freund's adjuvant (CFA). Moreover, no insightful properties were detected for this brain penetrant FAAH inhibitor, and compound **60** is found to be potent, specific reversible non-covalent modifying FAAH inhibitor [77]. In addition, Mofezolac **63** bearing isoxazole scaffold was an effective and selective COX-1 inhibitor and was broadly active in medication. Several considerations were focussed on its analogues to explore novel COX-1 inhibitors to overthrown its side effects [78]. In further, indole containing isoxazole **62** showed similar or more Secretory phospholipase A2 (sPLA2) inhibitory activity when compared to positive control Ursolic Acid. Additionally, this compound can bind the proximity of active site amino acid residues; HIS-47, TYR-21, GLY-22, PHE-5, GLY-29, CYS-44, CYS-28, PHE-98, ASP-48 and TYR-51. Furthermore, compound **62** is significant for correlations and binding capabilities with sPLA2

could be liable for its sPLA2-inhibitory effect [79]. In addition, in animal models of nonspecific inflammatory responses or Th1-type immune responses, isoxazole compound **61** proved an efficient anti-inflammatory drug. The use of compound **61** in the form of ointment is the added value in the management of skin inflammation [80]. On the other hand, compound **64**, 4,5-Diaryl-isoxazole-3-carboxylic acid, inhibits leukotriene biosynthesis and acts as an effective anti-inflammatory agent [81]. Tri-substituted indole derivative of isoxazole **65** [82], and 3,5-disubstituted isoxazole furfuryl derivative **66** [83], have also exhibited significant effect as anti-inflammatory agent.

Oxazole derivatives were synthesized, their anti-inflammatory effect was tested, and they were compared to the standard medicine nimesulide using the HRBC membrane stabilization technique. The percentage protection of the newly synthesized compound was in the values of 55.1, 50, 59 and 60%, and the nimesulide protection percentage was found to be 61% at 50 μg/ml. These compounds have exhibited comparable activity with the standard drug, nimesulide. But these compounds don't exhibit any increased anti-inflammatory or analgesic activity upon increasing the concentration to 100 μg/ml [84].

Quinolyl oxazoles with various substitutions were synthesized, and they are highly effective inhibitors of phosphodiesterase 4 (PDE4). Some of the compounds

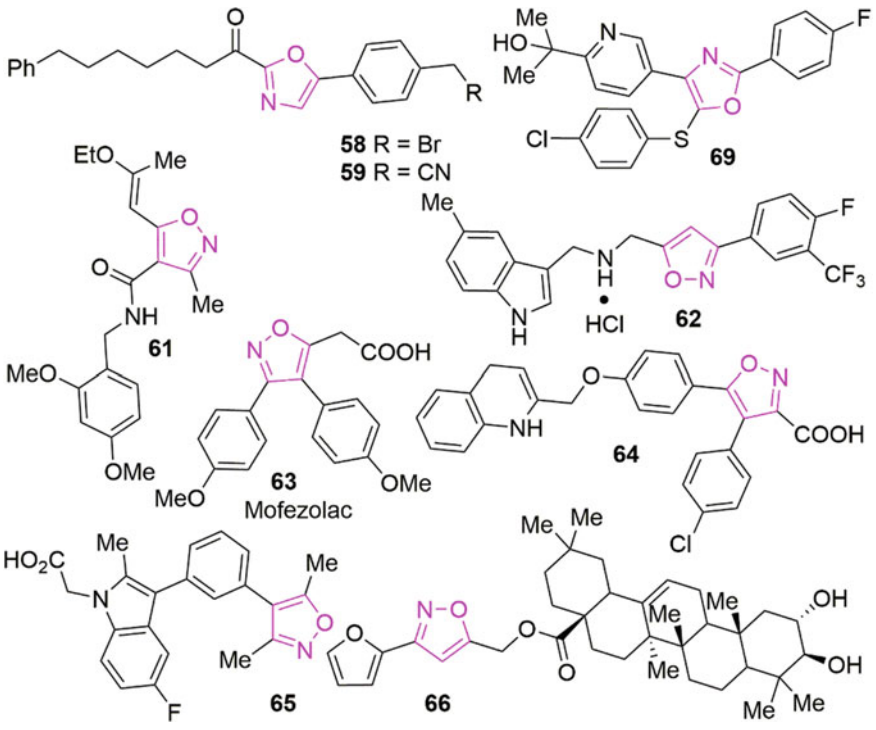


Fig. 8 Anti-inflammatory and analgesic compounds [75–83]

were considered to be more potent against PDE4 IC_{50} values of 1 to 1.4 nm. *N*-benzylcarboxamide has shown the highest selectivity against phosphodiesterase 4. Further optimization led to highly selective PDE4 inhibitors with picomolar potency with the values of 0.05, 0.03, 0.06 and 0.04 nm. This data shows that the oxazole ring containing compounds exhibit good anti-inflammatory activity [67].

