Düzce University Journal of Science and Technology
*Düzce Üniversitesi Bilim ve Teknoloji Dergisi*

14 (2), 2026, 651-665.
https://doi.org/10.29130/dubited.1717358

e-ISSN: 2148-2446
https://dergipark.org.tr/en/pub/dubited

Review Article

# Advances in Isoxazole-Containing Anticancer Drugs: From Synthesis to Clinical Potential

Nurcan Berber[1*]

[1] Çanakkale Onsekiz Mart University, School of Health Services, Çanakkale, Türkiye.
ror.org/05rsv8p09

*Corresponding author:
nberber@comu.edu.tr

**Abstract:** Cancer is one of the most common and deadly diseases worldwide, and the development of new therapeutic strategies to overcome treatment resistance and improve clinical outcomes remains a critical challenge. Heterocyclic compounds have long been recognized as fundamental building blocks in medicinal chemistry. Among them, the isoxazole ring has emerged as a promising pharmacophore in anticancer drug design due to its unique electronic properties and hydrogen-bonding capability. Isoxazole is a five-membered heterocyclic ring containing nitrogen and oxygen atoms at the 1st and 2nd positions, enabling diverse interactions with enzymes and receptors and resulting in a wide range of biological activities. In this review, scientific studies on the development of isoxazole-containing compounds as anticancer agents have been systematically examined from the past to the present. The selected studies were evaluated based on their reported anticancer activity, molecular mechanisms of action, and clinical development status. Isoxazole derivatives have demonstrated significant activity against various cancer types, including breast, lung, colorectal cancers, and leukemia, through mechanisms such as apoptosis induction, cell cycle arrest, kinase inhibition, and suppression of angiogenesis. Moreover, the clinical approval of certain isoxazole-based drugs further supports the translational potential of this scaffold. Overall, the isoxazole core represents a promising and clinically relevant pharmacophore for the development of next-generation targeted anticancer therapies.

***Keywords:*** *Heterocyclic coumponds, Isoxazole derivatives, Dipolar cycloaddition, Anticancer agents*

Received: 11.06.2025
Revision: 19.02.2026
Accepted: 18.03.2026
Online: 19.04.2026

## I. INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide despite significant advances in early diagnosis and therapeutic strategies. Although chemotherapy, targeted therapy, and immunotherapy have improved survival rates in several malignancies, treatment resistance, dose-limiting toxicity, poor selectivity, and tumor heterogeneity continue to limit long-term therapeutic success. Therefore, the identification of novel pharmacophores capable of modulating multiple oncogenic pathways with improved safety profiles remains an urgent need in anticancer drug discovery (Debela et al., 2021; Emran et al., 2022; Ferlay et al., 2015).

Heterocyclic compounds have long been recognized as essential scaffolds in medicinal chemistry (Baaloudj et al., 2025; Jampilek, 2019; Kidwai et al., 2002). Among these, the isoxazole ring has emerged as a particularly promising pharmacophore in the design of anticancer agents due to its favorable electronic properties and hydrogen-bonding capacity (Agrawal & Mishra, 2018; Chikkula & Raja, 2017; Kakkar & Narasimhan, 2019). Isoxazole is a five-membered heterocyclic ring containing nitrogen and oxygen atoms at the 1- and 2-positions (Agrawal & Mishra, 2018; Zhu et al., 2018). This structural feature enables isoxazole derivatives to form non-covalent interactions with a broad range of enzymes and receptors under physiological conditions, thereby contributing to diverse biological activities (Kaur et al., 2014; Malik & Pal, 2024; Pandhurnekar et al., 2023; Rusu et al., 2023).

In recent years, the limitations of single-target therapies have shifted research efforts toward multi-target-directed ligands and hybrid molecular designs. The isoxazole core is particularly advantageous in this context, as it can be readily incorporated into hybrid structures to enhance biological activity and selectivity. Numerous studies have reported promising anticancer effects of isoxazole-containing derivatives against breast, lung, and colorectal cancers, as well as leukemia, through mechanisms including apoptosis induction, cell cycle arrest, kinase inhibition, and angiogenesis suppression (Ardestani et al., 2022; Chene et al., 2016; Gaikwad et al., 2021; Veeraswamy et al., 2012; Wazalwar et al., 2023). However, despite the growing body of research, the existing literature remains fragmented and lacks an integrated evaluation of synthetic strategies, structure–activity relationships, mechanistic insights, and translational potential.

In this context, this review provides a systematic and critical assessment of recent advances in isoxazole-containing compounds as the broad spectrum of biological activities. It addresses synthetic approaches, molecular mechanisms of



This is an open access paper distributed under the terms and conditions of the Creative Commons Attribution-NonCommercial 4.0 International License.

action, structure–activity relationships, and clinical/translational perspectives. By integrating dispersed findings and highlighting emerging multi-target and hybrid design strategies, this review aims to clarify the therapeutic value of the isoxazole scaffold and guide the rational development of next-generation anticancer agents.

## II. MATERIAL AND METHOD

The aim of this review is to demonstrate the broad spectrum of biological activities associated with isoxazole-containing compounds. This review was conducted in a narrative format to evaluate the literature on isoxazole-containing compounds with anticancer activity. A comprehensive literature search was performed using Google Scholar, employing combinations of keywords such as "isoxazole," "isoxazole derivatives," "anticancer activity," "hybrid anticancer agents," and "structure–activity relationship." Priority was given to recent and scientifically significant publications. To ensure thoroughness, key studies were cross-checked using additional databases, including SciFinder, Google Patents, ScienceDirect, Scopus, PubMed, PubChem, ResearchGate, and Elsevier. Original research articles reporting the synthesis and biological evaluation of isoxazole-containing compounds were included, with particular emphasis on studies providing mechanistic insights, structure–activity relationship analyses. Review articles, studies lacking anticancer biological data, and research unrelated to isoxazole were excluded. The selected studies were systematically analyzed based on their scientific relevance and contribution to the field.

### *A.1. Chemical and Biological Significance of the Isoxazole Ring*

The isoxazole ring is a five-membered heterocycle consisting of three carbon atoms, one nitrogen atom, and one oxygen atom, its partially saturated analogs are known as isoxazolines, (Figure 1) (Agrawal & Mishra, 2018; Zhu et al., 2018). This unique arrangement imparts the ring with aromatic character and electron delocalization, which contributes to its chemical stability and reactivity in various biological environments (Kaur et al., 2014; Malik & Pal, 2024; Pandhurnekar et al., 2023; Rusu et al., 2023).

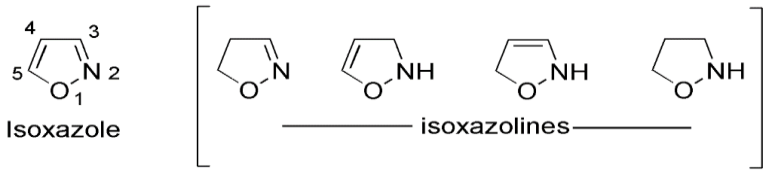



Figure 1. Structure of isoxazole and analogues.

From a medicinal chemistry perspective, the isoxazole skeleton is considered a privileged structure due to its frequent occurrence in bioactive molecules with a wide spectrum of pharmacological activities. Isoxazole-containing compounds have been investigated for their antimicrobial (Vashisht et al., 2025), anti-inflammatory (Zimecki et al., 2018), antiviral (Dawood et al., 2011), antidiabetic, antiobesity (Algethami et al., 2021) and anticancer properties (Hawash et al., 2021; Sysak & Obmińska-Mrukowicz, 2017). Some beta-lactamase resistant antibiotics and steroid drugs contain the isoxazole group, given in (Figure 2) (Kaur et al., 2015; Kumar & Jayaroopa, 2013; Verma et al., 2022).

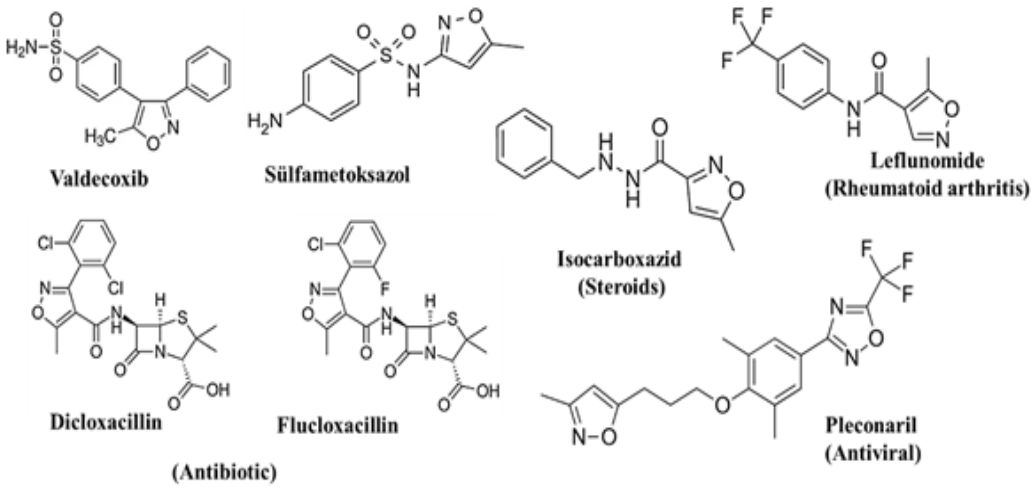



Figure 2. Some drug structures containing the isoxazole group.

In the context of cancer therapy, isoxazole derivatives have shown promising results in modulating key pathways, such as apoptosis induction, inhibition of angiogenesis, cell cycle arrest, and suppression of tumor cell proliferation.

Owing to the presence of nitrogen and oxygen atoms within the heterocyclic ring, the isoxazole scaffold can favorably modulate the molecular architecture of compounds and promote potential interactions with protein active sites through hydrogen bonding and other non-covalent interactions (Arya et al., 2019). These findings highlight the isoxazole ring as a valuable motif for the rational design of novel anticancer agents. This review will explore various synthetic pathways of isoxazole compounds and discuss their potential anticancer and other biological activities.

