1,3,4-OXADIAZOLE: Synthesis Derivatives &Biological Activities. A Review article

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Article Info:

Received 25 Jan 2025
Revised 30 Mar 2025
Accepted 14 Apr 2025
Published 31 Dec 2025
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DOI: https://doi.org/10.32947/ajps.v25i5.1294

Abstract:

Heterocyclic compounds serve as crucial structural elements in the field of pharmaceutical medicinal chemistry. The five-membered heterocyclic nucleus of 1,3,4-oxadiazole occupies a distinctive position within medicinal chemistry and plays a vital role in the development of anticancer agents.

Recognized as a significant pharmacophore for approximately 85 years, 1,3,4-oxadiazole is in high demand across various biological and chemical disciplines. This small and straightforward nucleus is found in numerous compounds that are the focus of research concerning their properties, synthesis, derivatives, and pharmacological activities, including anticancer, antibacterial, antimalarial, anti-inflammatory, antidepressant, analgesic, and antiviral effects. The information regarding these activities presented in this article may prove beneficial to researchers, facilitating the discovery of new therapeutic agents for the benefit of society.

Key words: 1,3,4-Oxadiazoles synthesis ,1,3,4-oxadiazole derivatives, pharmacological activities heteroaromatic ring.

1،3،4- أكساديازول، التوليف والمشتقات والأنشطة البيولوجية. مقالة مراجعة

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الخلاصة:

تعمل المركبات غير المتجانسة الحلقية كعناصر هيكلية حاسمة في مجال الكيمياء الطبية الصيدلانية. تحتل النواة الحلقية غير المتجانسة المكونة من خمسة أعضاء في 1،3،4،3،4 أوكساديازول مكانة مميزة في الكيمياء الطبية وتؤدي دورًا حيويًا في تطوير العوامل المضادة للسرطان. تم الاعتراف بـ 1،3،4،3،4 أوكساديازول كنواة صيدلانية مهمة منذ حوالي 85 عامًا، ويزداد الطلب على 1،3،4-أوكساديازول في مختلف التخصصات البيولوجية والكيميائية. وتوجد هذه النواة الصغيرة والمباشرة في العديد من المركبات التي هي محور الأبحاث المتعلقة بخصائصها وتركيبها ومشتقاتها وأنشطتها الدوائية، بما في ذلك مضادات السرطان ومضادات الجراثيم ومضادات الملاريا ومضادات الالتهاب ومضادات الاكتئاب والمسكنات ومضادات الفيروسات. قد تكون المعلومات المتعلقة بهذه الأنشطة المعروضة في هذه المقالة مفيدة للباحثين، مما يسهل اكتشاف عوامل علاجية جديدة لصالح المجتمع.

الكلمات المفتاحية: 1،3،4-أوكساديازول تخليق 1،3،4-أوكساديازول، مشتقات 1،3،4-أوكساديازول، الأنشطة الدوائية حلقة غير متجانسة.

Introduction

Heteroaromatic ring systems are an important component of the molecular structure of bioactive drugs. This is mainly due to their structural similarity to various bioactive compounds in the human body, including nucleic acids, hormones, and neurotransmitters. Among the various heteroaromatic rings, oxadiazole is a major heterocyclic compound characterized by two nitrogen and one oxygen atoms within a five-membered ring. [1,2]It represents one of the four isomers of oxadiazole and can be derived from furan with two nitrogen atoms instead of two methylene groups (-CH=), similar to the nitrogen atom in pyridine (-N=). The available isomers of oxadiazole are shown in Figure. 1. [3]

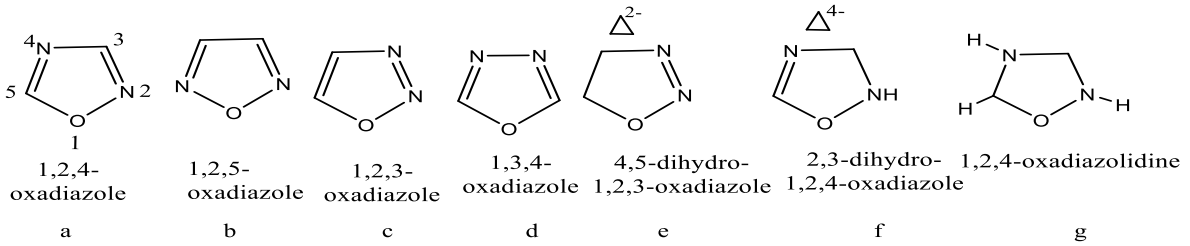


Figure-1- isomers for oxadiazole [3]

The suffix –ole (1e-f) is used to indicate the position of double bonds in partially reduced rings, such as Δ2- or Δ4-. On the other hand, the suffix –olidine refers to a fully saturated ring. Substituents in these compounds are typically positioned at N-2(R), N-4(R'), or C-5(R) (1g). Numerous medications, including raltegravir, fasiplon, butylamines, oxolamine, pleconaril, and Nesapidil, incorporate stable oxadiazoles in their structures. [4,5]

Among five-membered nitrogen-containing heterocyclic compounds, the oxadiazole core exhi-bits a wide array of pharmacological properties. In particular, 1,3,4-oxadiazole has emerged as a critic-al structural motif in synthetic medicinal chemistry, serving as a bio isostere for carboxylic acids, car-boxamides, and esters. [6] Its relevance is highlighted by ongoing research into its diverse biological activities, such as anticancer [7], antimicrobial [8], antiviral [9], fungicidal [10], antineoplastic effects [11], tyrosinase inhibition [12], antibacterial [13], anti-inflammatory properties [14] , antitubercular effects [15] , and analgesic [16] .

The structure–activity relationship (SAR) of 1,3,4-oxadiazole derivatives reveals several influential substitutions. For instance, replacing the phenyl ring with distinct groups such as p-NO_2 or p-t-Bu enhances their biological potential. Furthermore, modifying the methylation pattern to a methyl-sulfonyl configuration boosts pharmacological interest. However, substituting the phenyl ring with a pyridine ring tends to reduce activity. Similarly, introducing an acetyl group at the nitrogen atom of the oxadiazole ring does not significantly alter observed activity, Figure-2- [17]

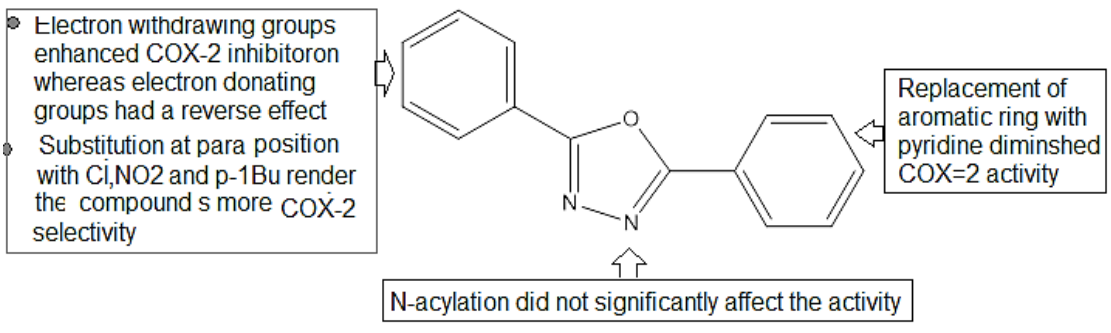
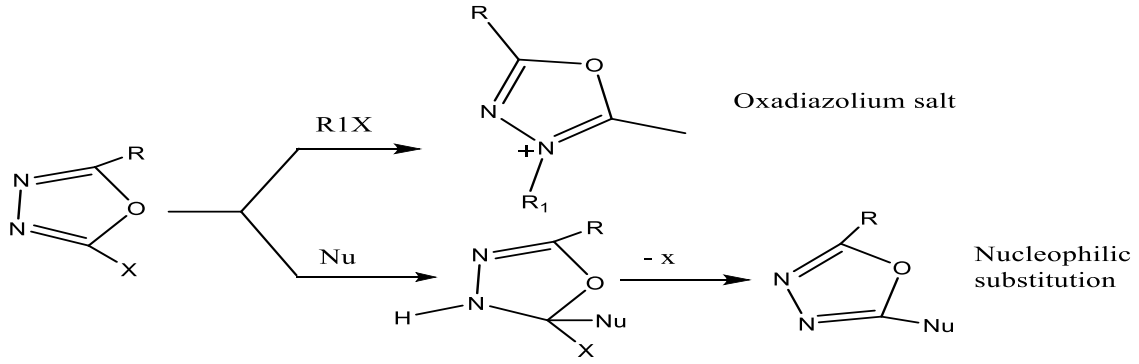


Figure-2- The structure–activity relationship (SAR) of 1,3,4-oxadiazole

The 1,3,4-oxadiazole ring exhibits the ability to interact with a wide variety of pharmacological targets through mechanisms such as acting as a hydrogen bond acceptor, participating in π-π stacking or cation-π interactions. Chemically, it may react via nucleophilic substitution or through salt formation, as shown in Scheme (1)[18]

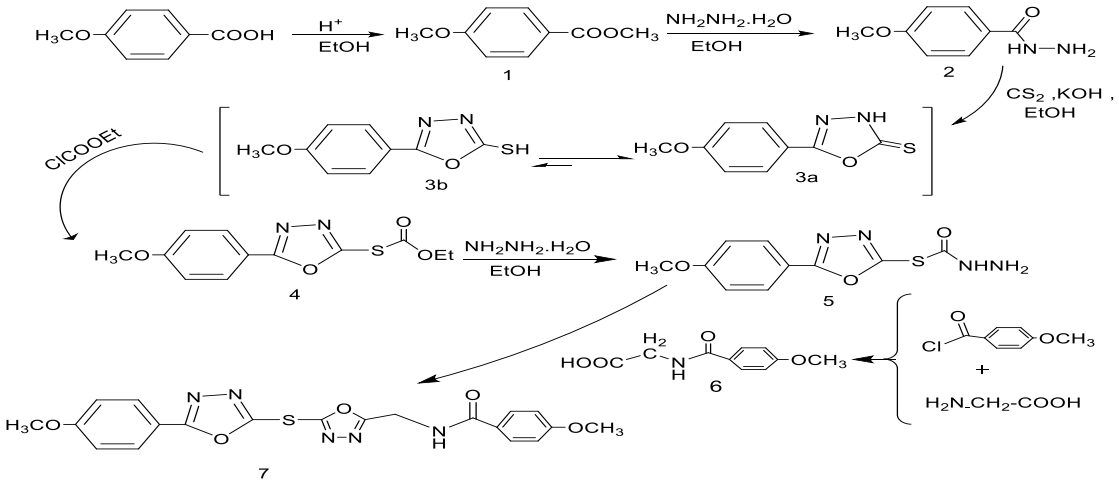


Scheme (1): Nucleophilic substitution or salt formation 1,3,4-oxadiazole ring[18]

This article presents an overview of general methodologies for synthesizing various 1,3,4-oxadiazole derivatives as published in the literature. These methods aim to assist researchers working in the field of organic synthesis to develop new derivatives incorporating the 1,3,4-oxadiazole moiety, facilitating the creation of novel drugs for combating a range of pathological conditions.