8 Antidiabetic Activity of Oxazole Derivatives

The G-protein coupled receptor 40 (GPR40) is broadly populated in pancreatic β cells and recognizes endogenous fatty acids, leading in an increase in insulin output when glucose levels are high [85–87]. Furthermore, compound **67** consisting of Isoxazole (Fig. 9) showed better impact as GPR40 agonist, exceptional pharmacokinetic possessions across species, and minimum central nervous system (CNS) dispersion. OGTT study in human GPR40 knock-in mice showed this compound decreases the plasma glucose levels [88]. In continuation, bis-substituted isoxazole **68** containing thiophene moiety increases the assembly of mRNAs encrypting a select group of β cell proteins vital for glucose detecting and insulin gene transcription [89]. In addition, the tri-substituted oxazole compound **69** was displayed noteworthy activity on the GPR40 receptor. In continuation, arylsulfonyl 3-(pyridin-2-yloxy) aniline compound **70** consisting 1,2,4-oxadiazole scaffold showed exciting activity as GPR119 agonist [90].

PPARs (peroxisome proliferator-activated receptors) are also important therapeutic targets for Type 2 Diabetes Mellitus therapy (DMT2). Furthermore, most existing PPAR ligands comprise a thiazolidinedione (TZD) structure or a carboxylic acid (CA) that is crucial for activity. Furthermore, the 1,2,4-Oxadiazole compound **71** might bind to Peroxisome proliferator-activated receptors (PPARα and PPARδ) via an acetamide scaffold and an adjacent methyl group. In addition, skeletal muscle

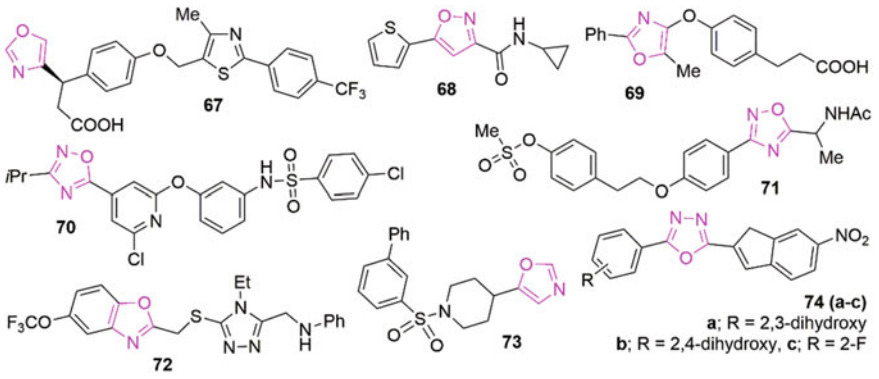


Fig. 9 Antidiabetic compounds of oxazoles [88–90]

significantly interesting target tissues are extensively working for the treatment of insulin resistance. It is worth mentioning that one of the most imperative protein targets for insulin resistance is fatty acid transport protein 1 (FATP1), a member of Acyl-CoA synthetase. FATP1 is a transmembrane protein and highly over-expressed in skeletal muscle. Thus, inhibition of FATP1 could lead to the interruption of free fatty acid transport in insulin resistant cells. Fascinatingly, compound 71 contains benzoxazole scaffold has shown significant FATP1 inhibition in mouse and human thus reflected as a potential candidate for free fatty acid regulator in insulin resistant condition [91]. In continuation, oxadiazole compounds **74a**, **74b** and **74c** were found to be more active with antidiabetic activity in contrast with the typical drug Acarbose [92]. Furthermore, suppression of the intracellular enzyme 11-beta-hydroxysteroid dehydrogenase type 1 (11βHSD1) has been proposed as a therapeutic strategy for the treatment of DMT2. The compound **73** comprising 5-oxazole with piperidyl ring at fourth position was found to express stimulating inhibitory action against the 11β-HSD1 enzyme [93].

The 1,3-dioxane carboxylic acid derivatives were synthesized and they act as dual agonists for PPAR α/ϒ. As a lipophilic heterocyclic tail, substituted oxazole must be incorporated. These compounds were produced and tested in animal models for their agonistic activity on the PPAR receptor, as well as hypoglycaemic and hypolipidemic effectiveness. One of the compounds of this series exhibited potent hypoglycaemic, hypolipidemic and insulin-sensitizing effects [94].

9 Summary/Conclusion

Oxazole-based scaffold and its analogues are well-accepted as promising moieties in the development and progress of novel drugs revealing immense biological and pharmaceutical activities. It has been acknowledged from the foregoing deliberations that various oxazole-embedded molecules can have appreciable attention in the synthesis and evaluation of new agents effectively employable for the treatment of insomnia, cancer, Alzheimer's disease, inflammation, etc. Some of the molecules defined in this chapter are applicable for medicinal studies, and their appraisal is continuing, grasping great potential for the identifications of innovative pharmaceutical drugs. This chapter established the fact that oxazole-based scaffolds as useful templates for further derivatization or modification to design more effective medicinally active compounds.

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