*A.2. Synthesis Methods of Isoxazole Derivatives*

Cycloaddition reactions usually occur between unsaturated compounds containing π (pi) bonds. In this process, two reactants combine to form a cyclic compound, resulting in the loss of two π bonds and the formation of two new σ bonds (Kobayashi & Jørgensen, 2002).

The idea of a 1,3-dipolar cycloaddition reaction was first put forward by L. I. Smith in 1938 (Smith, 1938). However, this idea did not progress further until 1963. In 1963, the conceptual framework for 1,3-dipolar cycloadditions (Huisgen reaction) was created by German chemist Rolf Huisgen, providing much-needed mechanistic rationalization for the process (Singh et al., 2016). 1,3-dipolar cycloaddition reaction is very suitable and widely used method for constructing five-membered heterocyclic compounds. In these reactions, a 1,3-dipole reacts with usually an alkene or alkyne to form a five-membered ring containing heteroatoms (N, O, or others). A brief list of the common products formed by [3+2] cycloaddition reactions, particularly the interaction of 1,3-dipoles with dipolarophiles such as alkenes and alkynes, is given in (Table 1) (Carruthers, 2013; Huisgen, 1963).

Table 1. Common 1,3-dipoles and their [3+2] cycloaddition products.

| 1,3-Dipole | General Structure | Typical Dipolarophile | [3+2] Product | Product Class / Notes |
|---|---|---|---|---|
| **Azide (R–$N_3$)** | $^{-}N^{+}=N=N$ | Alkyne/ Alkene | 1,2,3-Triazole | Aromatic, stable, used in "click" chemistry |
| **Nitrile Oxide** | $R–C\equiv N^{+}–O^{-}$ | Alkene/ Alkyne | Isoxazoline/ Isoxazole | Isoxazoline(non-aromatic), Isoxazole (aromatic) |
| **Nitrile Imine** | $R–C^{-}=N^{+}–N=R'$ | Alkene/ Alkyne | Pyrazoline/ Pyrazole | Analogous to nitrile oxide reactions |
| **Nitrone** | $R_2C=N^{+}–O^{-}$ | Alkene | Isoxazolidine | Non-aromatic, used in drug synthesis |
| **Azomethine Ylide** | $R_2C^{-}–N^{+}=CR_2$ | Alkene/ Carbonyl | Pyrrolidine | Versatile scaffold in natural products |
| **Diazoalkane** | $R_2C=N^{+}=N^{-}$ | Alkene/ Carbonyl | Pyrazoline/ Pyrazole | Often needs thermal or photochemical activation |
| **Thionitroso Compound** | $R–S^{+}=N^{-}=O$ | Alkene | Thiazoline/ Thiazole | Contains sulfur and nitrogen |

1,3-dipolar compounds usually contain one negatively charged center (nucleophilic) and one positively charged center (electrophilic) in their structures. Resonance structures at these extremes indicate that the molecule is polar in terms of electron density. This polarization explains why 1,3-dipole compounds readily add to π bonds. The possible reaction mechanism of 1,3-dipolar cycloaddition reactions is given in (Figure 3) (Padwa, 1976).

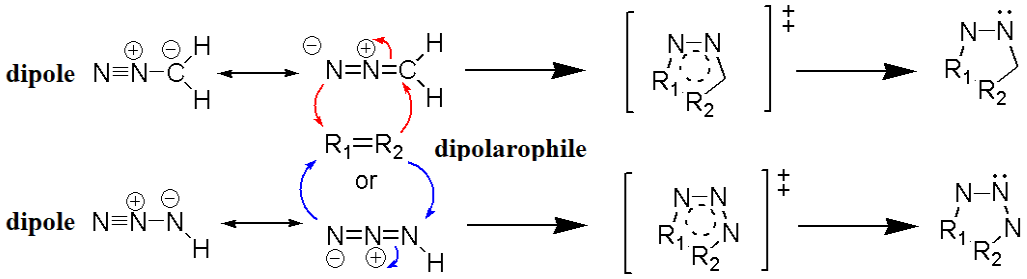



Figure 3. Mechanism of 1,3-dipolar cycloaddition reactions.

Himo et al. (2005) synthesized of 3,5-disubstituted isoxazoles *via* 1,3-dipolar cycloaddition from Cu(I)-catalyzed synthesis, as shown in (Figure 4). What is particularly impressive here is that the reaction proceeds rapidly at room temperature while achieving a high cycloaddition selectivity of greater than 95:5 (Himo et al., 2005).

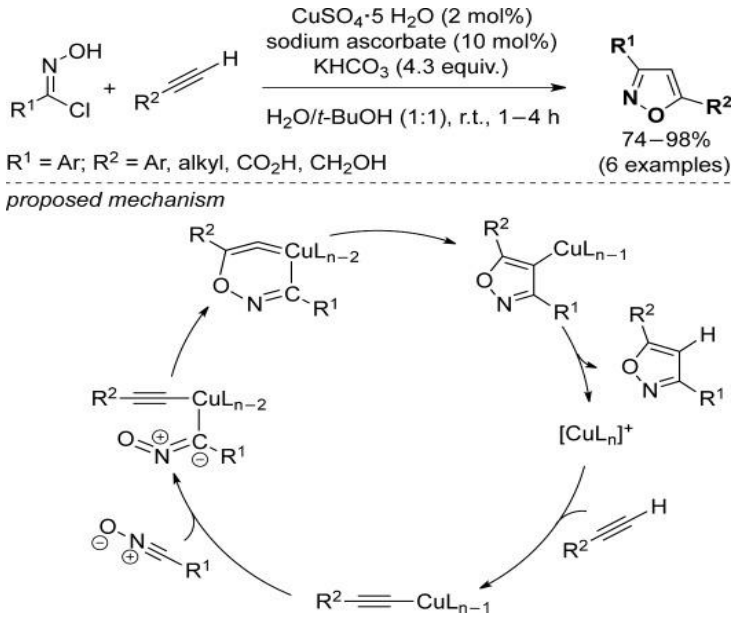



Figure 4. Synthesis and reaction mechanism of copper(I)-catalyzed 1,4-disubstituted 1,2,3-triazoles (Hu & Szostak, 2015).

Vieira et al. (2009) regioselectively synthesized of unsymmetrical 3,5-disubstituted isoxazoles from alkynes and imidoyl chloride via a Cu(I)-catalyzed 1,3-dipolar cycloaddition. These compounds exhibited liquid-crystalline behavior with various polymorphic phases, including SmC, SmA, and nematic (N) phases (Vieira et al., 2009).

The cycloadiation with Nitrile Oxides is a classical route to the formation of biologically significant isoxazole or isoxazoline analogues. Synthesis of spirooxindole-linked isoxazole analogues (4) from an efficient three-component reaction of (E)-2-(1-propargyl-2-oxoindoline-3-ylidene)acetophenones (1), arylnitrile oxides (2), and arylazides (3) using Cu(I) as catalyst,of by using these synthetic routes was reported by Sakly et al. (2017) and has been depicted in (Figure 5) (Sakly et al., 2017).

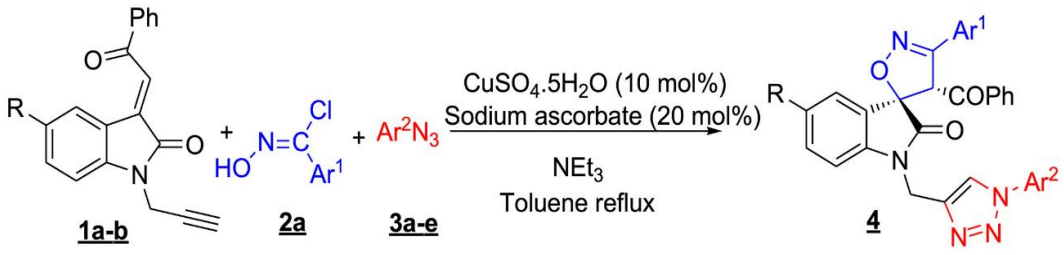



Figure 5.Synthesis of spirooxindole-linked isoxazoline/triazoles.

Pandey et al. (2024) reported the synthesis of novel isoxazole/dihydroisoxazole ring linked β-lactam hybrids (7) via a 1,3-dipolar cycloaddition using cis-1-phenyl-3-phenylthio-3-propargyloxy-4-phenylazetidin-2-one (5) and 4-chloro-N-hydroxybenzimidoyl chloride (7), as shown in (Figure 6). The developed methodology demonstrated high regioselectivity and broad substrate scope, allowing for the efficient synthesis of a wide variety of novel hybrid compounds under mild reaction conditions (Pandey et al., 2024).

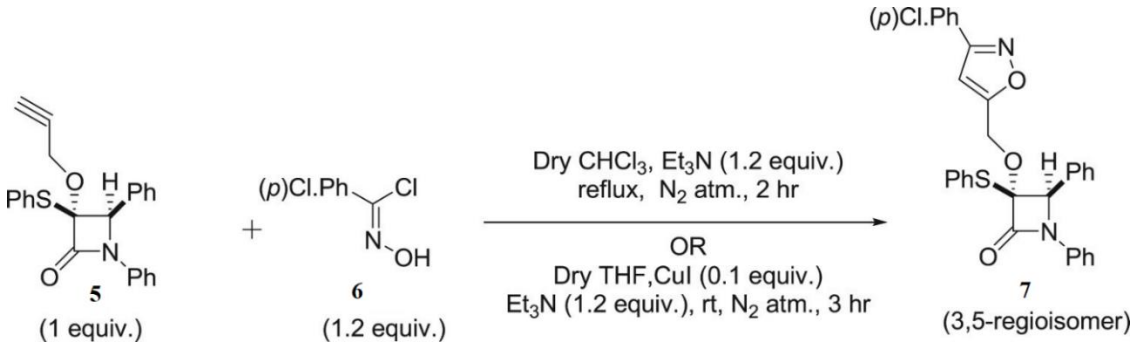



Figure 6. Synthesis of cis-3-phenylthio-3-propargyloxy-β-lactams 5 & cis-3-allyl-3-phenylthio-β-lactams.