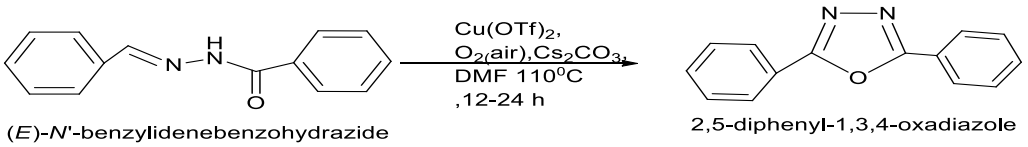
General Methods for the Synthesis of 1,3,4-Oxadiazoles and its derivatives

In 2011, Ivan [19] and his team reported the synthesis of a bis-1,3,4-oxadiazole derivative that includes a glycine moiety. Their approach began with the esterification of anisic acid, followed by a reaction with hydrazine hydrate. The resulting acid hydrazide underwent ring closure to form a thione–thiol oxadiazole tautomer (compound 3) through a well-defined synthetic pathway., as illustrated in Scheme-2.



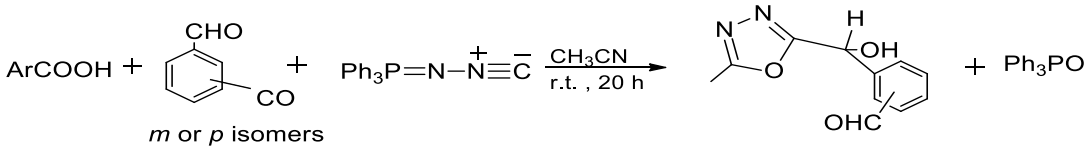
Scheme-2: glycine moiety within bis-1,3,4-oxadiazole containing [19]

Guin et al (2011) [20] reported direct route to symmetrical and asymmetrical 2,5 - disubstituted-1,3,4-oxadiazoles as an imine C-H functionalization of N-arylidenearoyl-hydrazide with Cu $(OTf)_2$, Scheme -3.



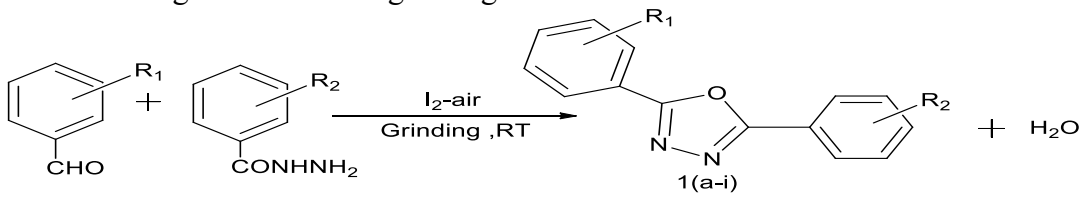
Scheme- 3: Direct route to synthesize of,5-diphenyl-1,3,4-oxadiazole [20]

Ali Ramazani and his team introduced a one-pot method for synthesizing 1,3,4-oxadiazole derivatives in 2011. In this technique, N-isocyanimino triphenyl phosphorane reacts with aromatic bis-aldehydes, such as isophthalaldehyde, in the presence of aromatic or heteroaromatic carboxylic acids. This reaction facilitates the formation of sterically hindered 1,3,4-oxadiazole derivatives. Notably, the process can be performed at room temperature under neutral conditions. As highlighted in Plan 4, the approach offers advantages such as simplicity, clean execution, compatibility with mild conditions, and the elimination of side effects, Scheme 4 .[21]



Scheme- 4. Synthesis of sterically congested 1,3,4-oxadiazole derivatives [21].

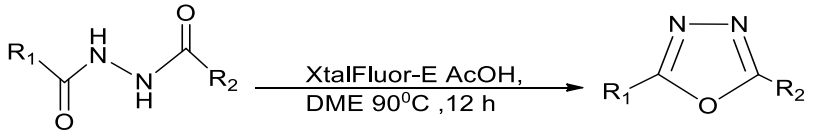
In the same year, Ashish and collaborators reported an iodine-mediated, green synthesis of 1,3,4-oxadiazoles using a solvent-free grinding technique. This alternative method emphasizes environmental sustainability, scheme-5. [22]



	a	b	c	d	e	f	g	h	i
R1	H	4-Cl	4-Cl	4-Cl	4-Cl	4-Cl	4-Br	4-CH3	4-OCH3
R2	4-Cl	4-Cl	2-Cl	4-OCH3	3-CH3	4-NO2	2-Cl	4-NO2	4-OCH3

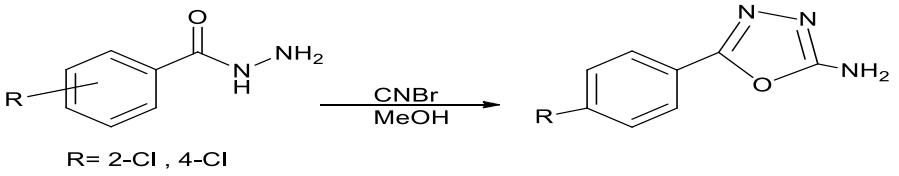
Scheme-5- Iodine-mediated green synthesis of 1,3,4-oxadiazoles [22]

In 2012, Pouliot and colleagues developed a method for synthesizing 1,3,4-oxadiazoles from 1,2-diacylhydrazines using a novel ring-dehydrating agent—diethyl amino-difluoro-sulfonium tetra-fluoroborate ([Et2NSF2] BF4), also referred to as Xtal Fluor-E, Scheme -6. [23]



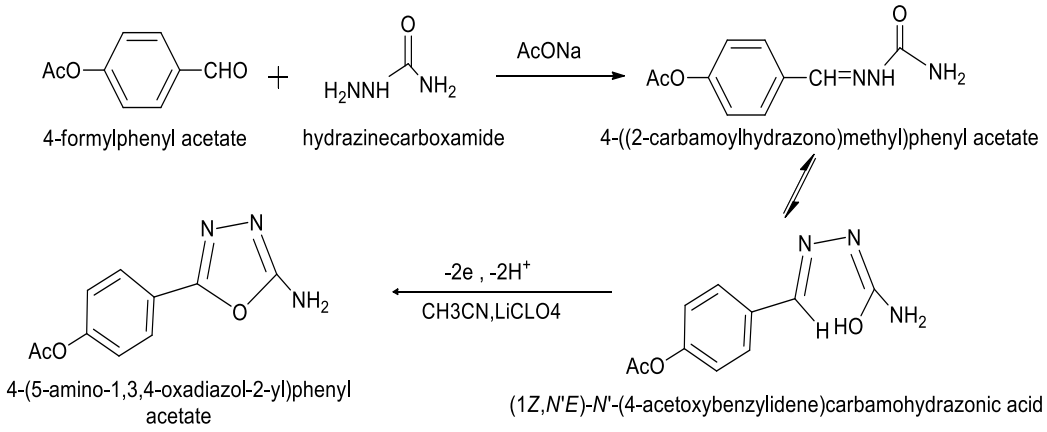
Scheme-6- Synthesize of 1,3,4-oxadiazoles new cyclodehydration agent [23]

Also in 2012, Kerimov and his team synthesized derivatives of 2-amino-1,3,4-oxadiazoles incorporating a benzimidazole moiety. This was achieved through the reaction of acetohydrazide derivatives with cyanogen bromide, as depicted in Scheme 7. [24]



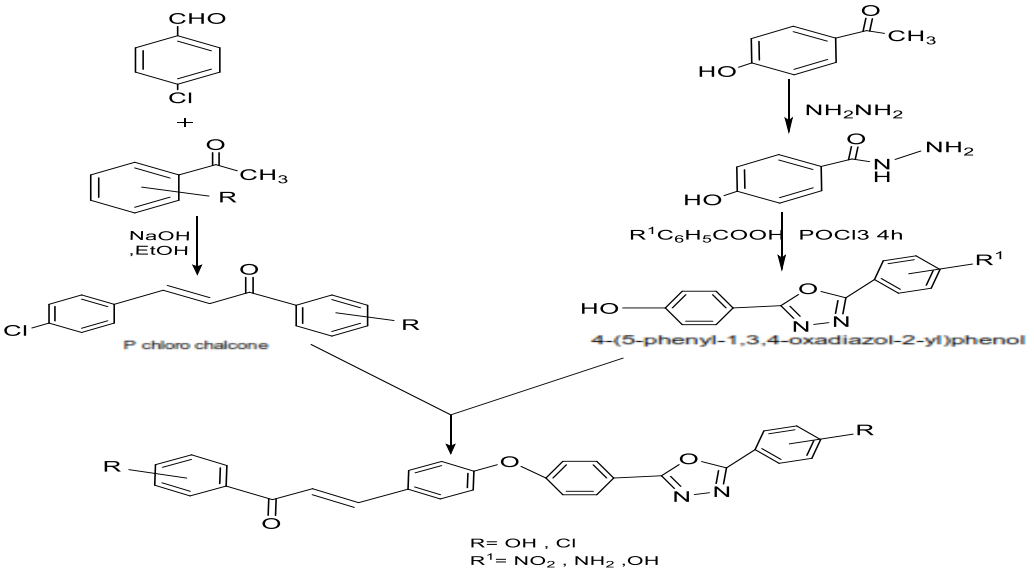
Scheme-7. Preparation of 5-aryl-2-amino-1,3,4-oxadiazole compounds [24]

Sanjeev and colleagues (2013) synthesized 1,3,4-oxadiazole derivatives using a multi-step electrolytic method. The process begins with the deprotonation of a precursor to form an anion, which then undergoes rearrangement and generates a free radical following one-electron oxidation. A second electron oxidation converts the free radical into a carbocation, which facilitates the formation of a carbon-oxygen bond, completing the ring structure as outlined in Scheme-8. [25]



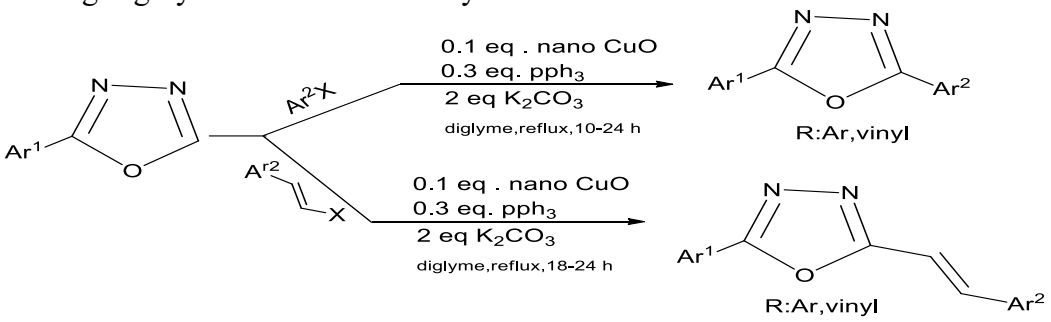
Scheme- 8: Electrochemical synthesis of 2-Amino-5-substituted 1,3,4-oxadiazole [25]

Thasneem and collaborators (2014) synthesized chalcone-linked 1,3,4-oxadiazoles by combining substituted chalcones with substituted oxadiazoles. The reaction steps are illustrated in Scheme-9. [26]



