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(REVIEW ARTICLE)

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A review on microwave assisted synthesis, mechanism of action and structure activity relationship of 1, 3, 4-oxadiazole derivatives as anticancer agent

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Abstract

1, 3, 4-oxadiazole derivatives received considerable attention of different research groups, as they have wide variety of biological activities. 1, 3, 4-oxadiazole derivatives exhibited noteworthy anticancer activities. In recent years, microwave-induced organic reactions attained significant attention due to several benefits, such as short reaction time, cost-effectiveness, excellent yield, and ease of work. In view of above in present work, SAR and mechanism of action of 1, 3, 4-oxadiazole derivatives as anticancer agents, reported by different research groups in recent years are summarized. Present review also highlighted the various synthetic approaches for efficient microwave-assisted green synthesis of 1, 3, 4-oxadiazole derivatives.

Keywords: 1, 3, 4-Oxadiazole derivatives; Structure activity relationship (SAR); Mechanism of action (MOA); Anti-cancer, Microwave-assisted green synthesis

1. Introduction

Due to many applications of heterocyclic compounds, developed into one of the essential areas of research in the pharmaceutical industry. Heterocyclic compounds having oxygen and nitrogen atoms demonstrated maximum compelling biological activities [1]. Oxadiazoles are five-membered heterocyclic compounds having one oxygen and two nitrogen atoms. 1,3,4-oxadiazole derivatives belong to an important heterocyclic family oxadiazoles [2]. As it showed multipurpose lead molecule [3] and exhibited miscellaneous biological activities [4,5,14,15,6–13]. 1,3,4-oxadiazole moiety also existent in different clinical used drugs such as antiviral (Raltegravir) [16], antihypertensive (Tiodazosin, Nesapidil) [7,17,18], and antibiotics (Furamizole) [19], Zibotentan (in clinical trial), having 1,3,4-oxadiazole moiety, showed promising affect against various types of cancer, including colorectal, breast, prostate, lungs, and ovarian cancers (Figure.1.) [20,21].

In synthesis of chemical compounds, the use of microwave irradiation intensifies the pureness of the products, improve the percentage yield, and reduce reaction time. A solvent-free reaction causes safe, environmentally sustainable, and cost-effective technology. Hence, reactions on solid support without the use of solvent in microwave ovens are currently being used by synthetic chemists to create environmentally safe atmosphere [22–24]. In view of above facts, SAR and mechanism of action of various 1,3,4-oxadiazole derivatives as anticancer agents reported by different research groups in recent years are summarized. Further, in present review various efficient microwave-assisted green synthesis of 1,3,4-oxadiazole derivatives discussed.

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2. Mechanism of action of 1,3,4-oxadiazole derivatives as anticancer agent

There is the various reported anticancer mechanism of action of 1,3,4-oxadiazole derivatives, such as inhibition of telomerase activity [25], focal adhesion kinase (FAK) inhibitors [26], targeting thymidylate synthase [27], an inhibitor of the B-cell lymphoma 2 [28], inhibitor of NF-kB signaling pathway [29] and targeting tubulin polymerization [30]. (Figure 2.)

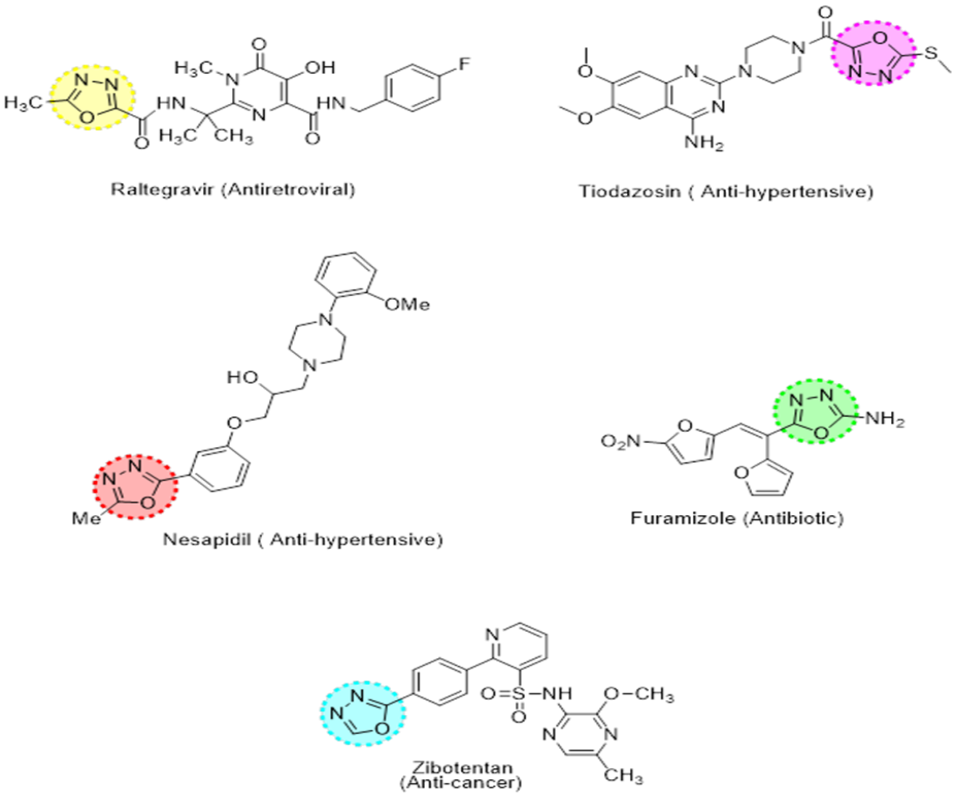


Figure 1 Examples of marketed and clinical trial drugs having 1,3,4-oxadiazole scaffold