Bouzammit et al. (2024) reported the successful synthesis of two novel isoxazole–triazole hybrid heterocycles (9a-b) using 3-formylchromone as the starting material, achieving good yields, as shown in (Figure 7). They also evaluated the antibacterial activities of the compounds by both in vitro and in silico studies. Compound 9b was reported to exhibit potent antibacterial activity against Escherichia coli ATCC 25922 and Pseudomonas aeruginosa strains compared to standard antibiotics (Bouzammit et al., 2024).

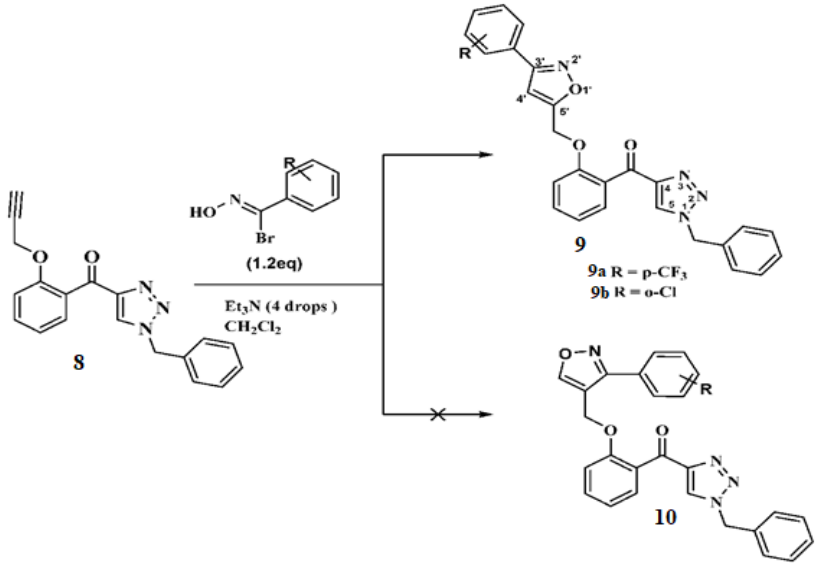



Figure 7. Synthesis of two novel isoxazole–triazole hybrid heterocycles.

Microwave-assisted 1,3-dipolar cycloaddition reactions are also widely used in the synthesis of isoxazole derivatives. For example, Koufaki et al. (2014) reported the synthesis of 3,5-disubstituted isoxazoles via one-pot uncatalysed microwave-assisted 1,3-dipolar cycloaddition reactions and the evaluation of their antiaging activity (Koufaki et al., 2014). In another study, Zheng et al. (2020) reported synthesis of 3-substituted bis-isoxazole ether bearing 2-chloro-3-pyridyl under microwave radiation (Zheng et al., 2020). Similarly, various isoxazole derivatives were synthesized via microwave-assisted 1,3-dipolar cycloaddition reactions by creating greener synthesis environments without catalyst, solvent etc. (Plumet, 2020; Pineiro & Pinho e Melo, 2009; Maiuolo et al., 2017).

*A.3. Isoxazole derivatives as anticancer agents*

*A.3.1. Synthesis of new derivative isoxazole and evaluation of their activities in breast cancer*

Breast cancer remains the most prevalent type of cancer among women in both developed and developing countries. According to global health statistics, approximately 2.3 million new cases and 670,000 deaths were reported worldwide in 2022 (Bray et al., 2024). Ongoing research into breast cancer treatment focuses on addressing tumor resistance to

current therapies and discovering more effective agents with fewer side effects [48,49]. Natural products continue to play a crucial role in the discovery of novel anticancer agents, and numerous studies have highlighted the anticancer potential of natural compounds containing the isoxazole moiety (Altharawi et al., 2025; Kim et al., 2025; Martis & Gaonkar, 2025; Wang et al., 2023). For instance, Altharawi et al. and Ahmet et al. developed stereoisomeric isoxazoline–thiazolidinone hybrids derived from (R)-carvone, which exhibited strong binding affinities to molecular targets such as HSP90 and HIF1A—proteins known to play significant roles in breast cancer progression. Carvone is a naturally occurring bioactive monoterpene found in various essential oils (Anjum & Raza, 2025). In a separate study, Rodrigues et al. reported that isoxazole-curcumin (C2) (compound 11) demonstrated approximately sevenfold greater anticancer activity against breast cancer cells compared to native curcumin, as illustrated in (Figure 8) (Rodrigues et al., 2021).

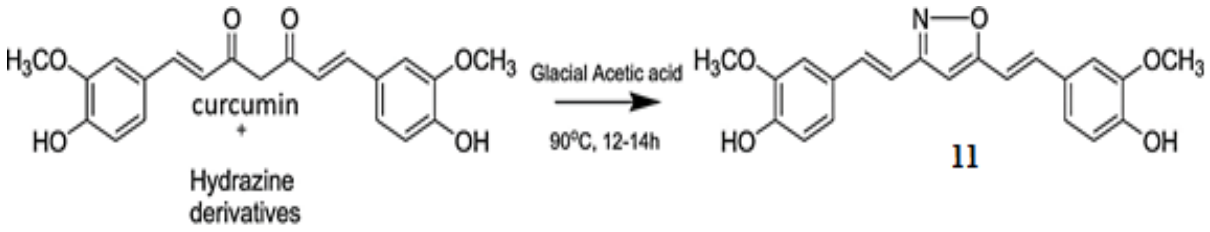



Figure 8. Synthesis of isoxazole-curcumin (C2).

Numerous isoxazole-containing compounds have been identified by researchers as possessing significant anticancer potential (Alminderej et al., 2023; Hawash et al., 2021; Kumbhare et al., 2012; Watterson et al., 2016). Some of these compounds have already been approved for clinical use, including Tivozanib for kidney cancer, Acivicin for the treatment of malignant tumors, and Quizartinib for acute myeloid leukemia (Gunawardane et al., 2013; Poster et al., 1981; Sochacka-Ćwikła et al., 2022). Meanwhile, several other isoxazole derivatives have progressed to clinical trial stages (Kong et al., 2016; Montenegro et al., 2016; Taldone et al., 2008; Wagner et al., 2020). For example, Jensen et al. (2008) synthesized Luminespib (NVP-AUY922), a potent small-molecule HSP90 inhibitor that demonstrated effective inhibition of human breast cancer cell proliferation (Brough et al., 2008; Montenegro et al., 2016). In another study, Burra et al. (2017) regioselectively synthesized forskolin-based 3,5-disubstituted isoxazole derivatives (12) via nitric oxide alkyne/alkene cycloadditions (NOAC). Several of these compounds exhibited significant anticancer activity against p53-positive MCF-7 breast cancer cells, as illustrated in (Figure 9) (Burra et al., 2017).

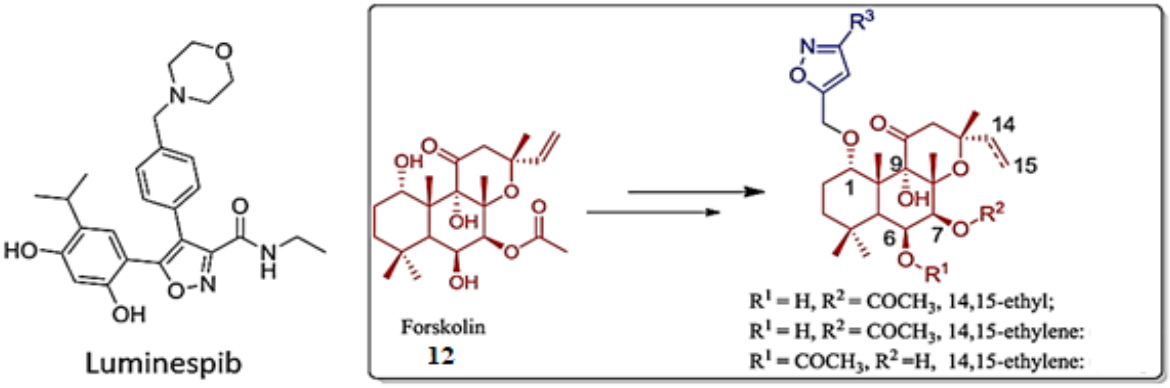



Figure 9. Structure of Luminespib (NVP-AUY922) and forskolin 3,5-disubstituted isoxazole derivatives.

Reddy et al. (2020) synthesized novel methyl β-orsellinate based 3, 5-disubstituted isoxazole hybrids (15-30) via a 1,3-dipolar cycloaddition reaction of terminal alkyne and corresponding nitriloxides and performed against a panel of human breast cancer cell line, MCF-7 cancer lines and compound 24 showed remarkable anti-proliferative effect against MCF-7 breast cancer cell ($IC_{50}$: 7.9 ± 0.07 μM), as shown in (Figure 10) (Reddy et al., 2020).

