Strategies to Synthesis of 1,3,4-Oxadiazole Derivatives and Their Biological Activities: A Mini Review

Baby Ramana M[1], Mothilal M[2], Maheswara Rao G[1], Mannam Krishna Murthy[3], Ravi Varala[4], Hari Babu Bollikolla[1]*

[1]*Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar-522510, Guntur, India*
[2]*Department of Chemistry, Loyola College, PB 3301, Sterling Road, Nungambakkam, Chennai- 600 034*
[3]*Department of Chemistry (P.G.), S.V.R.M. College, Nagaram-522268, Guntur, India*
[4]*Scrips Pharma, Mallapur-500 076, Hyderabad, India*

Use yor device to scan and read the article online

Citation B. Ramana M, Mothilal M, M. Rao G, M.K. Murthy, Ravi Varala, H. Babu Bollikolla*. **Strategies to Synthesis of 1,3,4-Oxadiazole Derivatives and Their Biological Activities: A Mini Review.** *J. Chem. Rev.*, **2022**, *4*(3), 255-271.

https://doi.org/10.22034/JCR.2022.341351.1170

Article info:
Received: 8 May 2022
Accepted: 7 June 2022
Available Online: 12 June 2022
ID: JCR-2205-1170
Checked for Plagiarism: Yes
Language Editor: Dr. Fatimah Ramezani
Peer Reviewers Approved by:
Dr. Parvin Hajiabbasi
Editor who Approved Publication: Prof. Dr. Ghasem Rezanejade Bardajee

Keywords:
1,3,4-Oxadiazoles, Synthesis; Biological activity; Pharmacological relevance

ABSTRACT

Molecules with 1,3,4-oxadiazole ring structures have potential pharmacological relevance. These organic molecules are potentially reported for their medicinal importance. In this mini-review, different strategies for the synthesis of biologically important molecules of 1,3,4-oxadiazole ring are briefly summarized. Antimicrobial, anticancer, anti-inflammatory, anti-tubercular, molluscicidal, hypoglycemic, anticonvulsant, and antiprotozoal activities of the title compounds are also briefly reviewed. Significant papers were chosen and compiled the report until March 2022.

List of content

***Corresponding Author: Hari Babu Bollikolla** (dr.b.haribabu@gmail.com)*

1. Introduction

Pharmacologically relevant heterocyclic compounds play a key role in the fight against diseases affecting both human and animal living organisms, as well as plants. Finding out about new molecules with a potential biological effect, not yet described in the literature, is one of the most important aspects in the development of medicine, agriculture, and other allied sectors. Compounds showing desirable biological activity include heterocyclic moieties such as 1,3,4-oxadiazoles. Oxadiazole is a heterocyclic compound which has the molecular formula $C_2H_2N_2O$. 1,3,4-Oxadiazole (**Figure 1**) is one of the four isomers of oxadiazole [1-2].

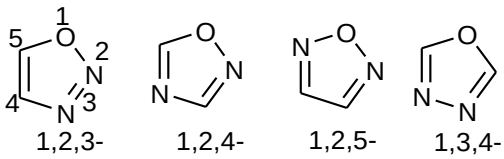


Figure 1. Structures of oxadiazole isomers

There are several studies which indicate that compounds with the 1,3,4-oxadiazole ring in their structure have a multidirectional pharmacological action [3-13]. Derivatives of 1,3,4-oxadiazole have antibacterial [14], antimalarial [15], anti-inflammatory [16], anti-depressive [17], anticancer [18], analgesic, and antiviral [19] effects. The anti-cancer effects of 1,3,4-oxadiazole derivatives appear to be of special interest, given the ever-increasing incidence of many types of cancer. 1,3,4-Oxadiazole, itself is not commonly used in organic chemistry, but many of its derivatives have biological activities [20-21] and are used in the medicinal field [22-25]. The stable oxadiazoles appear in a many pharmaceutical drugs which include raltegravir, fasiplon, butalamine, oxolamine, pleconaril, and nesapidil. Few examples of drugs which possess 1,3,4-oxadiazole rings are displayed in **Figure 2**.