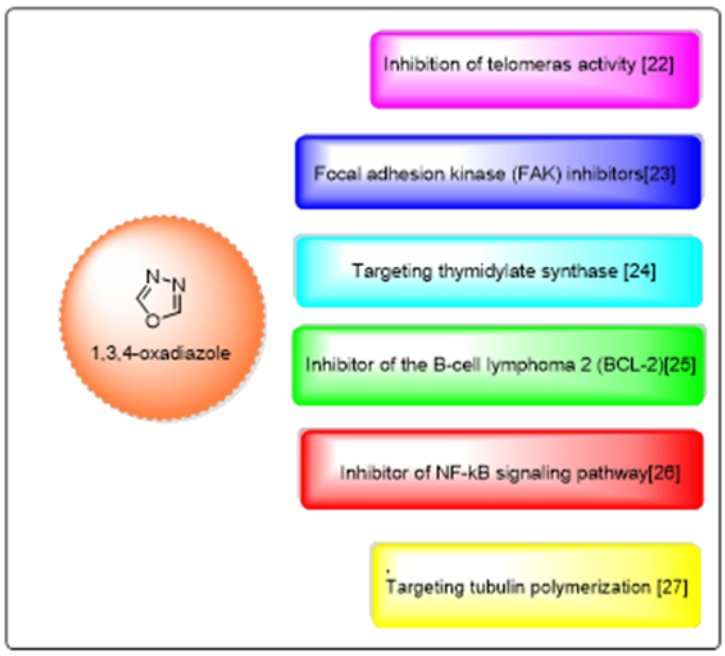
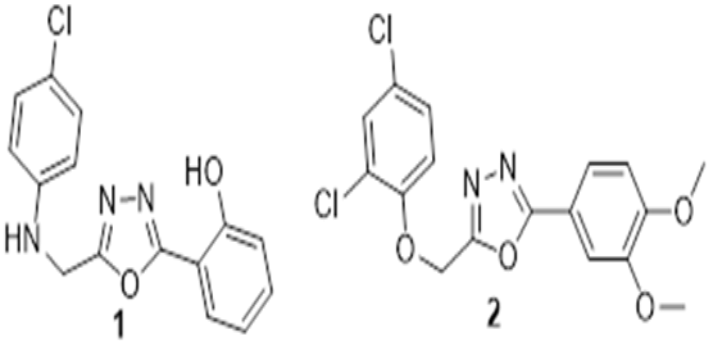


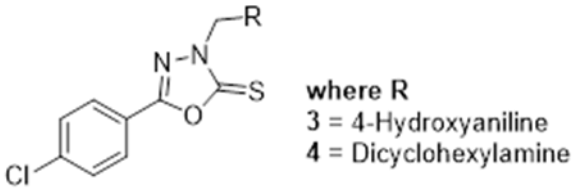
Figure 2 Various mode of action of 1,3,4-oxadiazole as anticancer agents

3. Anticancer activity of 1,3,4-oxadiazole derivatives

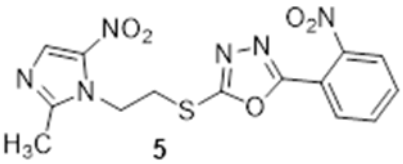
Ahsan *et al* (2018), synthesized 2,5-disubstituted-1,3,4-oxadiazoles and explored their cytotoxicity by tubulin inhibition. The outcome of the study indicated that analogues 1 and 2 displayed higher anti-cancer activity with 71.56% and 72.68% growth inhibition at a concentration of 10 μM. The polymerization of tubulin also significantly inhibited by compounds 1 (IC50 = 2.8 μM) and 2 (IC 50 = 2.2 μM) [30].



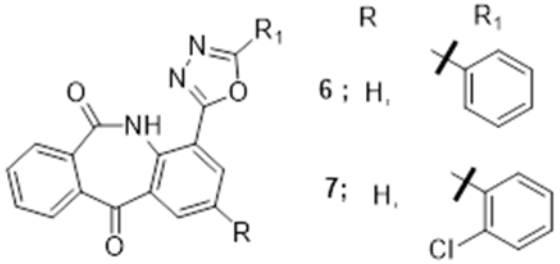
Bajaj *et al* (2018), synthesized 1,3,4-oxadiazole-2-thione analogues and estimated anticancer activity against breast cancer cell line (MCF-7) and thymidine phosphorylase (TP). Among all the synthesized derivatives compound **3** exhibited the potent anticancer activity (GI_{50} = 0.041 μM) against the MCF-7 cell line. On the other side compound, **4** showed the highest TP inhibitory activity (IC_{50} = 22.83 μM) as compared to other derivatives. Results showed that compounds with amine groups have better binding affinity against TP as compared to other compounds. SAR analysis indicated that the presence of benzene with electron withdrawing group and less steric amine group improved inhibition activity [21].