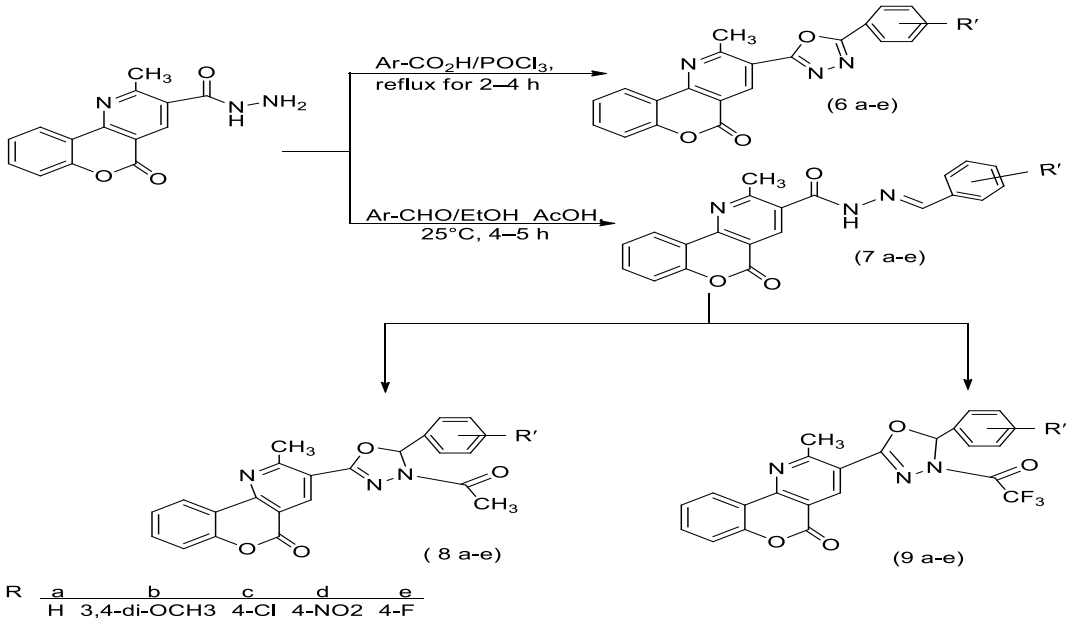
Scheme -9: synthesis of 3-(4-(4-(5-(2,4-dihydroxyphenyl)-1,3,4-oxadiazol-2-yl) phenoxy) phenyl)-1-phenylprop-2-en-1-one. [26]

Salva (2015) reported the synthesis of 2-aryl- and 2-alkenyl-1,3,4-oxadiazoles using copper oxide nanoparticles as a catalyst. The reaction involved 1,3,4-oxadiazoles with aryl or alkenyl halides, achieving high yields. The noteworthy advantage of this method is the catalyst's reusability, making it practical for large-scale synthesis. The detailed is depicted in Scheme-10. [27]



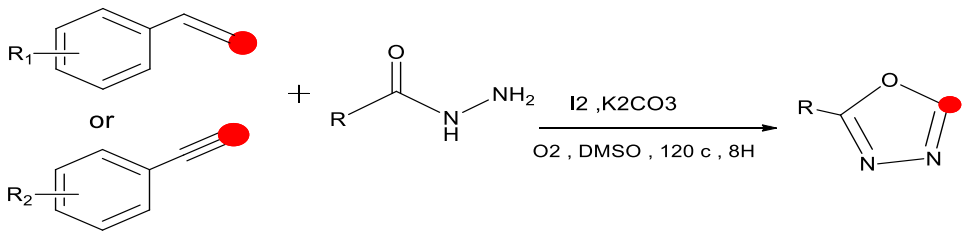
Scheme -10: Synthesize 2-Aryl- and 2-alkenyl-1,3,4-oxadiazoles [27]

Ghanshyam and his team (2016) developed 1,3,4-oxadiazole derivatives of chromium [4,3-b] pyridine compounds (6a-e, 8a-e, and 9a-e). Their method utilized 4-hydroxycoumarin to initiate the reaction, forming carbohydrazides that subsequently underwent cyclization with various carboxylic acids under phosphorus oxychloride reflux to yield derivatives 6a–e. Additionally, carbohydrazides were precursors for oxadiazole synthesis, including derivatives 8a-e and 9a-e. Cyclization of Schiff bases (7a-e), formed by the reaction of carbohydrazides with aldehydes, yielded compounds 8a-e and 9a-e. The steps are described in Scheme 11. [28]



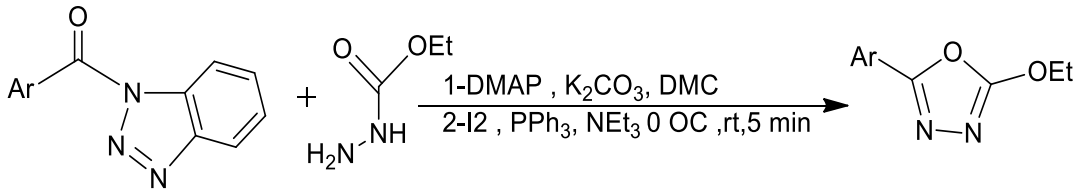
Scheme-11: Synthesize of 2,5-Disubstituted 1,3,4-oxadiazole derivatives [28]

Fan and his team (2016) synthesized 1,3,4-oxadiazoles through direct annulation of hydrazides with methyl ketones using K_2CO_3 as a pivotal component for cyclization. This efficient method is presented in Scheme-12. [29].



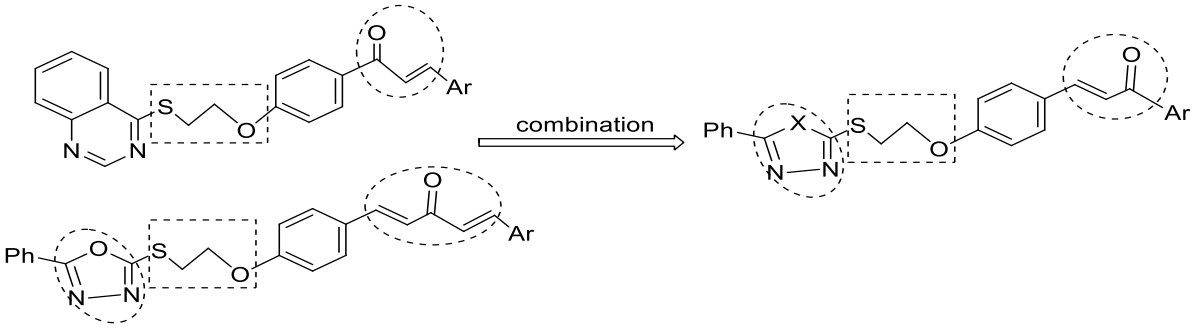
Scheme-12- Oxidative cleavage reaction [29]

Chinnari and colleagues (2016) conducted photo redox-catalyzed decarboxylative cyclization using α-oxocarboxylic acids to produce 2,5-disubstituted 1,3,4-oxadiazoles with high yields. Details of this synthesis are represented in Scheme-13. [30]



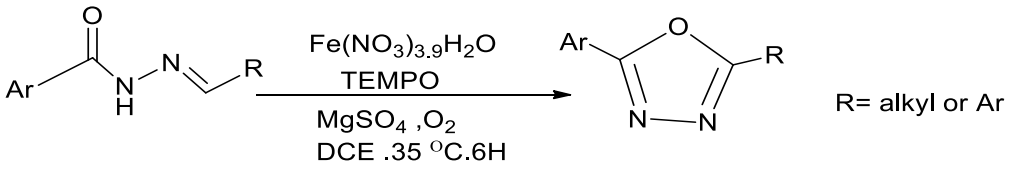
Scheme-13 a photo redox-catalyzed decarboxylative cyclization reaction [30]

Xiuhai et al. (2017) employed a mechanochemical approach to synthesize 2,5-disubstituted 1,3,4-oxadiazoles, providing a greener and faster alternative to solvent-based methods. This strategy successfully yielded oxadiazole derivatives within minutes while accommodating diverse functional groups. The results are summarized in Scheme-14.[31]



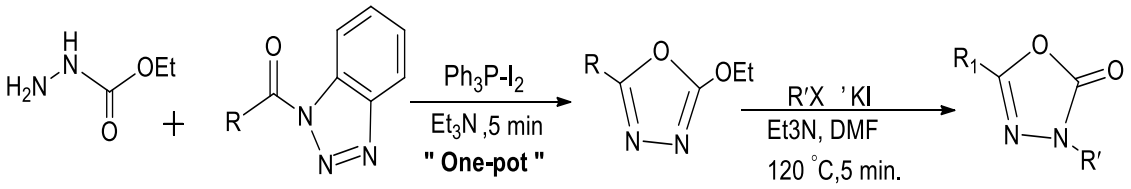
scheme-14- microscale thermophoresis methods [31]

Guofu et al. (2017) demonstrated a greener mechanochemical approach for synthesizing 2,5-disubstituted 1,3,4-oxadiazoles. This method avoided solvents and successfully generated oxadiazole derivatives in excellent yields within minutes while considering various reactive functional groups Scheme 15. [32]



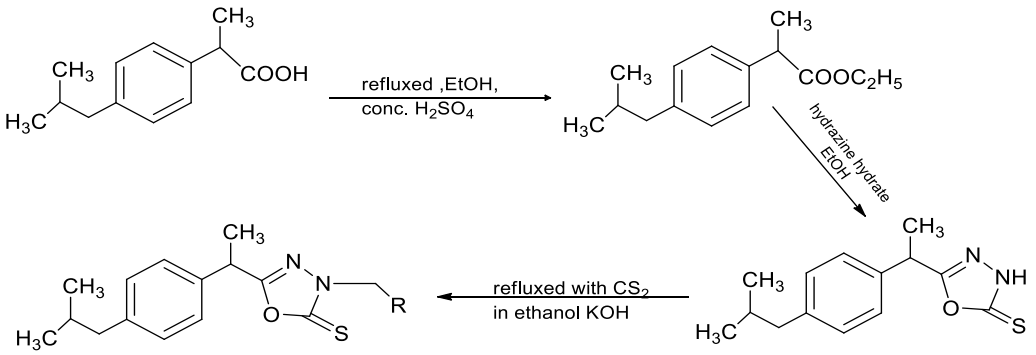
Scheme-15- alternative to conventional solvent-based methods [32]

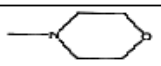
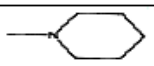
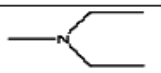
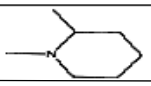
Wet-osot and colleagues (2017) developed a one-pot sequential process for synthesizing 5-substituted-2-ethoxy-1,3,4-oxadiazoles through N-acylation followed by dehydrative cyclization. The reaction involved ethyl carbazate and N-acylbenzotriazoles, utilizing Ph3P−I2 as the dehydrating agent. The subsequent inclusion of alkyl halides (X = Cl, Br, I) enabled efficient production of diverse 3,5-disubstituted 1,3,4-oxadiazol-2(3H)-ones, as shown in Scheme 16. [33]



Scheme-16: one-pot sequential *N*-acylation/dehydrative cyclization [33]