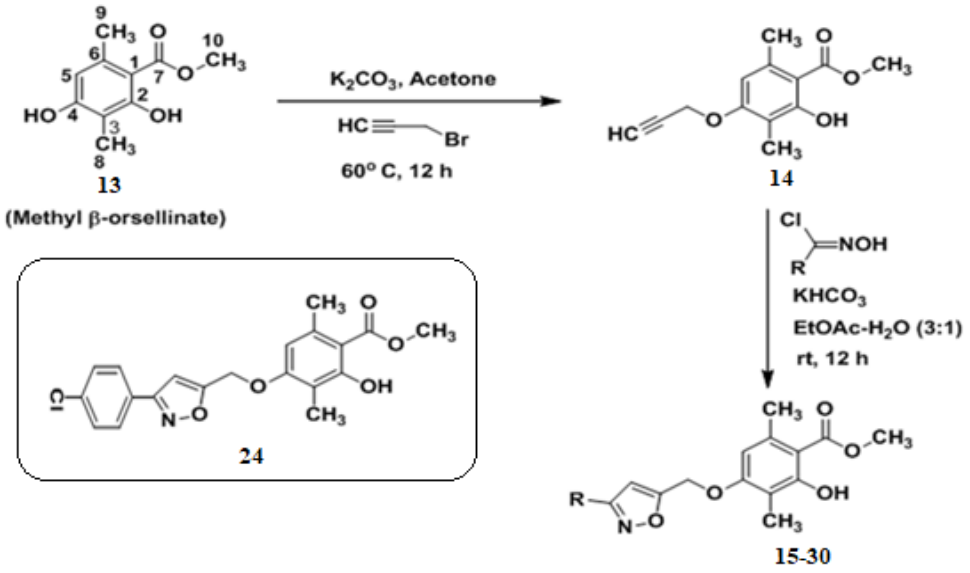



Figure 10. The synthesis of methyl β-orsellinate based 3,5-disubstituted isoxazole hybrid structures.

Similarly, Keshavarzipour et al. (2024) developed new isoxazole derivatives (32-38) and evaluated the potential of these compounds as Hsp90 inhibitors. Compound 35 showed the highest cytotoxicity with an $IC_{50}$ value of approximately 14 μM in MCF-7 and HeLa cancer cell lines. The synthesis steps of the compounds are given in (Figure 11) (Keshavarzipour et al., 2024).

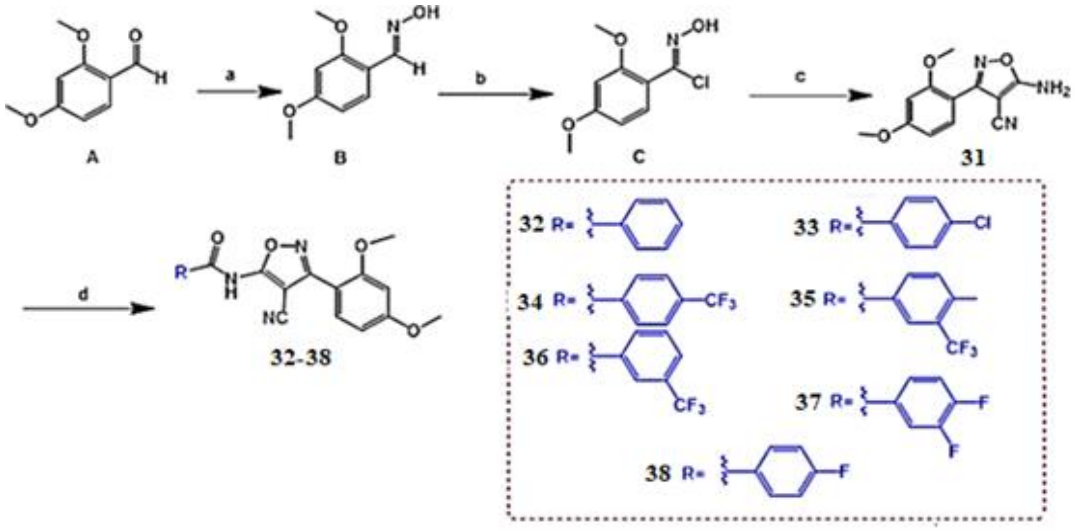



Figure 11. Synthesis route of isoxazole Hsp90 inhibitors and the chemical structure of synthesized heterocyclic compounds 31–38. Reagents and reaction conditions: (a) $NH_2OH.HCl$, Py, EtOH, rt; (b) NCS, DMF, rt, 24 h; (c) $(CN)_2CH_2$, $CH_3ONa$, EtOH, 0°C, 20 min, rt, 24 h; (d) $Et_3N$, THF, RCOCl, rt, 24 h.

*A.3.2. Synthesis of new derivative isoxazole and evaluation of their activities in lung cancer*

In 2022, lung cancer remained the leading cause of cancer-related morbidity and mortality worldwide, with approximately 2.5 million new cases and over 1.8 million deaths, accounting for 12.4% of all cancer diagnoses and 18.7% of cancer-related deaths (Bray et al., 2024). Owing to the versatile and potent biological properties of isoxazole compounds in cancer therapy, the potential therapeutic effects of synthetic, semi-synthetic, and natural isoxazole derivatives against lung cancer have been extensively investigated in various studies. For instance, Kamal et al. (2011) synthesized a series of novel 3,5-diaryl isoxazoline/isoxazole-linked 2,3-dihydroquinazolinone hybrids, which were evaluated for their anticancer activity against 18 human cancer cell lines, with a particular focus on lung cancer. These compounds demonstrated notably promising anticancer activity (Kamal et al., 2011). Similarly, Arya et al. (2019) reported the synthesis of Hy-Isoxazole and Hy-Isoxazolone hybrids by attaching the isoxazole ring to plant-derived hydnocarpin derivatives using the (3+2) cycloaddition method. These compounds demonstrated strong cytotoxic activity by inducing apoptosis in human lung adenocarcinoma (A549) and melanoma (A375) cell lines (Arya et al., 2019).

Furthermore, Lingala et al. (2022) synthesized a new series of isoxazole-fused thiazole-oxazole compounds (46a-j) via a $Pd(OAc)_2$/ Triphenylphosphine/ $K_2CO_3$-catalyzed reaction using oxazole-4-carbothioamide (39) and 1-iodo-4-nitrobenzene (40) as starting materials, as shown in (Figure 12). These compounds were subsequently evaluated for their anticancer activity using the MTT assay on human cancer cell lines, where they demonstrated superior cytotoxic effects compared to the positive control group (Lingala et al., 2022).

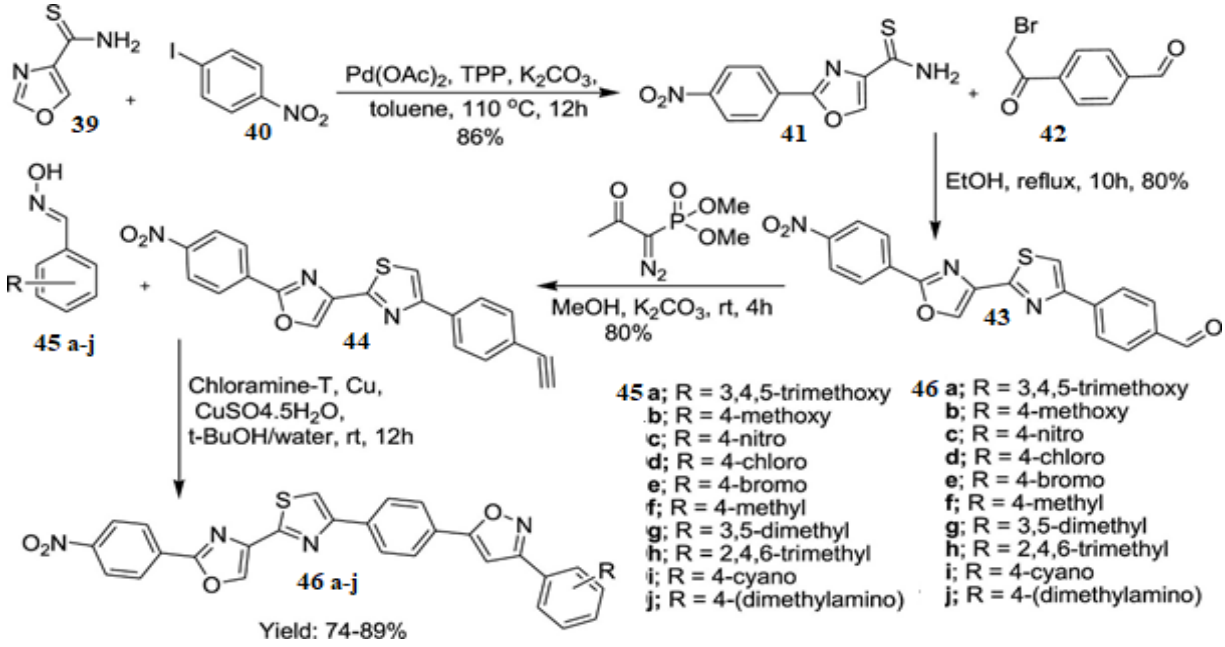



Figure 12. Synthesis route of a new series of isoxazole-fused thiazole-oxazole compounds.

*A.3.3. Synthesis of new derivative isoxazole and evaluation of their activities in leukemia cancer*

Leukemia, commonly referred to as blood cancer, is a hematological malignancy characterized by the excessive proliferation of abnormal white blood cells (leukocytes) in the bone marrow and peripheral blood. The treatment of leukemia generally involves a combination of approaches, including targeted therapies, immunotherapy, chemotherapy, and bone marrow transplantation. However, due to treatment resistance, side effects, and the lack of target selectivity, there is a growing need for new therapeutic molecules. In this regard, compounds containing isoxazole rings have emerged as promising pharmacophores in the treatment of leukemia (Majirská et al., 2024). In this context, Ashwini et al. (2015) synthesized a series of 1,2-benzisoxazole–1,2,3-triazole hybrids (51) by introducing various alkynes at the third position of the benzisoxazole ring via copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC). The resulting compounds exhibited significant antiproliferative activity against human acute myeloid leukemia (AML) cells, as shown in (Figure 13) (Ashwini et al., 2015). Similarly, Hu et al. reported the synthesis of 5-imidazole-3-methylbenzo[d]isoxazoles as novel, potent and selective CBP/p300 bromodomain inhibitors (Hu et al., 2025).