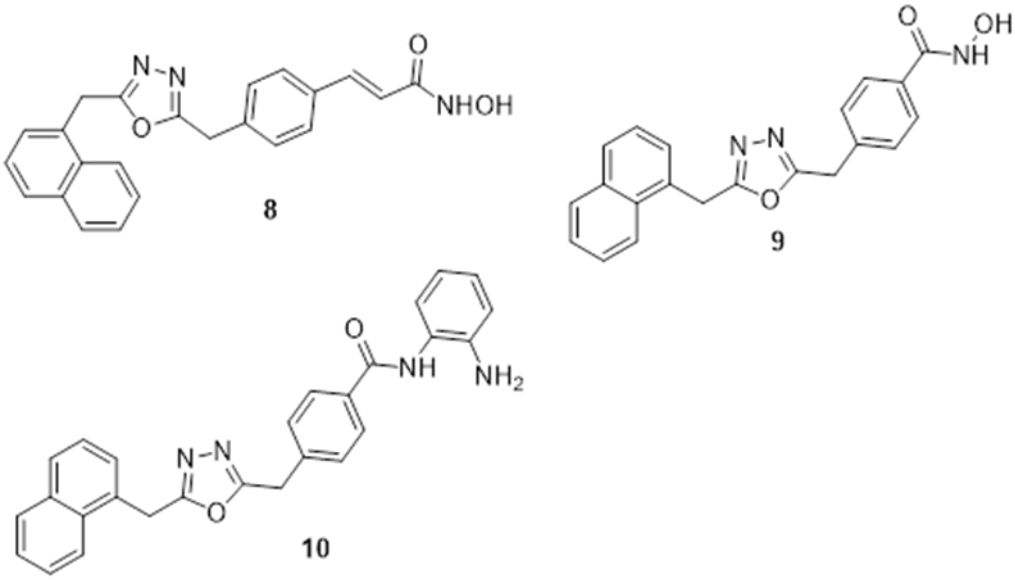
Du *et al* (2013), estimated cytotoxicity of 1,3,4-oxadiazole thioether against human hepatoma, human gastric cancer, and human breast cancer cell line. The Result showed that compound **5** with a nitro substituent showed greater *in vitro* anticancer activities with IC_{50} values of 0.7 μM, 30.0 μM, and 18.3 μM, respectively [27].



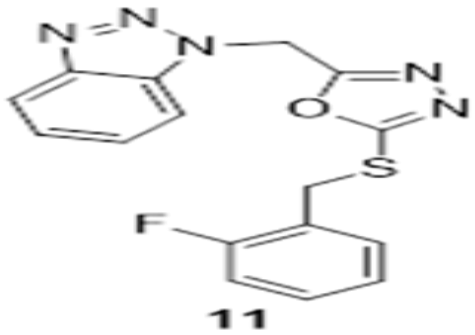
He *et al* (2018), prepared 1,3,4-oxadiazole containing 5H-dibenzo[b,e]azepine-6,11-dione derivatives and investigated their cytotoxicity against human ovarian cancer cell line. Compounds **6** (IC_{50} = 1.66 μM) and **7** (IC_{50} = 1.40 μM) showed higher activity as compared to other compounds. SAR analysis revealed that compounds having benzene and chlorobenzene at 2nd position of 1,3,4-oxadiazole possess powerful anticancer activity [31].



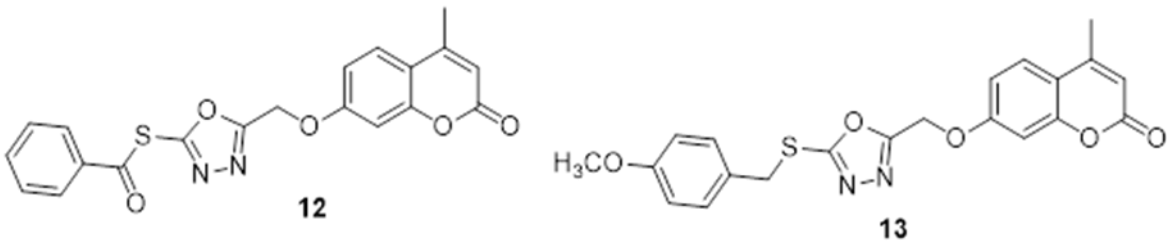
Valente *et al* (2014), developed derivatives of 1,3,4-oxadiazole. These derivatives act as histone deacetylase 1 (HDAC1) inhibitors. Amongst all the synthesized analogues, **8** (IC_{50} = 0.2 μM), **9** (IC_{50} = 0.2 μM), and **10** (IC_{50} = 0.2 μM) were powerful and selective against HDAC1, and showed comparable activity to control SAHA (IC_{50} = 0.3 μM) [32].



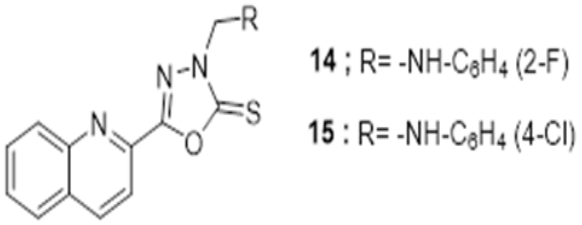
Zhang *et al* (2013), developed hybrid of 1,3,4-oxadiazole and benzotriazole analogues as focal adhesion kinase inhibitors against breast cancer (MCF-7) and colorectal cancer (HT29) cell lines. Result outcome revealed that compound **11** having 2-fluorobenzylthio substituents at 2nd position of 1,3,4-oxadiazole, exhibited strong activity against MCF-7 (IC_{50} = 5.68μg/ml), and HT29 (IC_{50} = 10.21μg/ml), superior to standard drug Cisplatin (IC_{50} = 11.20 μg/ml and 15.83 μg/ml). Compound **11** displayed the highest FAK inhibitory activity with IC_{50} = 1.2 μM, higher than Cisplatin (IC_{50} = 8.6 μM) [26].