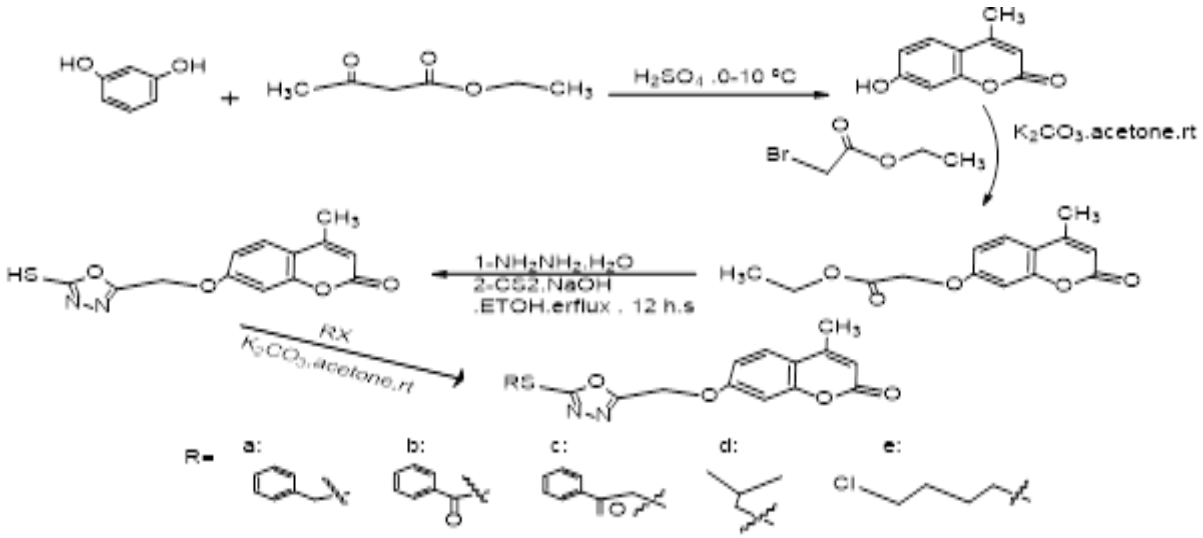
Anuj and Gupta (2018) synthesized four novel 1,3,4-oxadiazole derivatives derived from ibuprofen. These compounds were designed as bioactive agents exhibiting numerous biological activities such as anti-inflammatory, antimicrobial, anticancer, antitubercular, anticonvulsant, anti-HIV, hypoglycemic, and antioxidant properties (Scheme 17).[34]



Compound	R	R	Compound	R	R
a		Morpholine	c		Piperidine
b		Diethyl amine	d		2-Methyl Piperidine

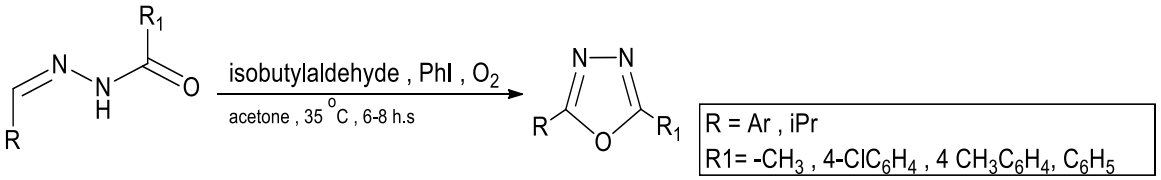
Scheme-17: Synthesis of 5-(1-(4-isobutylphenyl) ethyl)-3-(-R-)-1,3,4-oxadiazole-2(3H)-thione[34]

Nerella and his team (2019) synthesized coumarin-1,3,4-oxadiazole hybrids to produce new heterocyclic compounds with significant anticancer potential. Their study focused on the inhibitory effects of these compounds on specific human carbonic anhydrase isoforms: CA I, CA II, CA IX, and CA XII. The results demonstrated selective inhibition of tumor-associated isoforms CA IX and CA XII over CA I and CA II (Scheme 18). [35]



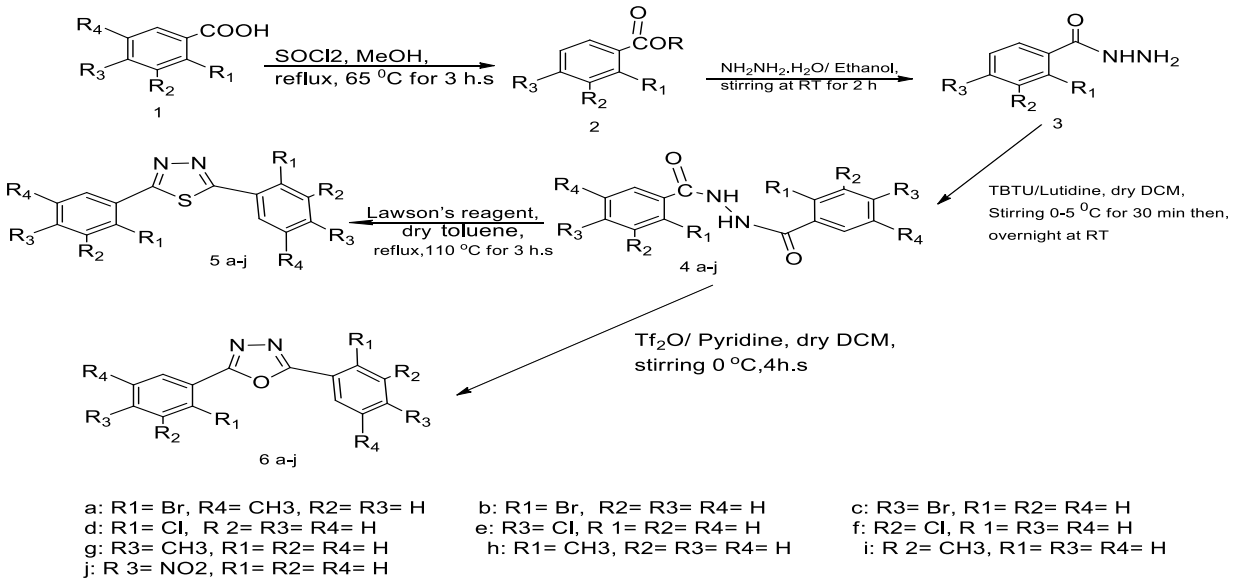
Scheme 18. 1,3,4-oxadiazole core as coumarin derivatives [35]

Jyoti and colleagues (2019) [36] developed a simple yet efficient oxidative cyclization method for aroyl hydrazones using a cationic Fe (III)/TEMPO catalyst in the presence of oxygen. This approach enables the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives with excellent yields. The reaction showcases broad applicability and a strong tolerance for different functional groups, as illustrated in Scheme-19.



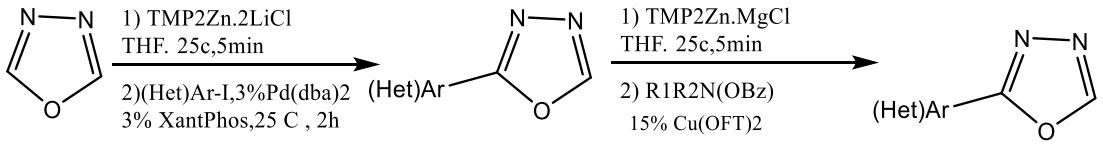
Scheme-19- cationic Fe (III)/TEMPO-catalyzed oxidative cyclization methods [36]

In 2020, Zabiullah and colleagues introduced an ultrasound-assisted approach to synthesize 2-amino derivatives of 1,3,4-oxadiazole, substituted at the 5-position with aryl and methyl groups. Their method, as illustrated in Scheme 20, significantly reduced synthesis time to just a few hours while maintaining high product yields.[37]



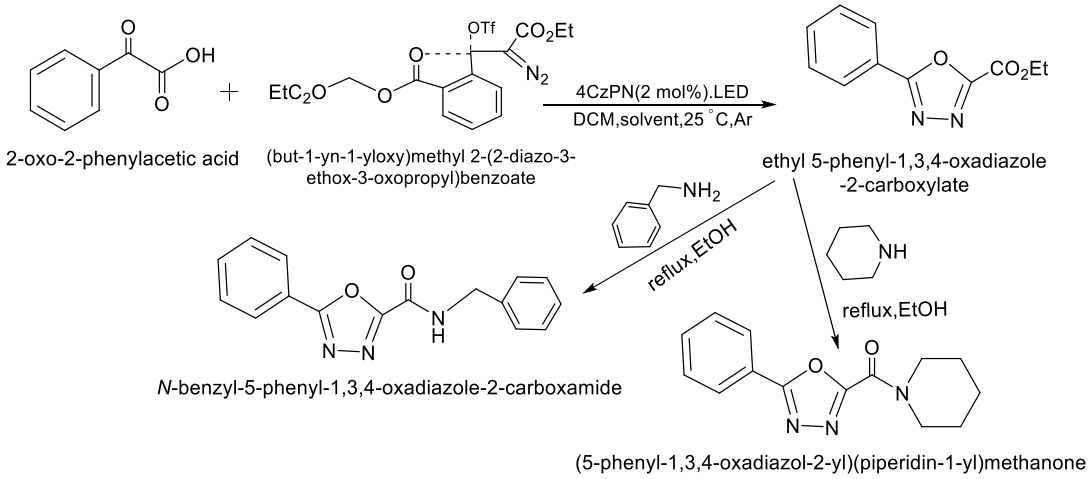
Scheme 20. Synthesis of thiadiazole (5a-j) and oxadiazole (6a-j) analogues [37]

Kuno and collaborators (2020) developed a strategy for synthesizing unsubstituted 1,3,4-oxadiazole through the reaction of N, N'-diformylhydrazine with phosphorus pentoxide as the catalyst. This reaction was carried out under elevated temperatures for 30 minutes, as shown in Scheme 21.[38]



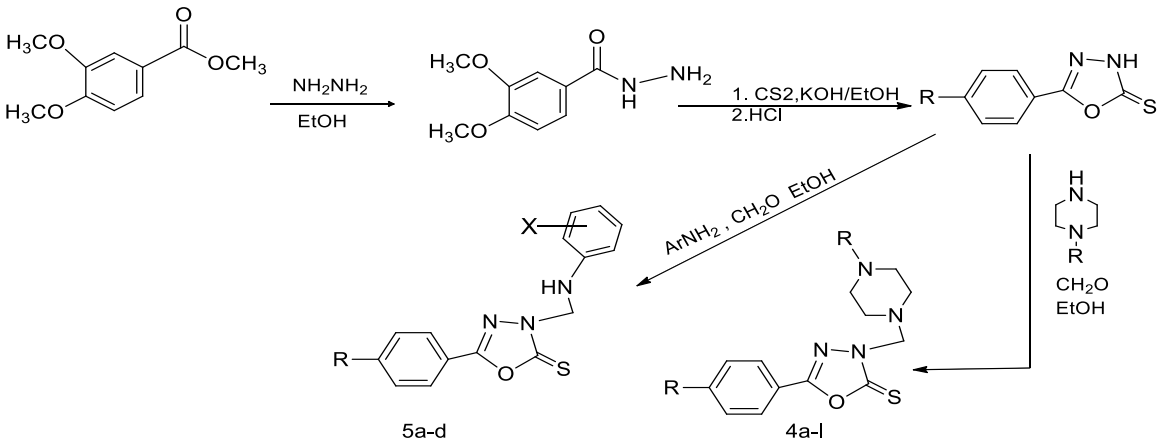
Scheme -21. The reaction of N, N'-diformylhydrazine and phosphorus pentoxide [38]