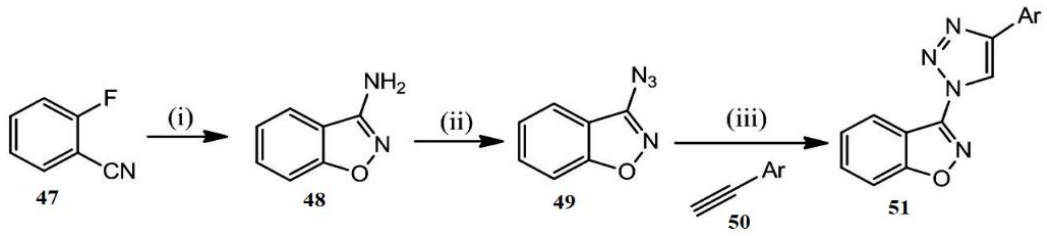



Figure 13. Schematic representation of the synthesis of 1-(3-benzisoxazolyl)-4-aryl-1,2,3-triazoles (51). Reagents and conditions: (i) Acetohydroxamic acid, t-BuOK, DMF, rt. (ii) Concd HCl, $H_2O$, $NaNO_2$, $NaN_3$, 0 °C. (iii) CuI, acetonitrile:$H_2O$ (2:1).

To provide a clearer and comparative overview of the anticancer potential of the discussed isoxazole-containing compounds, the key biological findings, cancer types, in vitro and in vivo evaluations, reported $IC_{50}$ values, and proposed mechanisms of action are summarized in (Table 2). This structured presentation enables a more comprehensive assessment of their therapeutic relevance and translational potential.

Table 2. Comparative overview of the anticancer activity of isoxazole-containing derivatives.

| Compound | Cancer Type | Cell Line | $IC_{50}$ | Clinical Status | Reference |
|---|---|---|---|---|---|
| **Isoxazole-curcumin (C2)** | Breast | MCF7 | -3.97 μM | Preclinical (in vitro) | (Anjum & Raza, 2025) |
| **Luminespib (NVP-AUY922)** | several types of cancer | several types of cell line | Hsp90 FP binding assay (IC50 = 21 nM) | Clinical trials | (Montenegro et al., 2016; Wagner et al., 2020) |
| **Methyl β-orsellinate isoxazole** | Breast | MCF-7 | 7.9 μM | Preclinical (in vitro) | (Burra et al., 2017) |
| **Isoxazole Hsp90 inhibitor** | Breast | MCF-7, HeLa | 14 μM | Preclinical (in vitro) | (Reddy et al., 2020) |
| **3,5-diaryl isoxazole hybrids** | Nine different types of cancer | sixty tumor cell lines | $GI_{50}$ < 1 μM | Preclinical (in vitro) | (Keshavarzipour et al., 2024) |
| **Benzisoxazole–triazole hybrids** | Leukemia | AML cells | 2 μM | Preclinical (in vitro) | (Ashwini et al., 2015) |

*A.4.Other Biological Activities of İsoxazole Derivatives*

Isoxazole derivatives possess a wide range of pharmacological activities, including antifungal, antiviral, antimicrobial, antioxidant, and anti-inflammatory properties, among others (Fox et al., 1999; Ni et al., 2023; Ormrod et al., 2002; Thakur et al., 2023; Yang et al., 2018). The clinical significance of this heterocyclic scaffold is further evidenced by the successful market introduction of several isoxazole-based drugs, such as tivozanib, valdecoxib, leflunomide, dicloxacilin, cloxacilin and oxacilin, is given in (Table 3).

Table 3. Isoxazole derivatives that is marketed globally as an active pharmaceutical ingredient for the treatment

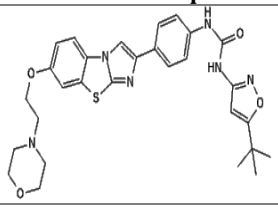
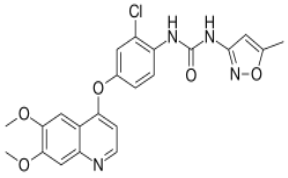
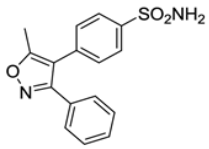
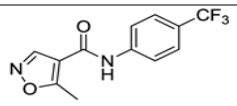
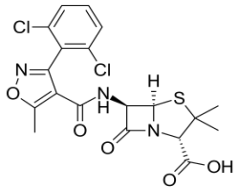
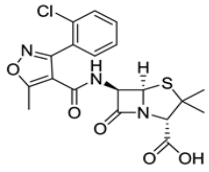
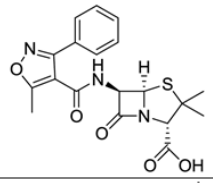
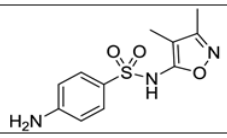
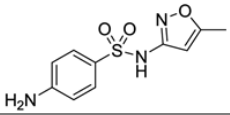
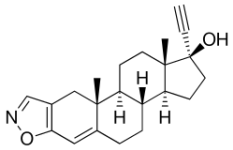
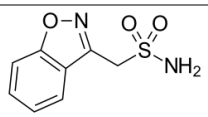
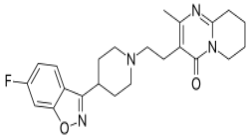
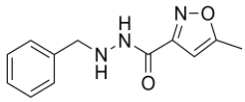
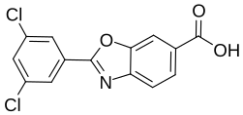
| | Compound | FDA approval | Structure of compound | Usage | Reference |
|---|---|---|---|---|---|
| 1 | Quizartinib | 2023 |  | Anticancer | (Poster et al., 1981; Sochacka-Ćwikła et al., 2022; Watterson et al., 2016 ) |
| 2 | Tivozanib | 2021 |  | Kinase inhibitor (anticancer) | (Frazer et al., 2024) |
| 3 | Valdecoxib | 2001 |  | Anti-inflammatory agents | (Ormrod et al., 2002) |
| 4 | Leflunomide | 1998 |  | Anti-inflammatory agents | (Fox et al., 1999) |
| 5 | Dicloxacillin | 1968 |  | Antibacterial (β-lactam antibiotic) | (Olsson et al., 1992) |
| 6 | Cloxacillin | 1965 |  | Antibacterial (β-lactam antibiotic) | (Olsson et al., 1992) |

Table 3. (cont) Isoxazole derivatives that is marketed globally as an active pharmaceutical ingredient for the treatment

| | | | | | |
|---|---|---|---|---|---|
| 7 | Oxacillin | 1971 |  | Antibacterial (β-lactam antibiotic) | (Sutherland et al., 1970) |
| 8 | Sulfisoxazole | 1953 |  | Antibacterial (sulfonamide) | (Im et al., 2019) |
| 9 | Sulfamethoxazole | 1973 |  | Antibacterial (sulfonamide) | (Eliopoulos & Huovinen, 2001) |
| 10 | Danazol | 1976 |  | Androgenic | (Barbieri & Ryan, 1981) |
| 11 | Zonisamide | 2000 |  | Antiparkinsonian | (Leppik, 2004) |
| 12 | Risperidone | 2003 |  | Antipsychotic | (Möller, 2005) |
| 13 | Isocarboxazid | 1982 |  | Antidepressant | (Schwartz, 1962) |
| 14 | Tafamidis | 2019 |  | Transthyretin-induced amyloid cardiomyopathy | (Hussain et al., 2022) |

## III. CONCLUSION

In conclusion, this review systematically evaluated the clinical potential of isoxazole-containing compounds and examined their therapeutic effects across various cancer types. The isoxazole ring represents a chemically versatile and biologically significant scaffold in the ongoing search for effective anticancer agents. Due to its unique electronic configuration and hydrogen-bonding capabilities, isoxazole-containing compounds exhibit diverse and potent pharmacological activities against cancers such as breast, lung, and leukemia. Modern synthetic approaches particularly 1,3-dipolar cycloaddition reactions enable the efficient and regioselective production of novel isoxazole derivatives with promising therapeutic profiles.

The broad spectrum of biological activities observed in numerous studies including anticancer, antibacterial, antitubercular, anti-inflammatory, and antidepressant effects supports the hypothesis that molecular hybridization of these N, O-heterocyclic units enhances or synergizes their pharmacological profiles compared to the parent monomers. This is further corroborated by the ability of these hybrids to inhibit multiple enzymes and receptors, such as P2Y1 receptor, GATA4, OX2R, SCD, ACC, ALPK1, FAAH, PRMT5, LPA, PXR, CRTh2 receptor, p38 kinase, and cathepsin K. Additionally, these compounds can modulate the activity of several other receptors, including RORγ, GABA A α5, Erα, GPR120, PPARs, nAChR, and mGlu5 (Bąchor et al., 2025).

The reviewed studies demonstrate that isoxazole-containing compounds can modulate key oncogenic pathways, induce apoptosis, inhibit cell proliferation, and interfere with angiogenesis. Importantly, the clinical approval and ongoing evaluation of certain isoxazole-based drugs further confirm the translational relevance of this scaffold in oncology. Nevertheless, further investigations are needed to optimize selectivity, reduce toxicity, and improve pharmacokinetic properties. Future research should focus on rational drug design strategies, structure–activity relationship (SAR) analyses, molecular docking studies, and in vivo validation to accelerate the development of safer and more effective next-generation anticancer and multifunctional therapeutic agents.

## DECLARATIONS

**Acknowledgements:** The author do not wish to acknowledge any individual or institution.

**Author Contributions:** All parts of the study were conducted by the Author.

**Conflict of Interest:** The author declare no conflict of interest.

**Supporting Institutions:** This research received no external funding.

**Ethical Approval:** This study does not involve human or animal participants. All procedures followed scientific and ethical principles, and all referenced studies are appropriately cited.

**Plagiarism Statement:** This article has been evaluated for plagiarism and no instances of plagiarism were detected.

**Use of AI Tools:** The author declare that no Artificial Intelligence (AI) tools were used in the creation of this article.