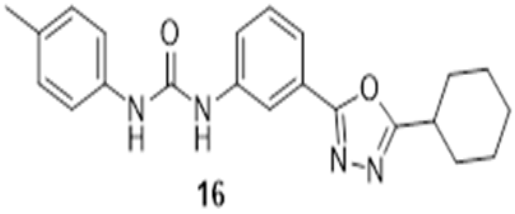
Narella *et al*, (2019), synthesized and estimated cytotoxicity of 1,3,4-oxadiazole-coumarin hybrids against the human carbonic anhydrase isoforms (CA I, CA II, CA IX, and CA XII). Result revealed that most of target derivatives had not displayed inhibition towards CA I and CA II (K_i >100 μM). Among all, derivative **12** (K_i = 0.16 μM) and **13** (K_i = 2.34 μM) showed potent anticancer activity against CA XII and CA IX, respectively [33].



Sun *et al* (2013), synthesized quinolone linked 1,3,4-oxadiazole analogues and evaluated cytotoxicity for SGC-7901 (gastric cancer), HepG2 (hepatoma), and MCF-7 (breast cancer) cell lines. Among synthesized derivatives **14** (IC_{50} = 1.2, 8.3, 6.8μM against HepG2, SGC-7901, MCF-7 respectively) and **15** (IC_{50} = 0.8, 7.6, 7.1 μM against HepG2, SGC-7901, MCF-7 respectively) exhibited potent inhibitory action, which was superior to positive control 5-Flurouracil (IC_{50} = 28.5, 21.9, 17.2 μM against SGC-7901, HepG2, MCF-7 respectively). SAR revealed that the most active anticancer action was seen by compounds containing fluorine at 4th position **(14)** and chlorine at para position **(15)** of anilines attached at 3rd position of 1,3,4-oxadiazole [34].

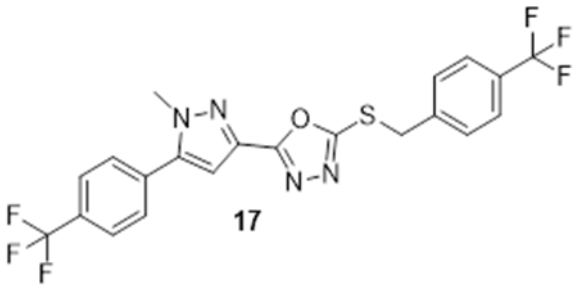


Kavitha *et al* (2016), developed 2, 5-disubstituted 1,3,4-oxadiazole derivatives and evaluated antitumour activity against HeLa (cervical), MCF-7 (breast) cancer cell lines. Amongst all compound having *p*-tolylurea substituent, **16** exhibited potent anticancer activity (IC_{50} = 30.4 μM, 23.5 μM against HeLa and MCF-7), however, inferior to standard drug Cisplastin (IC_{50} = 3.5 μM) [35].



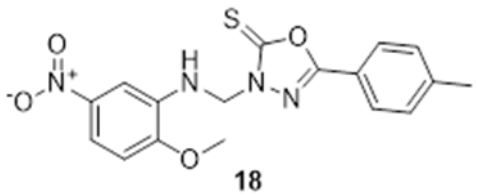
16

Puthiyapurayil *et al* (2012), synthesized trifluoromethylphenyl and pyrazole clubbed 1,3,4-oxadiazoles and evaluated antitumour activity for breast cancer (MCF-7) and alveolar adenocarcinoma (A549). Results revealed that compound **17** exhibited noteworthy anticancer activity toward all cell lines with IC_{50} = 20.54, 15.54, and 29.21 μM against EAC, MCF-7, and A549, respectively. High potency may be due to the existence trifluoromethylphenyl and pyrazole moieties in 1,3,4-oxadiazole ring [36].



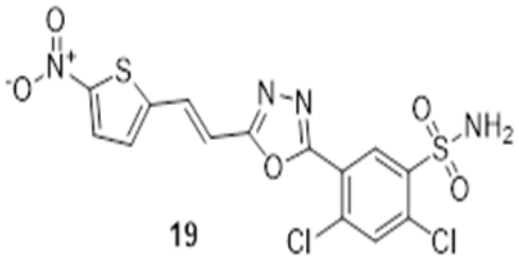
17

Shahzad *et al* (2014), prepared 1,3,4-oxadiazole analogues and evaluated anticancer action as thymidine phosphorylase (TP) inhibitor. Among these, compound **18** with nitro substituent showed the highest TP inhibition with IC_{50} = 14.40 μM even superior than standard inhibitor 7-Deazaxanthine with IC_{50} = 38.68μM [37].



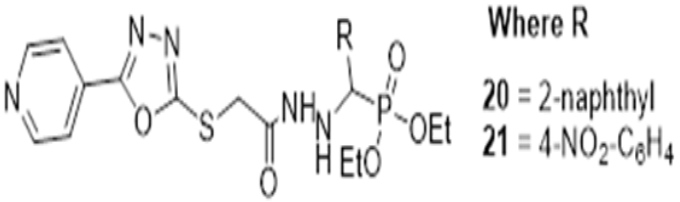
18

Szafranski *et al* (2020), evaluated anticancer action of (*E*)- 5-(2-arylvinyl)-1,3,4-oxadiazol-2-yl) benzene sulfonamides derivatives against HCT-116 (colon cancer), MCF-7 (breast cancer) and HeLa (cervical cancer). Result outcome revealed that compound **19**, having 5-nitrothiophene substituent, showed the potent cytotoxicity against the HCT-116 (IC_{50} = 0.5 μM), MCF-7(IC_{50} = 4 μM), and HeLa (IC_{50} = 4.5 μM) cell lines [38].