Jian et al. (2020) proposed a decarboxylative cyclization technique via photo redox catalysis to fabricate 2,5-disubstituted 1,3,4-oxadiazoles. White light-emitting diode irradiation was used to excite 4-CzPN, which underwent reductive quenching by benzoyl formic acid, resulting in reduced 4-CzPN and benzoyl cation radicals. Subsequent CO_2 release formed benzoyl radicals, while diazo radicals were generated through oxidation of reduced cyanoarene-based donor-acceptor photocatalyst(4-CzPN) using hypervalent iodine reagents. These radicals directly coupled to form intermediates that transformed into the final product, as illustrated in Scheme 22.[39]



Scheme-22 - **-Oxocarboxylic Acid Scope** [39]

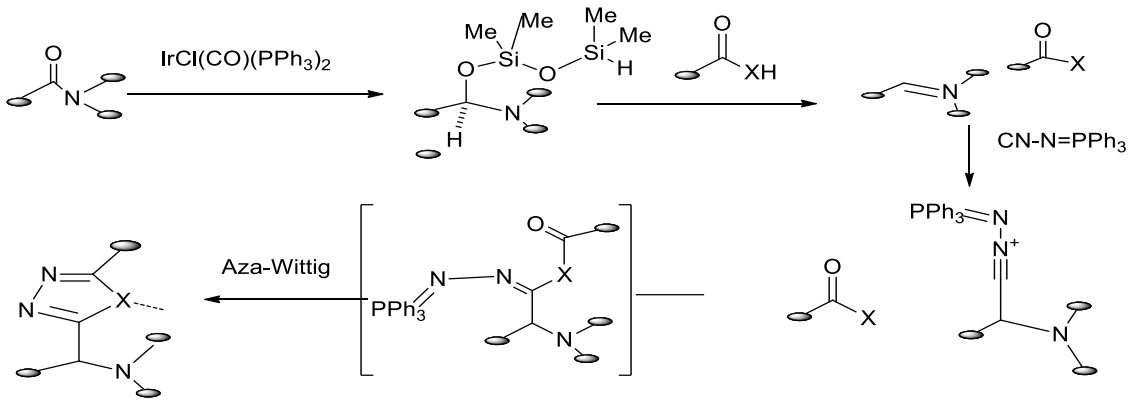
Lamya and her team (2021) utilized N-Mannich base chemistry to synthesize novel 1,3,4-oxadiazole derivatives. Their process involved reacting 5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione with formaldehyde solution and primary aromatic amines or substituted piperazines in ethanol at room temperature. This yielded two distinct sets of N-Mannich bases: 3-arylaminomethyl and 3-piperazinylmethyl derivatives of oxadiazole-thiones (4a–l and 5a–d), as detailed in Scheme 23.[40]



	a	b	c	d	e	f	g	h	i	j	K	l
R	H	4-f	3-Cl		4-Cl	2- NO_2	3- NO_2	4- NO_2	2-CF_3	3-CF_3	2,4-F_2	2,5-F_2	2,,4-Cl_2
X	C_6H_5	FC_6H_4	$C_6H_5CH_2$	2-$CF_3C_6H_4CH_2$								

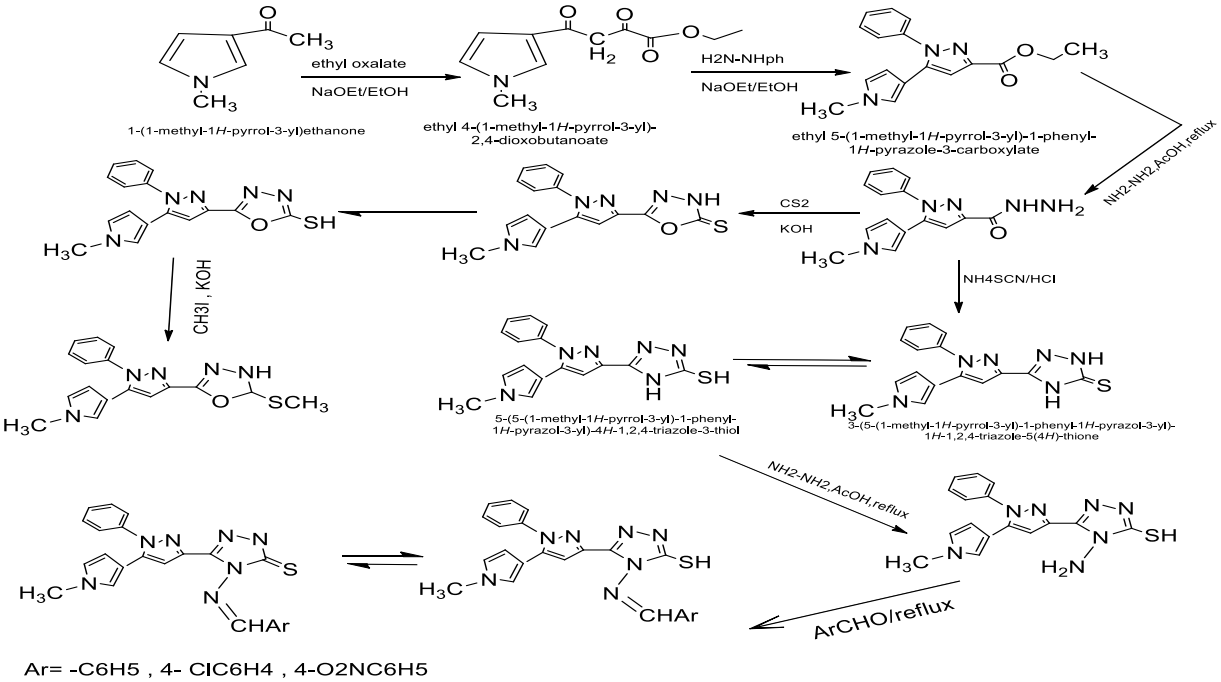
Scheme 23. Synthesis of compounds 4a–l and 5a–through 1,3,4-Oxadiazole N-Mannich Bases [40]

In another innovative approach, Daniel and his team (2021) employed iridium-catalyzed reductive three-component coupling to synthesize α-amino-1,3,4-oxadiazoles. Their method utilized tertiary amides or lactams, carboxylic acids, and (N-isocyanimino) triphenylphosphorane as reactants. By tweaking reaction conditions, they also produced α-amino hetero-diazoles and hetero-diazole-fused drug conjugates. This versatile methodology is summarized in Scheme 24.[41]



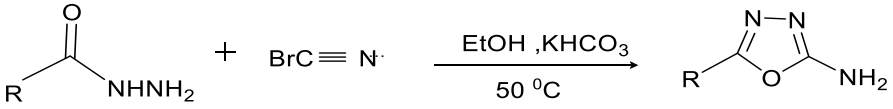
Scheme -24: reductive three-component coupling reaction [41]

El-Sayed (2021) presented a method for synthesizing [1,3,4] oxadiazole-2-thione and triazole-3-thione derivatives by cyclo-condensation of dicarbonyl esters with phenyl hydrazine. Hydrazinolysis yielded hydrazides that were treated with carbon disulfide or ammonium thiocyanate to form oxadiazole or triazolethione compounds. Subsequent reactions with aromatic aldehydes led to the formation of N-Mannich bases. The details are illustrated in Scheme 25.[42]



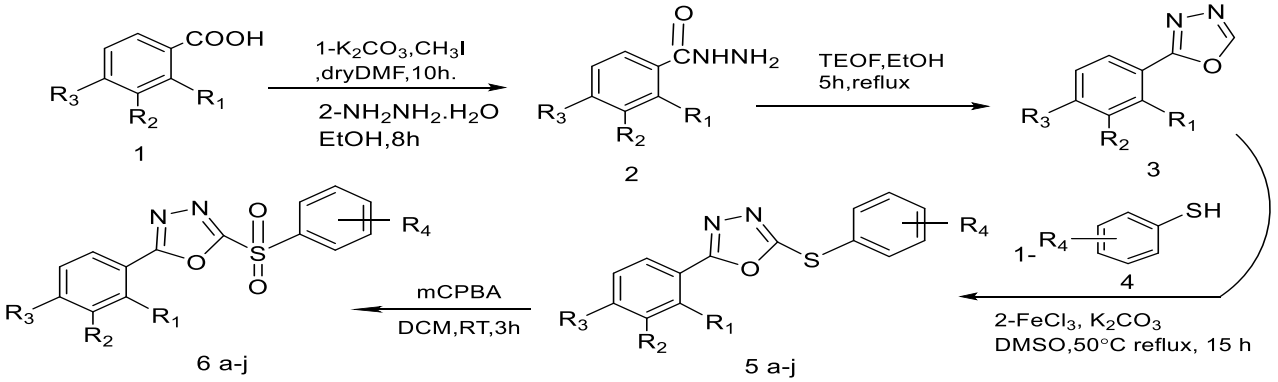
Scheme -25: Synthesis of 5-substituted-1,3,4-oxadiazole-2-thiol(thione)through Mannich bases. [42]

Hamid and collaborators (2021) devised a novel ultrasound-assisted synthesis route for creating 1,3,4-oxadiazol-2-amines. This method optimized reactions between hydrazides and cyanogen bromide to produce high yields. The synthesized compounds demonstrated promising antioxidant activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and were identified as potential candidates for anti-diabetic, anti-proliferative, anti-inflammatory, and anti-neurodegenerative applications, the meth-odology is described in Scheme 26. [43]



Scheme 26. Reaction scheme of the synthesis of 1,3,4-oxadiazol-2-amines. [43]

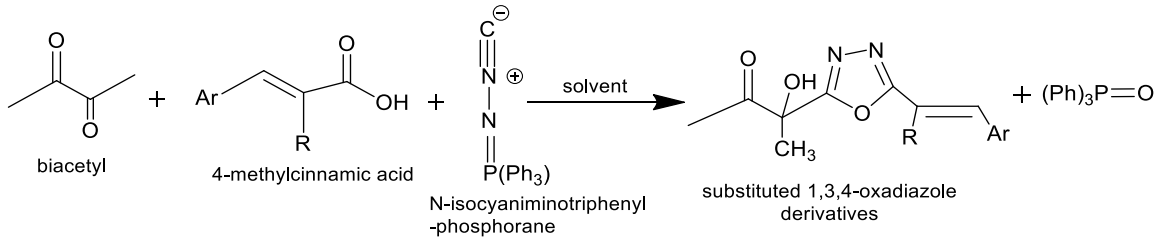
Boddapati et al. (2022) synthesized ten new 2-aryl-5-(arylsulfonyl)-1,3,4-oxadiazoles through a multistep process. First, aryl acids were reacted with hydrazine monohydrate in the presence of potassium carbonate to yield aryl hydrazides. Cyclization using ethanoic triethyl orthoformate (TEOF) produced 2-aryl-1,3,4-oxadiazoles with yields ranging from 56% to 68%. These compounds were further subjected to C-S cross-coupling with various thiophenols using iron(III) chloride to form 2-thioaryl-5-aryl-1,3,4-oxadiazoles (5a–j). Oxidation with meta-Chloroperoxybenzoic acid (mCPBA or mCPBA) in dichloromethane yielded the final products: 2-aryl-5-(aryl sulfonyl)-1,3,4-oxadiazoles (6a–j), Scheme 27[44]