## REFERENCES

Agrawal, N., & Mishra, P. (2018). The synthetic and therapeutic expedition of isoxazole and its analogs. *Medicinal Chemistry Research, 27*(5), 1309-1344. https://doi.org/10.1007/s00044-018-2152-6

Algethami, F. K., Saidi, I., Abdelhamid, H. N., Elamin, M. R., Abdulkhair, B. Y., Chrouda, A., & Ben Jannet, H. (2021). Trifluoromethylated flavonoid-based isoxazoles as antidiabetic and anti-obesity agents: Synthesis, in vitro α-amylase inhibitory activity, molecular docking and structure–activity relationship analysis. *Molecules, 26*(17), Article 5214. https://doi.org/10.3390/molecules26175214

Alminderej, F., Ghannay, S., Elsamani, M. O., Alhawday, F., Albadri, A. E. A. E., Elbehairi, S. E. I., Alfaifi, M. Y., Kadri, A., & Aouadi, K. (2023). In vitro and in silico evaluation of antiproliferative activity of new isoxazolidine derivatives targeting EGFR: Design, synthesis, cell cycle analysis, and apoptotic inducers. *Pharmaceuticals, 16*(7), Article 1025. https://doi.org/10.3390/ph16071025

Altharawi, A., Enneiymy, M., Ait Elmachkouri, Y., & Aldakhil, T. (2025). Synthesis, characterization, DFT, and in-Silico analysis of isoxazole-thiazolidinone hybrids: Reactivity and anticancer potential assessed through pharmacological network, molecular dynamics, molecular docking, and ADMET analysis. *Journal of Molecular Structure, 1336,* Article 142088. https://doi.org/10.1016/j.molstruc.2025.142088

Anjum, R., & Raza, C. (2025). Carvone: A bioactive monoterpene with diverse pharmacological applications. *Current Pharmacology Reports, 11*(1), Article 22. https://doi.org/10.1007/s40495-025-00402-5

Ardestani, M., Khorsandi, Z., Keshavarzipour, F., Iravani, S., Sadeghi-Aliabadi, H., & Varma, R. S. (2022). Heterocyclic compounds as Hsp90 inhibitors: A perspective on anticancer applications. *Pharmaceutics, 14*(10), Article 2220. https://doi.org/10.3390/pharmaceutics14102220

Arya, J. S., Joseph, M. M., Sherin, D. R., Nair, J. B., Manojkumar, T. K., & Maiti, K. K. (2019). Exploring mitochondria-mediated intrinsic apoptosis by new phytochemical entities: An explicit observation of cytochrome c dynamics on lung and melanoma cancer cells. *Journal of Medicinal Chemistry, 62*(17), 8311-8329. https://doi.org/10.1021/acs.jmedchem.9b01098

Ashwini, N., Garg, M., Mohan, C. D., Fuchs, J. E., Rangappa, S., Anusha, S., Swaroop, T. R., Rakesh, K. S., Kanojia, D., Madan, V., Bender, A., Koeffler, H. P., Basappa, & Rangappa, K. S. (2015). Synthesis of 1, 2-benzisoxazole tethered 1, 2, 3-triazoles that exhibit anticancer activity in acute myeloid leukemia cell lines by inhibiting histone deacetylases, and inducing p21 and tubulin acetylation. *Bioorganic & Medicinal Chemistry, 23*(18), 6157-6165. https://doi.org/10.1016/j.bmc.2015.07.069

Baaloudj, O., Scrano, L., Bufo, S. A., Modley, L. A. S., Lelario, F., Zizzamia, A. R., Emanuele, L., & Brienza, M. (2025). Environmental fate, ecotoxicity, and remediation of heterocyclic pharmaceuticals as emerging contaminants: A review of long-term risks and ımpacts. *Organics, 6*(1), Article 1. https://doi.org/10.3390/org6010001

Bąchor, U., Mączyński, M., & Sochacka-Ćwikła, A. (2025). Therapeutic potential of isoxazole–(Iso) oxazole hybrids: Three decades of research. *International Journal of Molecular Sciences*, *26*(15), Article 7082. https://doi.org/10.3390/ijms26157082

Barbieri, R. L., & Ryan, K. J. (1981). Danazol: Endocrine pharmacology and therapeutic applications. *American Journal of Obstetrics and Gynecology, 141*(4), 453-463. https://doi.org/10.1016/0002-9378(81)90611-6

Bouzammit, R., Belchkar, S., El Fadili, M., Kanzouai, Y., Mujwar, S., Alanazi, M. M., Chalka, M., Nakkabi, A., Bakhouch, M.,Gal, E., Gaina, L. I., & Al Houari, G. (2024). New triazole-isoxazole hybrids as antibacterial agents: Design, synthesis, characterization, in vitro, and in silico studies. *Molecules, 29*(11), Article 2510. https://doi.org/10.3390/molecules29112510

Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 74*(3), 229-263. https://doi.org/10.3322/caac.21834

Brough, P. A., Aherne, W., Barril, X., Borgognoni, J., Boxall, K., Cansfield, J. E., Cheung, K.-M. J., Collins, I., Davies, N. G. M.,

Drysdale, M. J., Dymock, B., Eccles, S. A., Finch, H., Fink, A., Hayes, A., Howes, R., Hubbard, R. E., James, K., Jordan, A. M., … Wright, L. (2008). 4,5-diarylisoxazole Hsp90 chaperone inhibitors: Potential therapeutic agents for the treatment of cancer. *Journal of Medicinal Chemistry, 51*(2), 196-218. https://doi.org/10.1021/jm701018h

Burra, S., Voora, V., Rao, C. P., Kumar, P. V., Kancha, R. K., & Krupadanam, G. L. D. (2017). Synthesis of novel forskolin isoxazole derivatives with potent anti-cancer activity against breast cancer cell lines. *Bioorganic & Medicinal Chemistry Letters, 27*(18), 4314-4318. https://doi.org/10.1016/j.bmcl.2017.08.033

Carruthers, W. (2013). *Cycloaddition reactions in organic synthesis (Vol. 8).* Elsevier.

Chene, P., Garcia-Echeverria, C., Jensen, M. R., Quadt, C., Radimerski, T., & Schoepfer, J. (2016). *Isoxazole compound for the treatment of cancer.* U.S. Patent Application No. 15/096,397.

Chikkula, K. V., & Raja, S. (2017). Isoxazole–a potent pharmacophore. *International Journal of Pharmacy and Pharmaceutical Sciences, 9*(7), 13-24. https://doi.org/10.22159/ijpps.2017.v9i7.19097

Dawood, K. M., Abdel-Gawad, H., Mohamed, H. A., & Badria, F. A. (2011). Synthesis, anti-HSV-1, and cytotoxic activities of some new pyrazole-and isoxazole-based heterocycles. *Medicinal Chemistry Research, 20*(7), 912-919. https://doi.org/10.1007/s00044-010-9420-4

Debela, D. T., Muzazu, S. G., Heraro, K. D., Ndalama, M. T., Mesele, B. W., Haile, D. C., Kitui, S. K., & Manyazewal, T. (2021). New approaches and procedures for cancer treatment: Current perspectives. *SAGE Open Medicine, 9*(6), Article 20503121211034366. https://doi.org/10.1177/20503121211034366

Eliopoulos, G. M., & Huovinen, P. (2001). Resistance to trimethoprim-sulfamethoxazole. *Clinical Infectious Diseases, 32(*11), 1608-1614. https://doi.org/10.1086/320532

Emran, T. B., Shahriar, A., Mahmud, A. R., Rahman, T., Abir, M. H., Siddiquee, M. F. R., Ahmed, H., Rahman, N., Nainu, F., Wahyudin, E., Mitra, S., Dhama, K., Habiballah, M. M., Haque, S., İslam, A., & Hassan, M. M. (2022). Multidrug resistance in cancer: Understanding molecular mechanisms, immunoprevention and therapeutic approaches. *Frontiers in Oncology, 12*, Article 891652. https://doi.org/10.3389/fonc.2022.891652

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D., & Bray, F. (2015). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer, 136*(5), E359-E386. https://doi.org/10.1002/ijc.29210

Fox, R. I., Herrmann, M. L., Frangou, C. G., Wahl, G. M., Morris, R. E., Strand, V., & Kirschbaum, B. J. (1999). Mechanism of action for leflunomide in rheumatoid arthritis. *Clinical Immunology, 93*(3), 198-208. https://doi.org/10.1006/clim.1999.4777

Frazer, R., Arranz, J. Á., Estévez, S. V., Parikh, O., Krabbe, L. M., Vasudev, N. S., Dohaen, C., Marschner, N., Waddell, T., Ince, W., & Goebell, P. J. (2024). Tivozanib monotherapy in the frontline setting for patients with metastatic renal cell carcinoma and favorable prognosis. *Current Oncology Reports, 26*(12), 1639-1650. https://doi.org/10.1007/s11912-024-01613-7

Gaikwad, N. B., Bansod, S., Mara, A., Garise, R., Srinivas, N., Godugu, C., & Yaddanapudi, V. M. (2021). Design, synthesis, and biological evaluation of N-(4-substituted)-3-phenylisoxazolo [5,4–d]pyrimidin-4-amine derivatives as apoptosis-inducing cytotoxic agents. *Bioorganic & Medicinal Chemistry Letters, 49*, Article 128294. https://doi.org/10.1016/j.bmcl.2021.128294

Gunawardane, R. N., Nepomuceno, R. R., Rooks, A. M., Hunt, J. P., Ricono, J. M., Belli, B., & Armstrong, R. C. (2013). Transient exposure to quizartinib mediates sustained inhibition of FLT3 signaling while specifically inducing apoptosis in FLT3-activated leukemia cells. *Molecular Cancer Therapeutics, 12*(4), 438-447. https://doi.org/10.1158/1535-7163.MCT-12-0305

Hawash, M., Jaradat, N., Abualhasan, M., Amer, J., Levent, S., Issa, S., Ibrahim, S., Ayaseh, A., Shtayeh, T., & Mousa, A. (2021). Synthesis, chemo-informatics, and anticancer evaluation of fluorophenyl-isoxazole derivatives. *Open Chemistry, 19*(1), 855-863. https://doi.org/10.1515/chem-2021-0078