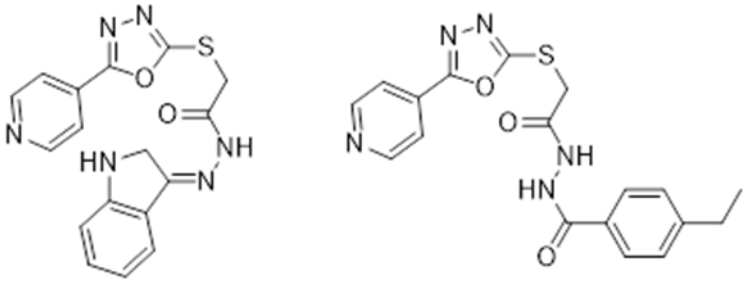


19

Ewies *et al* (2019), prepared and evaluated anticancer activity of α-amino phosphonate oxadiazole derivatives against human cancer cell lines of the colon (HCT116), breast (MCF7), and liver (HepG2). Results showed that compounds **20** (IC_{50} = 9.5μM) and **21** (IC_{50} = 9.2μM) found to be potent among all the tested compounds, against cell lines of the colon (HCT116), equipotent to the standard drug Doxorubicin (IC_{50} = 9.4μM). High potency may due to the presence of 2-naphthayl **(20)** and 4-NO_2-C_6H_5 **(21)** substituents. On the other hand, in case of the breast (MCF7) and liver (HepG2) cell lines, all the synthesized compounds exhibited considerably less cytotoxic effects as compared to Doxorubicin [39].

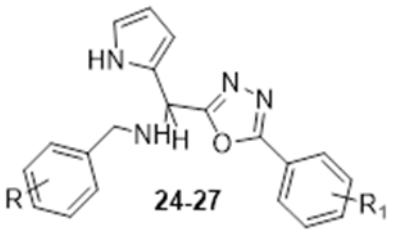


Khalil *et al* (2015), evaluated anticancer activity of 5-pyridyl-1,3,4-oxadiazoles against the MCF-7 (Breast Cancer cell line). Results revealed that compounds **22** having 3-indolyl and **23** having 4-ethylphenyl substituent possess potent activity with IC_{50} values of 0.010 μM and 0.012 μM, respectively, which was nearly twice over the potency of the reference drug, Erlotinib (IC_{50} = 0.020 μM) [40].



22 23

Ramazani *et al* (2014), developed 1-(5-aryl-1,3,4-oxadiazol-2-yl)-1-(1H-pyrrol-2 yl) methanamines and evaluated their anticancer activity against human alveolar basal epithelial adenocarcinoma (A549), human colorectal (HT29), human fibrosarcoma (HT1080) and human breast adenocarcinoma (MCF-7) cell lines. Results revealed that compound **24** (IC_{50} = 13.3μM and 18μM) showed potent activity against A549 and HT29, respectively. Compound **25** (IC_{50} = 14.7μM) and **26** (IC_{50} = 15.2μM) showed excellent activity against HT1080 and in case of MCF-7, compounds **27** (IC_{50} = 4.3μM) and **26** (IC_{50} = 13.9μM) showed excellent anticancer activity [41].

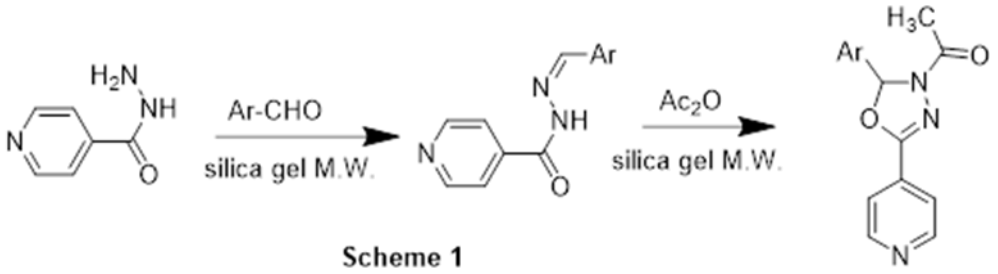


24 ; R = 3,4-Cl_2, R_1 = 3-Cl
25 ; R = 4-F, R_1 = 4-OMe
26 ; R = H, R_1 = 3,4-Cl_2
27 ; R = 4-Me, R_1 = 4-Br

Microwave-assisted organic synthesis is a valuable and eco-friendly synthetic methodology and becoming an important tool of green chemistry scheme [42].