R	a	b	c	d	e	f	g	h	i	j
1	H	H	H	H	H	H	H	H	C_2H_5	H
2	H	H	$CH(CH_3)_2$	H	CN	H	H	H	H	CH_3
3	CH_3	OCH_3	H	NO_2	H	Cl	H	H	H	CH_3
4	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	F	OCH_3	CH_3	CH_3

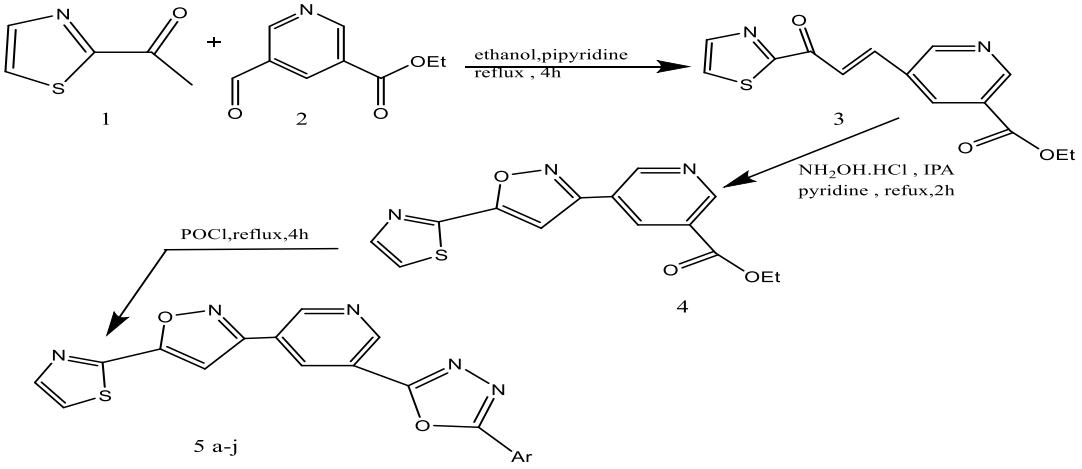
Scheme-27: Synthesis of 2-aryl-5-(aryl sulfonyl)-1,3,4-oxadiazoles (6a-j). [44]

Gheorghe and his team (2023) [45] successfully synthesized substituted 1,3,4-oxadiazole derivatives through the Aza-Wittig method. Typically, this approach includes an additional step involving the reaction of an α-functionalized carbene anion with an aldehyde or ketone to produce an alkene. Alternative methods utilizing metal carbene complexes for synthesis are also documented. The Wittig reaction remains a key process in such chemical transformations, Schme-28.



Schme-28: one of the were synthesized of substituted 1,3,4-oxadiazole derivatives [45]

In 2024, Krishna R. team`s synthesized a series of thiazol-isoxazol-pyridine derivatives incurporating a 1,3,4-oxadiazole moiety (9a-j), as outlined in Scheme 29. [46] The process began with the Claisen reaction of 1-(thiazol-2-yl) ethanone (1) and ethyl 5-formylpyridine-3-carboxylate (2), using a catalytic amount of piperidine in ethanol. The reaction mixture was stirred under reflux for four hours, producing a pure chalcone intermediate (3) which then react with hydroxylamine hydrochloride and pyridine in isopropyl alcohol under reflux for two hours, yielding the isoxazole compound (4) which subsequently, was treated with hydrazine hydrochloride in ethanol under reflux for four hours to produce the pure acid hydrazide (compound 5 a-j). These derivatives were subjected to preliminary anticancer evaluation against four human cancer cell lines: PC3 (prostate cancer), A549 (lung cancer), MCF-7 (breast cancer), and SiHa (cervix cancer) and compared to the standard chemotherapeutic agent etoposide. Most of the synthesized derivatives demonstrated significantly enhanced anticancer activity compared to the reference standard.



Ar:	a	b	c	d	e
	4-nitro	3,5-dinitro	3,4,5-timethoxy	4-methoxy	4-pyridyl
	f	g	h	i	j
	2-thiazolyl	isoexazole-5-yl	4-cyano	4-methyl	3,5-dimethyl

Scheme 29. Synthesis of 1,3,4-oxadiazole Linked Thiazole-Isoxazole-Pyridines. [46]

❖ Pharmacological activities of 1,3,4-Oxadiazole

The development of new medicinal agents represents a pivotal and complex task for pharmaceutical scientists, especially in the design of compounds with anti-microbial, anti-inflammatory, anti-convulsant, anthelmintic, anti-oxidant, anti-mycobacterial, analgesic, anti-tumor, and herbicidal properties. Efforts to formulate new medications typically follow two main approaches: (a) combining similar compounds and their derivatives to produce new substituted entities with enhanced therapeutic effects, and (b) investigating and incorporating novel compounds that are entirely unfamiliar to bacteria or other biological conditions. [47,48]

In this content, substituted 1,3,4-oxadiazoles have emerged as highly effective agents; the inclusion of the azole moiety and the toxophoric C-O linkage in these structures significantly boosts their lipophilicity and plays a key role in their wide range of pharmacological activities such as antimicrobial, anti-inflammatory, analgesic, anti-tumor, and anticonvulsant. Notably, 1,3,4-oxadiazole scaffolds have garnered significant interest due to their favorable metabolic properties and their capacity to engage in hydrogen bonding with receptors. [49-51]

Analgesic and Anti-inflammatory Activities:

In vivo assessments of anti-inflammatory effects were conducted by measuring the reduction in

paw thickness resulting from egg-white induced paw edema, serves as a foundation for evaluating anti-inflammatory activity.[47]

In 2012; Chawla et al. [52] synthesized and evaluated 2-(3-bromo-4-fluorophenyl)-5-substituted-1,3,4-oxadiazoles as potential anti-inflammatory agents. The pharmacological findings indicated that the compound, where the aryl ring was substituted with a naphthyl ring, exhibited the most significant anti-inflammatory activity, Figure-3.

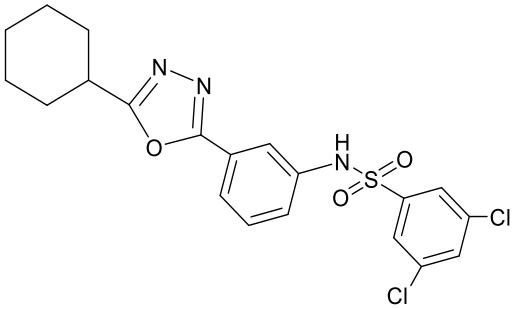
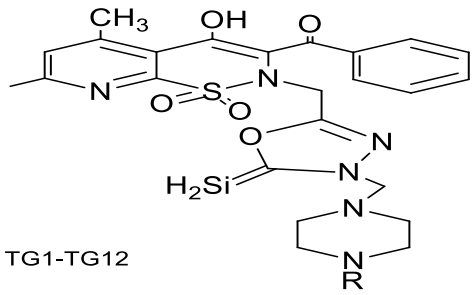


Figure-3- 3,5-dichloro-N-(3-(5-cyclohexyl-1,3,4-oxadiazol-2yl) phenyl) benzenesulfonamide.[52]

Mannich bases containing pyridothiazine-1,1-dioxide core with aryl piperazine and a 1,3,4-oxadiazole scaffold were created by Teresa G and colleagues in 2020[53]. The inhibitors discovered through these attempts were assessed as they were claimed to have potential anti-inflammatory activity, particularly for COX-1 and COX-2 enzymes. Using a colorimetric inhibitor screening assay, it was determined how well the novel compounds could block the activities of the enzyme's cyclooxygenase 1 and 2. After the use of TG6 and especially TG 4, considerable COX-2 inhibition was observed. The drug TG11 and meloxicam, which was used as a reference, also enhanced COX-2 activity. The Multi-Criteria Decision Analysis (MCDA) suggested that these compounds exhibit potent COX inhibitory activity. One can argue that TG11 and TG12 coupled with meloxicam are more active anti-inflammatory than meloxicam with TG11 being most potent in the model tested, Figure-4.

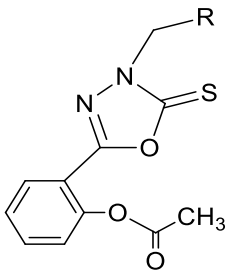


TG1-TG12

Compound	-R
TG1	-phenyl
TG2	-4-methylphenyl
TG3	-2-methylphenyl
TG4	-3-trifluofomethylphenyl
TG5	-2-flurophenyl
TG6	-2-4-difluorophenyl
TG7	-4-bromophenyl
TG8	-2-4-dichlorophenyl
TG9	-2-cyanophenyl
TG10	-2-nitrophenyl
TG11	-4-pyridyl
TG12	-2-pyrimidyl

Figure-4- Mannich bases - 1,3,4-oxadiazole scaffold [53]

Anuj et al. (2021) [54] conducted a study on the synthesis of a novel series of substituted 1,3,4-oxadiazole derivatives by condensing various amines with 2-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) phenyl acetate (III) in the presence of formaldehyde. The newly synthesized compounds were evaluated in vivo for their anti-inflammatory properties using the carrageenan-induced rat paw edema model. The results from the acute anti-inflammatory studies indicated that compounds a, b, d, and e demonstrated promising activity, while in the analgesic evaluations, compounds a and b exhibited superior efficacy compared to the standard drug, aspirin, Figure-5.

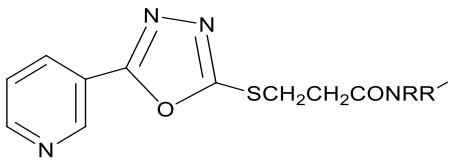


R= a: morpholin b: piperidin
c: 2-methylpiperidin d: piperazin-1-ylmethyl
e :4-methylpiperazin f:diethylamino
g:diphenylamino h:cyclohexylamino

Figure-5- Series of substituted 1,3,4-oxadiazole derivatives condensing various amines.[54]

- **Antibacterial and Antitubercular Activities:**

The various N-substituted-*β*-chloropropionamides were done by Rakesh R. et al (2008) [55] Thione and *β*-chloropropionamides were combined to create the target compounds 3a-i, which were then screened in vitro for antibacterial and anti-tubercular activity. The Mycobacterium tuberculosis H37Rv strain was tested for anti-tubercular activity at a concentration of 50 g/mL, while E. coli, S. aureus, P. aeruginosa, and S. typhi were tested for antibacterial activity at doses of 50 and 100 g/mL. All save compound 3f exhibited maximal inhibition against mycobacteria, while compounds 3b–I shown moderate to excellent antibacterial activity, Figure-6.



Compd.	R	R′	Compd.	R	R′
3a	H	*p*-Fluorophenyl	3e	H	*p*-Chlorophenyl
3b	H	*p*-Methoxyphenyl	3f	H	2,6-Dichlorophenyl
3c	H	*p*-Nitrophenyl	3g	H	*n*-Propyl
3d	H	*p*-Bromophenyl	3h	H	*n*-Butyl
			3i	Morpholinyl	

Figure-6-Chemical structures of substituted-β-chloropropionamides.[55]

Bhutani et al. (2011) [56] synthesized aniline derivatives featuring 1,3,4-oxadiazole moieties and assessed their antibacterial properties against *Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, and Escherichia coli*, using Amoxicillin as a reference drug. In their investigation of antifungal activity, all synthesized compounds were compared to the well-known antifungal agent, Ketoconazole. Furthermore, the biological activity of these compounds was evaluated for their anti-inflammatory effects, Figure-7.