Himo, F., Lovell, T., Hilgraf, R., Rostovtsev, V. V., Noodleman, L., Sharpless, K. B., & Fokin, V. V. (2005). Copper (I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates. *Journal of the American Chemical Society, 127*(1), 210-216. https://doi.org/10.1021/ja0471525

Hu, F., & Szostak, M. (2015). Recent developments in the synthesis and reactivity of isoxazoles: Metal catalysis and beyond. *Advanced Synthesis & Catalysis, 357*(12), 2583-2614. https://doi.org/10.1002/adsc.201500319

Hu, J. K., Tang, X., Luo, G. L., Zhang, C., Wu, T. B., Wang, C., Shen, H., Zhao, X. F., Wu, X. S., Smaill, J. B., Xu, Y., Zhang, Y., & Xiang, Q. P. (2025). Discovery of 5-imidazole-3-methylbenz [*d*] isoxazole derivatives as potent and selective CBP/p300 bromodomain inhibitors for the treatment of acute myeloid leukemia. *Acta Pharmacologica Sinica, 46*(6), 1706-1721. https://doi.org/10.1038/s41401-025-01478-x

Huisgen, R. (1963). 1,3-dipolar cycloadditions: Past and future. *Angewandte Chemie International Edition in English, 2*(10), 565-598. https://doi.org/10.1002/anie.196305651

Hussain, K., Macrinici, V., Wathen, L., Balasubramanian, S. S., Minga, I., Gaznabi, S., Kwak, E., Wang, C. H., Iqbal, S. H., Pursnani, A., & Sarswat, N. (2022). Impact of tafamidis on survival in a real-world community-based cohort. *Current Problems in Cardiology*, *47*(12), Article 101358. https://doi.org/10.1016/j.cpcardiol.2022.101358

Im, E.-J., Lee, C.-H., Moon, P.-G., Rangaswamy, G. G., Lee, B., Lee, J. M., Lee, J.-C., Jee, J.-G., Bae, J.-S., Kwon, T.-K., Kang, K.-W., Jeong, M.-S., Lee, J.-E., Jung, H.-S., Ro, H.-J., Jun, S., Kang, W., Seo, S.-Y., Cho, Y.-E., … & Baek, M.-C. (2019).

Sulfisoxazole inhibits the secretion of small extracellular vesicles by targeting the endothelin receptor A. *Nature Communications, 10*(1), Article 1387. https://doi.org/10.1038/s41467-019-09387-4

Jampilek, J. (2019). Heterocycles in medicinal chemistry. *Molecules, 24*(21), Article 3839. https://doi.org/10.3390/molecules24213839

Kakkar, S., & Narasimhan, B. (2019). A comprehensive review on biological activities of oxazole derivatives. *BMC Chemistry, 13(*1), Article 16. https://doi.org/10.1186/s13065-019-0531-9

Kamal, A., Bharathi, E. V., Reddy, J. S., Ramaiah, M. J., Dastagiri, D., Reddy, M. K., Visvanath, A., Reddy, T. L., Shaik, T. B., Pushpavilli, S. N. C. V. L., & Bhadra, M. P. (2011). Synthesis and biological evaluation of 3,5-diaryl isoxazoline/isoxazole linked 2,3-dihydroquinazolinone hybrids as anticancer agents. *European Journal of Medicinal Chemistry, 46*(2), 691-703. https://doi.org/10.1016/j.ejmech.2010.12.004

Kaur, J., Singla, P., & Goel, N. (2015). Adsorption of oxazole and isoxazole on BNNT surface: A DFT study. *Applied Surface Science, 328,* 632-640. https://doi.org/10.1016/j.apsusc.2014.12.099

Kaur, K., Kumar, V., Sharma, A. K., & Gupta, G. K. (2014). Isoxazoline containing natural products as anticancer agents: A review. *European Journal of Medicinal Chemistry, 77*, 121-133. https://doi.org/10.1016/j.ejmech.2014.02.063

Keshavarzipour, F., Abbasi, M., Khorsandi, Z., Ardestani, M., & Sadeghi-Aliabadi, H. (2024). Design, synthesis and biological studies of new isoxazole compounds as potent Hsp90 inhibitors. *Scientific Reports, 14*(1), Article 28017. https://doi.org/10.1038/s41598-024-79051-5

Kidwai, M., Venktaramanan, R., Mohan, R., & Sapra, P. (2002). Cancer chemotherapy and heterocyclic compounds. *Current Medicinal Chemistry, 9*(12), 1209-1228. https://doi.org/10.2174/0929867023370059

Kim, J., Harper, A., McCormack, V., Sung, H., Houssami, N., Morgan, E., Mutebi, M., Garvey, G., Soerjomataram, I., & Fidler-Benaoudia, M. M. (2025). Global patterns and trends in breast cancer incidence and mortality across 185 countries. *Nature Medicine, 31*(4), 1154–1162. https://doi.org/10.1038/s41591-025-03502-3

Kobayashi, S., & Jørgensen, K. A. (Eds.). (2002). *Cycloaddition reactions in organic synthesis*. John Wiley & Sons.

Kong, A., Rea, D., Ahmed, S., Beck, J. T., López López, R., Biganzoli, L., Armstrong, A. C., Aglietta, M., Alba, E., Campone, M., Hsu Schmitz, S. F., Lefebvre, C., Akimov, M., & Lee, S. C. (2016). Phase 1B/2 study of the HSP90 inhibitor AUY922 plus trastuzumab in metastatic HER2positive breast cancer patients who have progressed on trastuzumabbased regimen. *Oncotarget, 7*(25), 37680-37692. https://doi.org/10.18632/oncotarget.8974

Koufaki, M., Fotopoulou, T., Kapetanou, M., Heropoulos, G. A., Gonos, E. S., & Chondrogianni, N. (2014). Microwave-assisted synthesis of 3,5-disubstituted isoxazoles and evaluation of their anti-ageing activity. *European Journal of Medicinal Chemistry, 83*, 508-515. https://doi.org/10.1016/j.ejmech.2014.06.046

Kumar, K. A., & Jayaroopa, P. (2013). Isoxazoles: Molecules with potential medicinal properties. *International Journal of Pharmaceutical, Chemical And Biological Sciences, 3*(2), 294-304.

Kumbhare, R. M., Kosurkar, U. B., Ramaiah, M. J., Dadmal, T. L., Pushpavalli, S. N. C. V. L., & Pal-Bhadra, M. (2012). Synthesis and biological evaluation of novel triazoles and isoxazoles linked 2-phenyl benzothiazole as potential anticancer agents. *Bioorganic & Medicinal Chemistry Letters, 22*(17), 5424-5427. https://doi.org/10.1016/j.bmcl.2012.07.041

Leppik, I. E. (2004). Zonisamide: Chemistry, mechanism of action, and pharmacokinetics. *Seizure, 13*, S5-S9. https://doi.org/10.1016/j.seizure.2004.04.016

Lingala, A. K., Mothe, T., Murahari, K. K., Desireddi, J. R., Maiti, B., & Manchal, R. (2022). Design, synthesis and anticancer evaluation of isoxazole fused thiazole-oxazole derivatives. *Chemical Data Collections, 41*, Article 100907. https://doi.org/10.1016/j.cdc.2022.100907

Maiuolo, L., De Nino, A., Algieri, V., & Nardi, M. (2017). Microwave-assisted 1,3-dipolar cyclo-addition: Recent advances in synthesis of isoxazolidines. *Mini-Reviews in Organic Chemistry, 14*(2), 136-142. https://doi.org/10.2174/1570193X14666170206123513

Majirská, M., Pilátová, M. B., Kudličková, Z., Vojtek, M., & Diniz, C. (2024). Targeting hematological malignancies with isoxazole derivatives. *Drug Discovery Today*, *29*(8), Article 104059. https://doi.org/10.1016/j.drudis.2024.104059

Malik, U., & Pal, D. (2024). Cancer-fighting ısoxazole compounds: Sourcing nature's potential and synthetic advancements- a comprehensive review. *ES Food and Agroforestry, 15*, Article 1052. https://dx.doi.org/10.30919/esfaf1052

Martis, G. J., & Gaonkar, S. L. (2025). Advances in isoxazole chemistry and their role in drug discovery. *RSC Advances, 15*(11), 8213-8243. https://doi.org/10.1039/D4RA08339C

Montenegro, R. C., Clark, P. G. K., Howarth, A., Wan, X., Ceroni, A., Siejka, P., Nunez-Alanso, G. A., Monteiro, O., Rogers, C., Gamble, V., Burbano, R., Brennan, P. E., Tallant, C., Ebner, D., Fedorov, O., O'Neill, E., Knapp, S., Dixon, D., & Müller, S. (2016). BET inhibition as a new strategy for the treatment of gastric cancer. *Oncotarget, 7*(28), 43997-44012. https://doi.org/10.18632/oncotarget.9766

Möller, H. J. (2005). Risperidone: A review. *Expert Opinion on Pharmacotherapy, 6*(5), 803-818. https://doi.org/10.1517/14656566.6.5.803

Ni, T., Chi, X., Xie, F., Li, L., Wu, H., Hao, Y., Wang, X., Zhang, D., & Jiang, Y. (2023). Design, synthesis, and evaluation of novel tetrazoles featuring isoxazole moiety as highly selective antifungal agents. *European Journal of Medicinal Chemistry, 246*, Article 115007. https://doi.org/10.1016/j.ejmech.2022.115007

Olsson, R., Wiholm, B.-E., Sand, C., Zettergren, L., Hultcrantz, R., & Myrhed, M. (1992). Liver damage from flucloxacillin, cloxacillin and dicloxacillin. *Journal of Hepatology, 15*(1-2), 154-161. https://doi.org/10.1016/0168-8278(92)90029-O