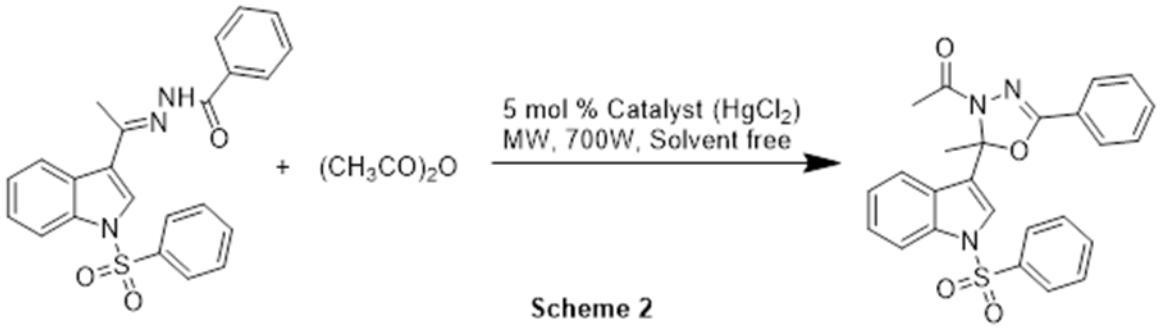
4. Microwave assisted synthesis of 1,3,4-oxadiazole analogues

Scheme 1 Bhardwaj *et al*, introduce a sequence of 2-substituted-1,3,4-oxadiazole analogues clubbed with pyridine. The synthesis includes the reaction of hydrazide with an aromatic aldehyde, followed by cyclization with help of acetic anhydride under microwave irradiation with silica gel [24].



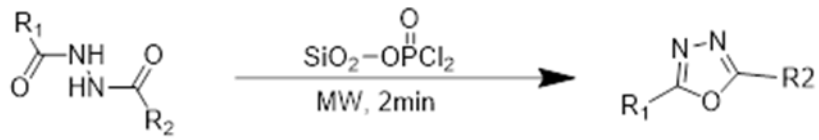
Scheme 1

Scheme 2 Che *et al*, synthesized a sequence of 2-alkyl-2-(N-arylsulfonylindol-3-yl)-3-N-acyl-5-aryl-1,3,4-oxadiazoline derivatives using microwave irradiation. N-benzenesulfonyl-3-acetylindole benzoyl hydrazone reacted with acetic anhydride, catalyzed by $HgCl_2$ under solvent-free conditions [43].



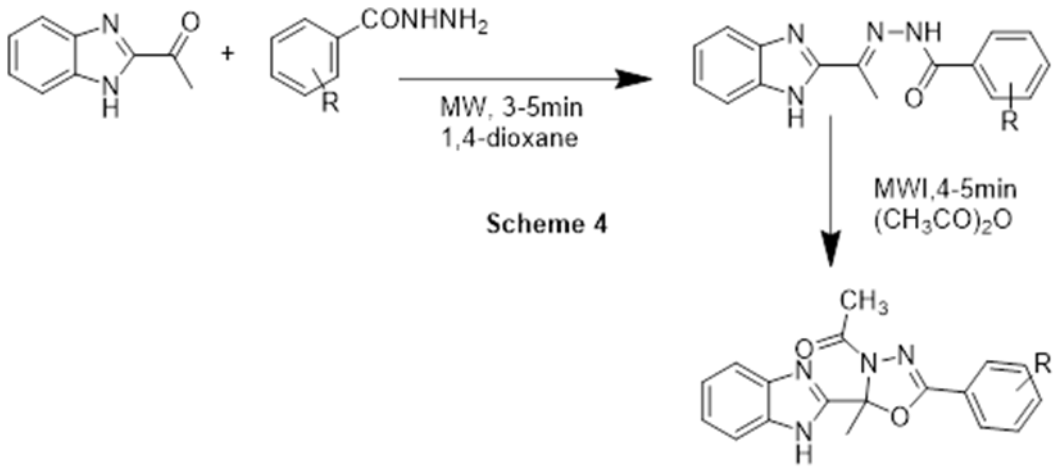
Scheme 2

Scheme 3 Li *et al*, introduced 2,5-disubstituted-1,3,4-oxadiazole derivatives by cyclization and dehydration of diacylhydrazide using silica-supported dichlorophosphate and microwave-assisted reaction without any solvent [44].



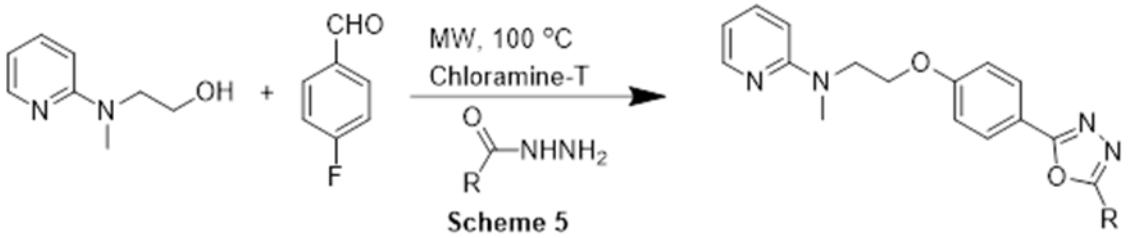
Scheme 3

Scheme 4 Desai *et al*, described the microwave-assisted synthesis of benzimidazole encompassing 1,3,4-oxadiazole analogues. 1-(1Hbenzo[d]imidazol-2-yl) ethanone reacted with aromatic acid hydrazides followed by cyclization with help of acetic anhydride [45].