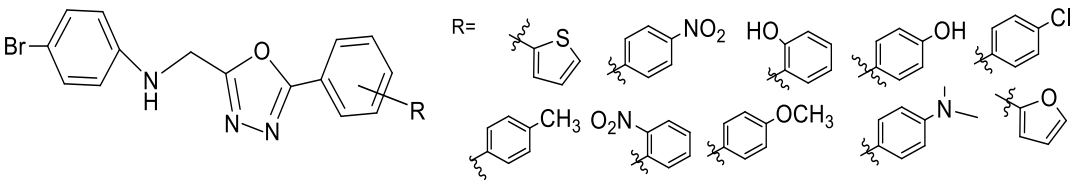
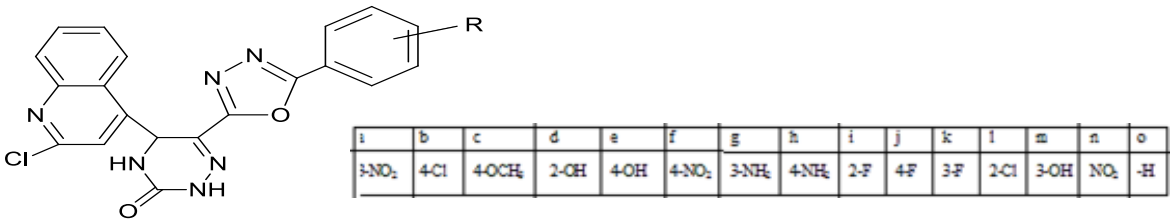


Figure-7- Aniline derivatives bearing 1,3,4-oxadiazole moieties.[56]

Godhani et al. (2019) [57] synthesized derivatives of dihydropyridine-substituted 1,3,4-oxa- diazole the antimicrobial activities of each final compound were evaluated in vitro against various bacterial strains, including Staphylococcus aureus, Klebsiella pneumoniae, E. coli, Acinetobacter baumannii, and Pseudomonas aeruginosa, as well as two fungal strains, Candida albicans and Cryptococcus neoformans var. grubii, Figure-8.



i	b	c	d	e	f	g	h	i	j	k	l	m	n	o
3-NO_2	4-Cl	4-OCH_3	2-OH	4-OH	4-NO_2	3-NH_2	4-NH_2	2-F	4-F	3-F	2-Cl	3-OH	NO_2	-H

Figure-8- Dihydropyridine- 1,3,4-oxadiazole derivatives. [57]

Raghu et al. (2020) [58] investigated the emergence of multi-drug resistance associated with interactions between anti-retroviral and anti-diabetic medications. In their quest to discover a novel anti-tuberculosis compound, they synthesized 2-(2, 3-dichlorophenyl)-5-aryl-1,3,4-oxadiazole derivatives 5a-l, which then the antimycobacterial efficacy of these compounds was assessed against the Mycobacterium tuberculosis H37RvMa strain (ATCC 27294) utilizing the broth micro-dilution method, Figure-9.

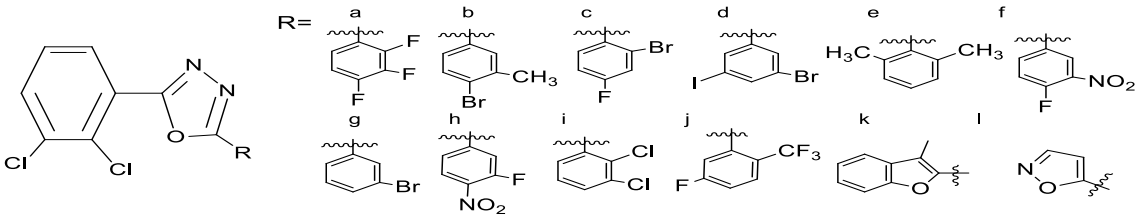
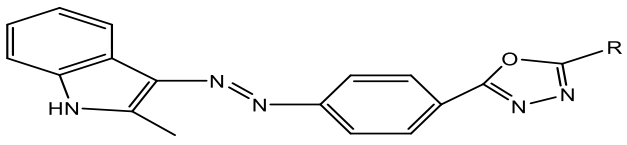


Figure-9- Structure of 2-(2, 3-dichlorophenyl)-5-aryl-1,3,4-oxadiazole derivatives 5a-l.[58]

In 2024, Farzaneh [59] developed a new series of 1,3,4-oxadiazole-containing azo derivatives Figure-10 and assessed their antibacterial properties through in vitro testing against both Gram-negative and Gram-positive bacteria. The results demonstrated a broader antibacterial spectrum for derivatives incorporating an indole ring in their structure. Notably, the majority of these compounds exhibited antibacterial activity against *Staphylococcus aureus* (ATCC 25923), whereas *Pseudomonas aeruginosa* (ATCC 27853) showed resistance to all the synthesized azo compounds.

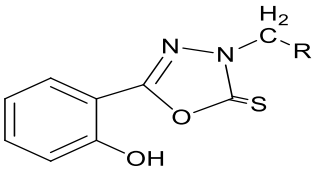


R= a :CH_3 b:$CHCH_3$ c: $CH_2CH_2CH_3$ d: $CH_2CH_2CH_2CH_3$

Figure-10- 1,3,4-oxadiazole-containing azo derivatives. [59]

➢ **Anti cancer**

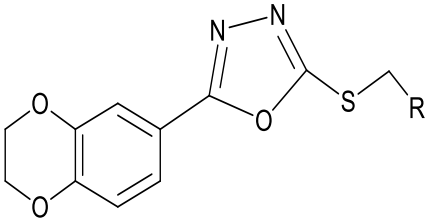
Aboraia et al. (2006) [60] synthesized a series of 5-(2hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole2-thione derivatives and evaluated them for their *in vitro* anticancer activity. In the primary assay some of the investigated compounds displayed high anticancer activity when they were tested for a full anticancer, Figure-11.



R= 1-Morpholine
1-phenylpiperazine
-NH-C_6H_4-(4-CH_3)
-NH-C_6H_4-(3-CH_3)
-NH-C_6H_4-(2-OCH_3)

Figure-11-5-(2hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole2-thione derivatives.[60]

A collection of novels 1,3,4-oxadiazole derivatives featuring a 1,4-benzodioxane moiety was synthesized and evaluated for antitumor efficacy by Zhang et al. (2011) [61]. The antiproliferative effects were assessed against HEPG2, HELA, SW1116, and BGC823 as cancer cell lines. The findings revealed that several compounds demonstrated remarkable antitumor activity in comparison to 5-fluorouracil, a commonly utilized chemotherapeutic agent. Additionally, the researchers investigated the inhibitory effects of these compounds on telomerase activity in cancer cells, Figure-12.

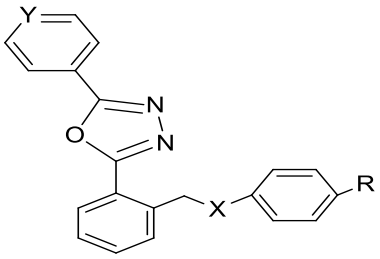


R=

a C6H5	g 4-F-C6H4	m 3-Br-C6H4
b 3-CH3-C6H4	h 3-NO2-C6H4	n 4-Br-C6H4
c 4-NO2-C6H4	i 4-Cl-C6H4	o 2-Cl-C6H4
d 2-F-C6H4	j 4-I-C6H4	p 3-Cl-C6H4
e 2-NO2-C6H4	k 2-CH3-C6H4	q 2,6,F-C6H4
f 4-CH3-C6H4	l 2-Br-C6H4	r 2,4-F-C6H4

Figure-12-1,3,4-oxadiazole derivatives have 1,4-benzodioxane moiety.[61]

Camelia et al (2021) [62]: designed and synthesized a series of novel 2,5-diaryl/heteroaryl-1,3,4-oxadiazoles with the objective of developing new chemotherapeutic agents exhibiting potent anticancer activities. The synthesized compounds were evaluated for their anticancer efficacy against colon adenocarcinoma (HT29) and breast adenocarcinoma (MDA-MB-231). The MTS assay was employed to assess cytotoxicity, while cell cycle arrest and apoptosis were analyzed using a flow cytometer. Figure-13.



	X	Y	R
a	S	CH	H
b	S	CH	CH_3
c	S	CH	H
d	SO_2	CH	H
e	S	CH	H

Figure-13- novel 2,5-diaryl/heteroaryl-1,3,4-oxadiazoles.[62]

In 2024, Noha and her team [63]: designed and synthesized a series of innovative multi-target quinoline hybrids (1–11). The antiproliferative activity of these quinoline-oxadiazole derivatives was evaluated against two cancer cell lines: hepatocellular carcinoma (HepG2) and breast adeno-carcinoma (MCF-7). The synthesized compounds (1–11) demonstrated significant cytotoxic effects, with IC50 values ranging from 0.137 to 0.332 µg mL−1 against HepG2 and from 0.164 to 0.583 µg mL−1 against MCF-7. These results compare favorably to the positive control, erlotinib, which ex-hibited IC50 values of 0.308 and 0.512 µg mL−1 against HepG2 and MCF-7, respectively. Also, an EGFR tyrosine kinase inhibition assay was carried out on the most promising candidates, revealing notable IC50 values of 0.14 µM and 0.18 µM for compounds 2 and 6, respectively, in comparison to lapatinib's IC50 value of 0.12 µM, Figure-14.

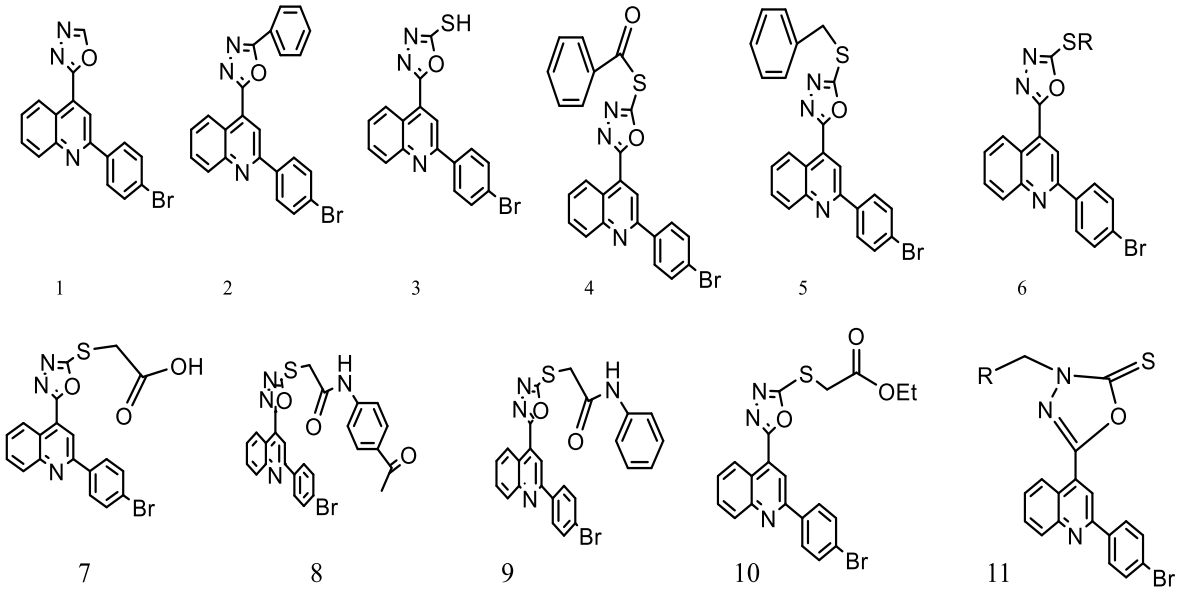


Figure-14- Quinoline-oxadiazole derivatives. [63]

➢ **Anti-Diabetic Activity:**

Sunil (2016) [64] synthesized derivatives of benzothiazole-oxadiazole, which were evaluated for their in vivo hypoglycemic activity using an alloxan-induced diabetic rat model. The results indicated that these derivatives exhibited significant biological efficacy when compared to a well-established anti-diabetic agent, Glibenclamide, demonstrating their effectiveness, Figure-15.