Ormrod, D., Wellington, K., & Wagstaff, A. J. (2002). Valdecoxib. *Drugs, 62*, 2059-2071. https://doi.org/10.2165/00003495-200262140-00005

Padwa, A. (1976). Intramolecular 1,3-dipolar cycloaddition reactions. *Angewandte Chemie International Edition in English, 15*(3), 123-136. https://doi.org/10.1002/anie.197601231

Pandey, S., Nagpal, R., Thakur, A., Bari, S. S., Nanda, P. K., & Thapar, R. (2024). Synthesis of novel isoxazole/dihydroisoxazole tethered β-lactam hybrids *via* regiospecific 1,3-dipolar cycloaddition methodology on 3-phenylthio-β-lactams. *Journal of Sulfur Chemistry, 45*(6), 950-971. https://doi.org/10.1080/17415993.2024.2398574

Pandhurnekar, C. P., Pandhurnekar, H. C., Mungole, A. J., Butoliya, S. S., & Yadao, B. G. (2023). A review of recent synthetic strategies and biological activities of isoxazole. *Journal of Heterocyclic Chemistry, 60*(4), 537-565. https://doi.org/10.1002/jhet.4586

Pineiro, M., & Pinho e Melo, T. M. V. D. (2009). Microwave-assisted 1,3-dipolar cycloaddition: An eco-friendly approach to five-membered heterocycles. *European Journal of Organic Chemistry, 2009*(31), 5287-5307. https://doi.org/10.1002/ejoc.200900644

Plumet, J. (2020). 1,3-dipolar cycloaddition reactions of nitrile oxides under "non-conventional" conditions: Green solvents, ırradiation, and continuous flow. *ChemPlusChem, 85*(10), 2252-2271. https://doi.org/10.1002/cplu.202000448

Poster, D. S., Bruno, S., Penta, J., Neil, G. L., & McGovren, J. P. (1981). Acivicin: An antitumor antibiotic. *Cancer Clinical Trials, 4*(3), 327-330.

Reddy, S. T., Mendonza, J. J., Makani, V. K. K., Bhadra, M. P., & Uppuluri, V. M. (2020). Synthesis of some novel methyl β-orsellinate based 3, 5-disubstituted isoxazoles and their anti-proliferative activity: Identification of potent leads active against MCF-7 breast cancer cell. *Bioorganic Chemistry, 105*, Article 104374. https://doi.org/10.1016/j.bioorg.2020.104374

Rodrigues, F. C., Kumar, N. V. A., Hari, G., Pai, K. S. R., & Thakur, G. (2021). The inhibitory potency of isoxazole-curcumin analogue for the management of breast cancer: A comparative in vitro and molecular modeling investigation. *Chemical Papers, 75*(1), 5995-6008. https://doi.org/10.1007/s11696-021-01775-9

Rusu, A., Moga, I. M., Uncu, L., & Hancu, G. (2023). The role of five-membered heterocycles in the molecular structure of antibacterial drugs used in therapy. *Pharmaceutics, 15*(11), Article 2554. https://doi.org/10.3390/pharmaceutics15112554

Sakly, R., Edziri, H., Askri, M., Knorr, M., Louven, K., Strohmann, C., & Mastouri, M. (2017). Synthesis of new spirooxindole-fused isoxazoline/triazole and isoxazoline/isoxazole derivatives from three-component 1,3-dipolar cycloaddition. *Journal of Heterocyclic Chemistry, 54*(6), 3554-3564. https://doi.org/10.1002/jhet.2981

Schwartz, M. A. (1962). Monoamine oxidase inhibition by isocarboxazid. *The Journal of Pharmacology and Experimental Therapeutics, 135*(1), 1-6. https://doi.org/10.1016/S0022-3565(25)26184-5

Singh, M. S., Chowdhury, S., & Koley, S. (2016). Progress in 1,3-dipolar cycloadditions in the recent decade: An update to strategic development towards the arsenal of organic synthesis. *Tetrahedron, 72*(13), 1603-1644. https://doi.org/10.1016/j.tet.2016.02.031

Smith, L. I. (1938). Aliphatic diazo compounds, nitrones, and structurally analogous compounds. Systems capable of undergoing 1,3-additions. *Chemical Reviews, 23*(2), 193-285. https://doi.org/10.1021/cr60075a001

Sochacka-Ćwikła, A., Mączyński, M., & Regiec, A. (2022). FDA-approved small molecule compounds as drugs for solid cancers from early 2011 to the end of 2021. *Molecules, 27*(7), Article 2259. https://doi.org/10.3390/molecules27072259

Sutherland, R., Croydon, E. A. P., & Rolinson, G. N. (1970). Flucloxacillin, a new isoxazolyl penicillin, compared with oxacillin, cloxacillin, and dicloxacillin. *British Medical Journal, 4*, 455-460. https://doi.org/10.1136/bmj.4.5733.455

Sysak, A., & Obmińska-Mrukowicz, B. (2017). Isoxazole ring as a useful scaffold in a search for new therapeutic agents. *European Journal of Medicinal Chemistry, 137*, 292-309. https://doi.org/10.1016/j.ejmech.2017.06.002

Taldone, T., Gozman, A., Maharaj, R., & Chiosis, G. (2008). Targeting Hsp90: small-molecule inhibitors and their clinical development. *Current Opinion in Pharmacology, 8*(4), 370-374. https://doi.org/10.1016/j.coph.2008.06.015

Thakur, A., Verma, M., Setia, P., Bharti, R., Sharma, R., Sharma, A., Negi, N. P., Anand, V., & Bansal, R. (2023). DFT analysis and in vitro studies of isoxazole derivatives as potent antioxidant and antibacterial agents synthesized via one-pot methodology. *Research on Chemical Intermediates, 49*(3), 859-883. https://doi.org/10.1007/s11164-022-04910-7

Vashisht, K., Sethi, P., Bansal, A., & Bansal, P. (2025). Antimicrobial activity of isoxazole derivatives: A brief overview. *Vietnam Journal of Chemistry. 63*(2), 195-213. https://doi.org/10.1002/vjch.202400029

Veeraswamy, B., Kurumurthy, C., Kumar, G. S., Rao, P. S., Thelakkat, K., Kotamraju, S., & Narsaiah, B. (2012). Synthesis of novel 5-substituted isoxazole-3-carboxamide derivatives and cytotoxicity studies on lung cancer cell line. *Indian Journal of Chemistry Section B: Organic Chemistry Including Medicinal Chemistry, 51*(9), 1369–1375.

Verma, H., Snehi, V., Pathak, D., Saha, S., & Kumar, S. (2022). Comprehensive Witting approach toward advancements in synthetic strategies and the pharmacological evaluation of isoxazole analogues through the angle of medicinal chemistry. *International Journal of Scientific Development and Research, 7*(12), 1191–1205.

Vieira, A. A., Bryk, F. R., Conte, G., Bortoluzzi, A. J., & Gallardo, H. (2009). 1, 3-Dipolar cycloaddition reaction applied to synthesis of new unsymmetric liquid crystal compounds-based isoxazole. *Tetrahedron Letters, 50*(8), 905-908. https://doi.org/10.1016/j.tetlet.2008.12.021

Wagner, E., Wietrzyk, J., Psurski, M., Becan, L., & Turlej, E. (2020). Synthesis and anticancer evaluation of novel derivatives of isoxazolo [4,5-*e*][1,2,4]triazepine derivatives and potential inhibitors of protein kinase C. *ACS Omega, 6*(1), 119-134. https://doi.org/10.1021/acsomega.0c03801

Wang, X., Hu, Q., Tang, H., & Pan, X. (2023). Isoxazole/Isoxazoline skeleton in the structural modification of natural products: A review. *Pharmaceuticals, 16*(2), Article 228. https://doi.org/10.3390/ph16020228

Watterson, S. H., Guo, J., Spergel, S. H., Langevine, C. M., Moquin, R. V., Shen, D. R., Yarde, M., Cvijic, M. E., Banas, D., Liu, R., Suchard, S. J., Gillooly, K., Taylor, T., Rex-Rabe, S., Shuster, D. J., McIntyre, K. W., Cornelius, G., D'Arienzo, C., Marino, A., … Dyckman, A. J. (2016). Potent and selective agonists of sphingosine 1-phosphate 1 ($S1P_1$): Discovery and SAR of a novel isoxazole based series. *Journal of Medicinal Chemistry, 59*(6), 2820-2840. https://doi.org/10.1021/acs.jmedchem.6b00089

Wazalwar, S. S., Banpurkar, A. R., & Perdih, F. (2023). Synthesis, crystal structure and molecular docking study of novel isoxazole derivatives as CYP450 inhibitors in search of anticancer agents. *Journal of Biomolecular Structure and Dynamics, 41*(19), 9476-9491. https://doi.org/10.1080/07391102.2022.2142667

Yang, Z., Li, P., & Gan, X. (2018). Novel pyrazole-hydrazone derivatives containing an isoxazole moiety: Design, synthesis, and antiviral activity. *Molecules, 23*(7), Article 1798. https://doi.org/10.3390/molecules23071798

Zheng, R., Feng, F., Zhang, Z., Fu, J., Su, Q., Zhang, Y., & Gu, Q. (2020). Microwave-assisted efficient synthesis of 3-substituted bis-isoxazole ether bearing 2-chloro-3-pyridyl via 1,3-dipolar cycloaddition. *Molecular Diversity, 24*(2), 423-435. https://doi.org/10.1007/s11030-019-09973-0

Zhu, J., Mo, J., Lin, H. Z., Chen, Y., & Sun, H. P. (2018). The recent progress of isoxazole in medicinal chemistry. *Bioorganic & Medicinal Chemistry, 26*(12), 3065-3075. https://doi.org/10.1016/j.bmc.2018.05.013

Zimecki, M., Bąchor, U., & Mączyński, M. (2018). Isoxazole derivatives as regulators of immune functions. *Molecules, 23*(10), Article 2724. https://doi.org/10.3390/molecules23102724