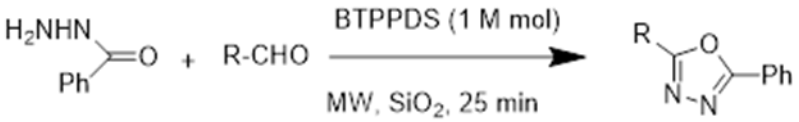
Scheme 4

Scheme 5 Gaonkar *et al*, developed microwave-assisted synthetic methods for 2,5-disubstituted 1,3,4-oxadiazole analogues clubbed with N-methyl-N-(2-phenoxyethyl) pyridin-2-amine. In this synthetic reaction the 2-(methyl (pyridin-2-yl) amino) ethan-1-ol reacted with 4-fluorobenzaldehyde, catalyzed by chloramine-T, under the microwave irradiation [46],



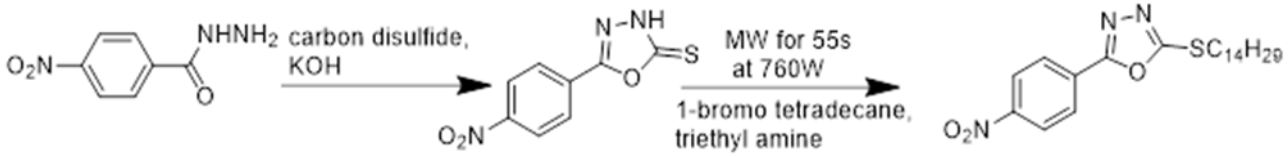
Scheme 5

Scheme 6 Gorgizadeh *et al*, introduced a series 2,5-disubstituted-1,3,4-oxadiazole derivatives. Microwave-assisted synthesis involved the reaction of benzohydrazide and aromatic aldehyde catalyzed by 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate (BTPPDS) [47].



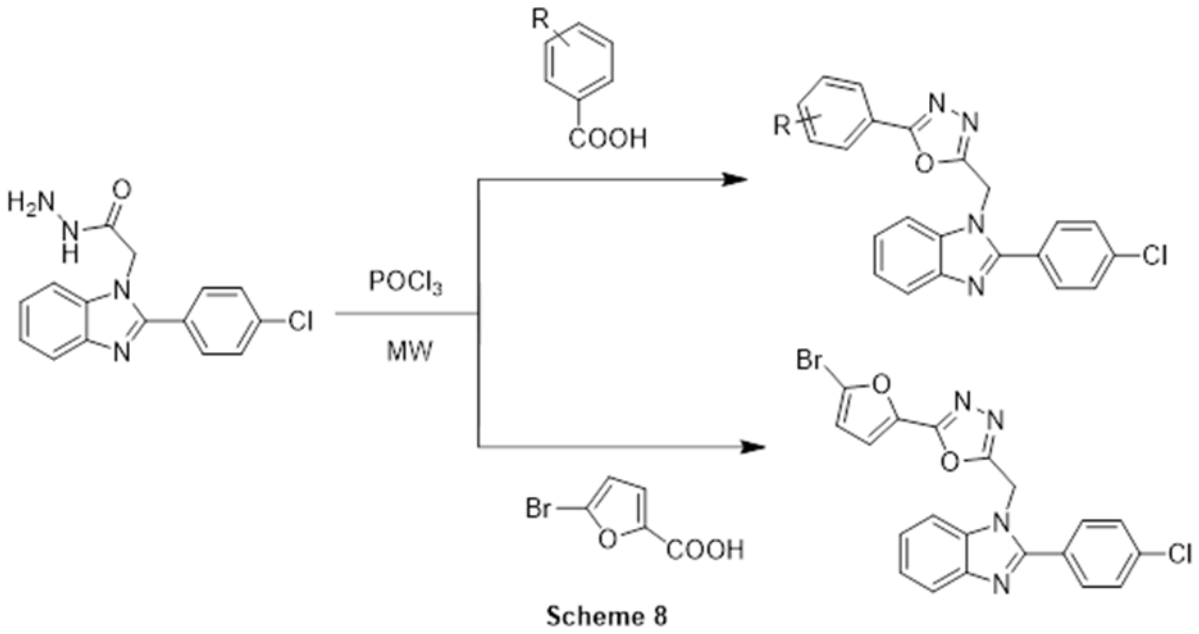
Scheme 6

Scheme 7 Modi *et al*, established the synthesis of 2,5-disubstituted oxadiazoles clubbed with tetradecylsulfane at 2nd position and *p*-nitrophenyl at 5th position. In the first step p-nitrophenylhydrazide cyclized with carbon disulphide and potassium hydroxide, followed by microwave-assisted reaction with 1-bromo tetradecane in presence of trimethyl amine [48].



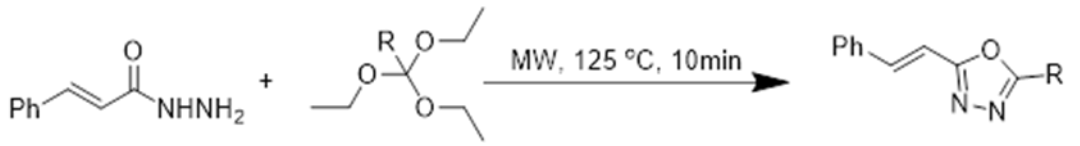
Scheme 7

Scheme 8 Kerimov *et al*, explored the one-pot synthesis of 5-aryl-1,3,4-oxadiazoles bearing benzimidazole nucleus. In this reaction 2-(2-(4-chlorophenyl)-1H-benzo[d]imidazol-1-yl) acetohydrazide reacted with different substituted aromatic carboxylic acids in the presence of $POCl_3$ under microwave irradiation [49].