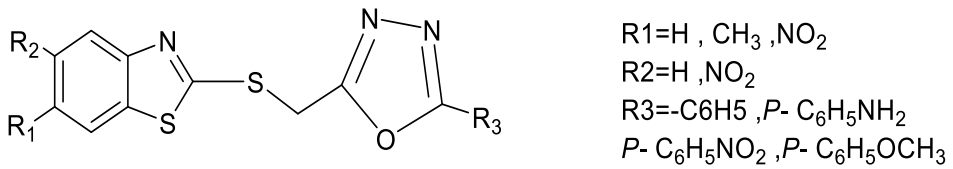


Figure-15- Derivatives of benzothiazole-oxadiazole. [64]

Bhutani et al. (2019) [65] developed a small series of novel benzothiazole-oxadiazole Minnich bases and assessed their anti-hyperglycemic activity in a STZ-induced model. The compounds displayed varying degrees of activity, ranging from good to moderate. Notably, the compound 5-(benzo[d]thiazol-2-yl)-3-((2-methyl-4-

nitrophenyl) amino) methyl)-1,3,4-oxadiazole-2(3H) thione exhibited the highest anti-diabetic activity among the series, Figure-16

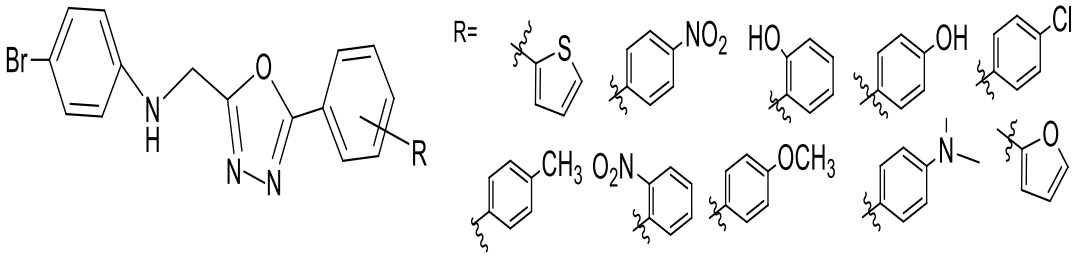


Figure-16-novel benzothiazole-oxadiazole Minnich base.[65]

In 2024, Mohini and her team [66] synthesized 1,3,4-oxadiazole derivatives and evaluated their antidiabetic potential. Through physico-chemical analysis, molecular docking, and in silico prediction studies, assessments were conducted for four derivatives (1, 2, 3, and 4), focusing on ligand-binding interactions of the synthesized compounds with key proteins. The docking studies revealed significant interactions between the compounds and the receptor protein (PDB ID: 3A4A). Among the tested derivatives, compound 3 demonstrated the highest binding energy at -12.8327 kcal/mol, showing superior affinity compared to the reference drug Metformin, which exhibited a binding energy of -9.01594 kcal/mol. The yields of the synthesized compounds ranged from 62.2% to 79.9%. Overall, the antidiabetic effects of these compounds ranged from moderate to excellent, underscoring their potential as promising therapeutic agents, Figure-17.

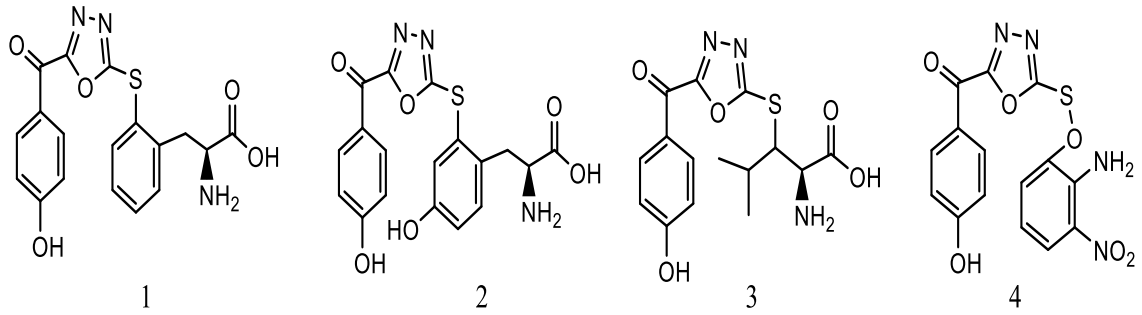


Figure-17-1,3,4-oxadiazole derivatives have antidiabetic activity.[66]

➢ **Anti-HIV Activity**

Tan et al. (2006) [67] and colleagues developed 1,3,4-oxadiazole derivatives that effectively inhibit viral antigens, specifically HBsAg and HBeAg, in a concentration-dependent manner without exhibiting cytotoxic effects. These compounds present a promising potential for treating hepatitis B virus (HBV) infections. Among these, derivative (i) demonstrated the highest efficacy, with an EC50 value of 1.63 µM, surpassing the effectiveness of the standard Lamivudine, Figure-18.

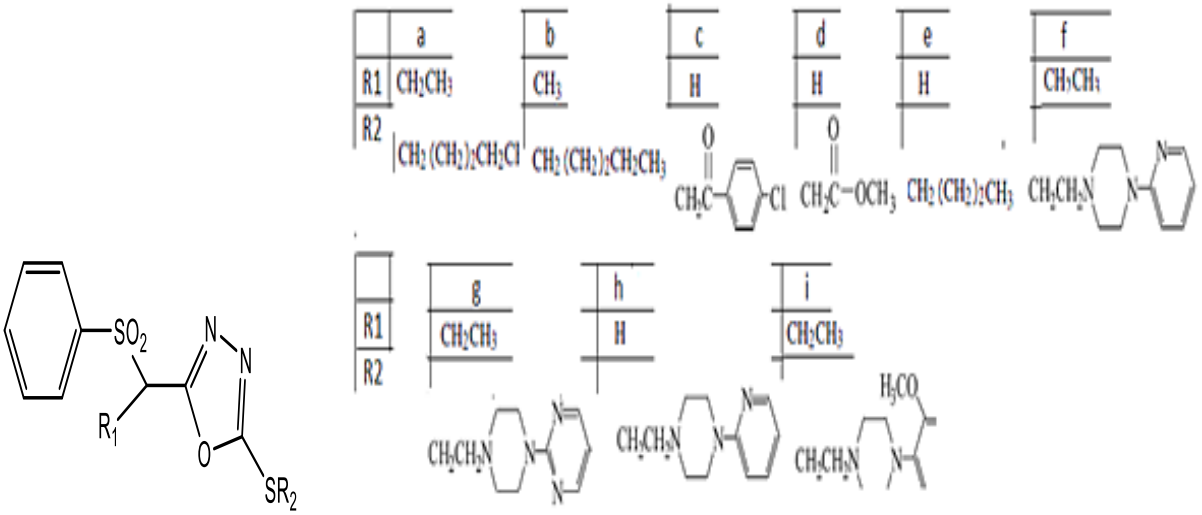


Figure-18- Effectively inhibit viral antigens as 1,3,4-oxadiazole derivatives.[67]

Saida et al. (2022) [68] designed and synthesized a new series of 3-acetyl-1,3,4-oxadiazoline hybrid molecules through the condensation of cyclo-nucleosides with substituted phenyl-hydrazone. These compounds were evaluated for their antileishmanial and antiviral activities against HCM, VZV, and SARS-CoV-2. Figure-19.

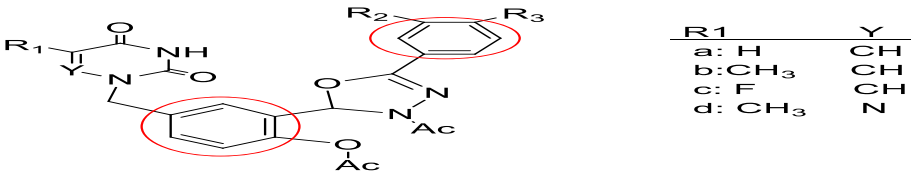


Figure-19-3-acetyl-1,3,4-oxadiazoline hybrid molecules have Anti-HIV Activity. [68]

In 2024, YoungHyun et al [69] conducted a high-throughput screening of a compound library using a dual-reporter assay, which led to the identification of a 1,3,4-oxadiazole scaffold effective against Tat and HIV-1 infection. Additionally, a detailed structure–activity relationship (SAR) study combined with biological assays revealed that two 1,3,4-oxadiazole derivatives, compounds 1 and 2, containing indole and acetamide groups, showed strong inhibitory activity against HIV-1 infecti-vity. These compounds demonstrated half-maximal effective concentrations (EC50) of 0.17 μM for compound 1 and 0.24 μM for compound 2, Figure-20.

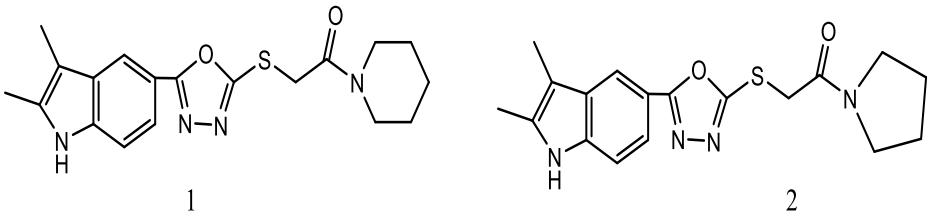


Figure-20- high-throughput screening of identification of a 1,3,4-oxadiazole scaffold.[69]

CONCLUSION:

This review presents a comprehensive overview of various synthesis methods for 1,3,4-oxadiazole and highlights the significant biological activities associated with the 1,3,4-oxadiazole scaffold and its derivatives, as derived from a thorough literature analysis. The findings indicate that oxadiazole derivatives possess considerable medicinal potential, exhibiting properties such as antimicrobial, anti-inflammatory, analgesic, anticancer, antidiabetic, and anti-HIV activities. Consequently, it can be inferred that these derivatives hold promise for further exploration in drug design and the development of innovative therapies aimed at improving treatment outcomes for serious conditions, including microbial infections, epilepsy, inflammation, viral infections, diabetes, and cancer. [68-72]

Competing Interests

The authors affirm that they possess no recognized financial conflicts of interest or personal affiliations that may have influenced the findings presented in this paper.

Acknowledgements

The authors express their gratitude to the College of Pharmacy at the University of Baghdad for providing the necessary resources to carry out this research**.**

Funding

The authors state that they have not received any financial assistance from any institution.

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