Scheme 8

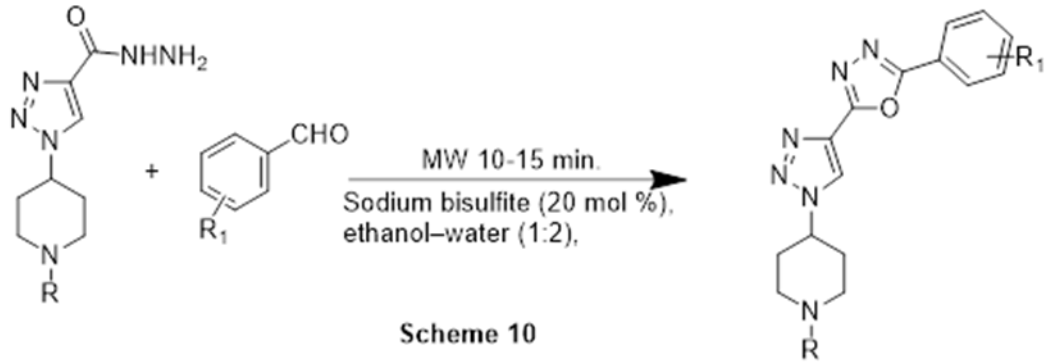
Scheme 9 Kudelko *et al*, carried out the synthesis of 2-styryl-1,3,4-oxadiazole analogues by a reaction between triethyl orthoesters and cinnamic acid hydrazide under microwave irradiation [50].



Scheme 9

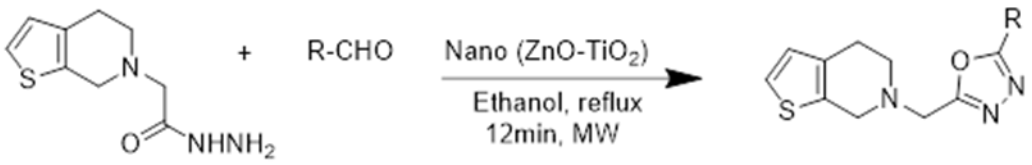
R = H, Me, Et, Ph

Scheme 10 Sangshetti *et al*, developed a method for microwave-assisted preparation of 2,5-disubstituted 1,3,4-oxadiazole analogues by condensation of different hydrazide analogues and substituted aromatic aldehydes in the presence of sodium bisulfite and ethanol-water (1:2) [51].



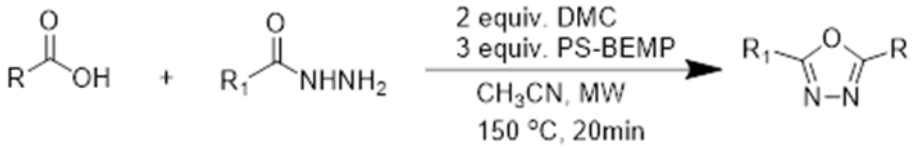
Scheme 10

Scheme 11 Sangshetti *et al*, synthesized a sequence of 2-((4,7-dihydrothieno[2,3-c] pyridin-6(5H)-yl) methyl)-1,3,4-oxadiazole using green chemistry protocol. It includes the reaction of hydrazide compounds and different aromatic aldehydes using combined nano (ZnO–TiO2) as a catalyst to develop the 1,3,4-oxadiazoles [52].



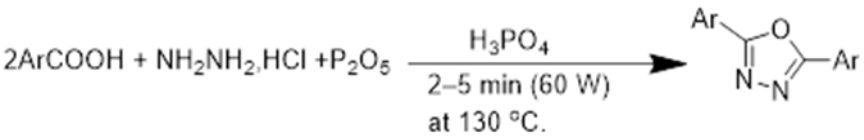
Scheme 11

Scheme 12 Wang *et al,* explored the green synthesis of 1,3,4-oxadiazoles by the reaction of acid hydrazides and carboxylic acids using either DMC/PS-BEMP or PS-PPh_3/CCl_3CN [53].



Scheme 12

Scheme 13 Bentiss *et al*, carried out the synthesis of 2,5-disubstituted 1,3,4-oxadiazole analogues by microwave irradiation. Aromatic acid, hydrazine hydrochloride, orthophosphoric acid were reacted in the presence of phosphorus pentoxide in microwave oven under a reflux condenser [54].



Scheme 13

5. Conclusion

Oxadiazoles are five membered heterocyclic compounds having one oxygen and two nitrogen atoms. 1,3,4-oxadiazoles exhibited diverse biological activities and act as a multipurpose lead molecule for the design and synthesis of possible bioactive agents. 1,3,4-oxadiazole derivatives exhibited noteworthy anticancer activities and act by various anticancer mechanism such as inhibition of telomerase activity, focal adhesion kinase (FAK), targeting thymidylate synthase, inhibitor of the B-cell lymphoma-2 (BCL-2), inhibitor of NF-kB signaling pathway and targeting tubulin polymerization. Further, SAR analysis showed, the substitution of phenyl ring with electron withdrawing groups *viz.* Cl, F, NO_2 and less steric amine; 2-fluorobenzylthio**,** tolylurea, 5-nitrothiophene, 2-naphthayl, benzotriazole, coumarin, quinolone and pyridine moieties enhanced the anticancer potency of 1,3,4-oxadiazole derivatives. Present review also summarizes the various synthetic approaches of 1,3,4-oxadiazole derivatives *via* microwave irradiation method.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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