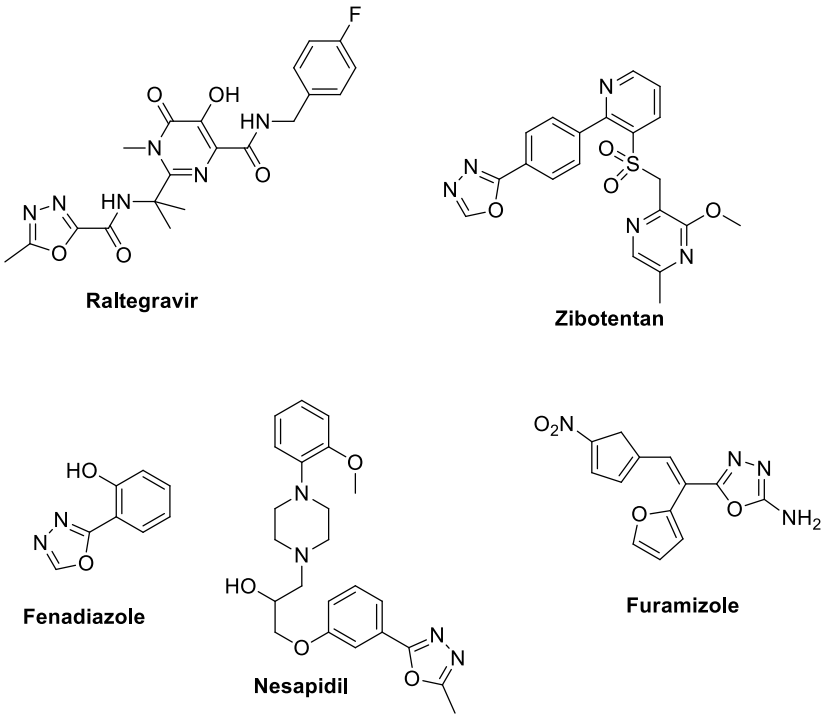


Figure 2. Pharmacologically relevant drugs containing 1,3,4-oxadiazole rings

In continuation of our vast experience in the chemistry of oxadiazoles, we, herewith, present a brief compilation of both synthetic strategies and biological activity of the title compounds [26-30].

2. Synthetic strategies for 1,3,4-oxadiazole

As depicted in **Figure 3**, 1,3-dibromo-5,5-dimethyl hydantoin is an efficient oxidizing agent for cyclization reactions involving acyl thiosemicarbazides (**2**) to produce 5-aryl-2-amino-1,3,4-oxadiazoles (**3**). The fundamental advantage of this protocol [31] is that the reagents utilized are inexpensive and safe to use in large-scale synthesis where alternative oxidizing agents are unavailable.

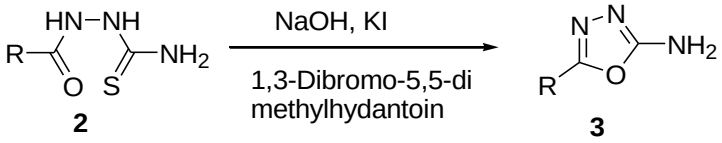


Figure 3. Synthesis of 5-aryl-2- amino-1,3,4-oxadiazoles

The synthesis of 5-substituted-1,3,4-oxadiazole-2-thiol (thione) **4** was reported by Koparir *et al*. [32], which requires an initial reaction between an acyl hydrazide and CS_2 in a basic alcoholic solution, followed by acidification of reaction mass as illustrated in **Figure 4**. According to a literature review, this method is used to make a wide range of 1,3,4-oxadiazole derivatives. For such compounds, thiol **4**-thione **5** tautomerism is known, and one of the two forms frequently predominates.

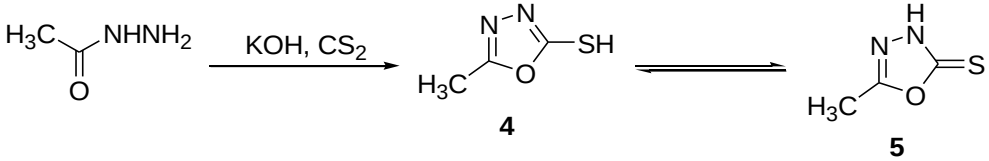


Figure 4. Synthesis of 5-substituted-1,3,4- oxadiazole-2-thiol (thione)

The preparation of 5-((naphthalen-2-yloxy) methyl)-*N*-phenyl-1,3,4-oxadiazol-2-amine (**7**) in reasonable yield by heating 2-[(naphthalen-2-yloxy)acetyl]-*N*-phenylhydrazine carboxamide (**6**) ethanol in the presence of NaOH and I_2 in KI is another interesting approach reported by El-Sayed *et al*. [33] (**Figure 5**).

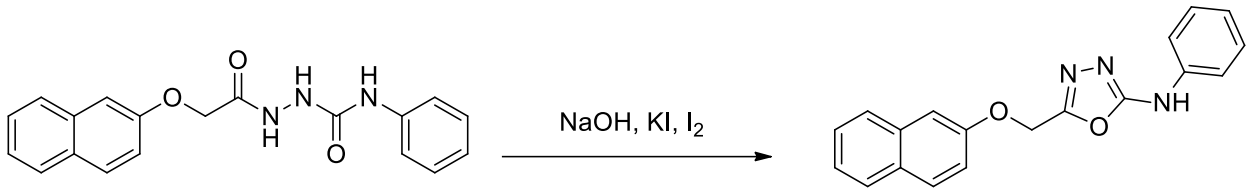


Figure 5. Synthesis of 5-((naphthalen-2-yloxy) methyl)-*N*-phenyl-1,3,4-oxadiazol-2-amine

Jha *et. al*. [34] explored the synthesis of 1,3,4-oxadiazole with 2,5-disubstitution (**8**) by cyclization process with substituted aromatic hydrazides in CS_2 and aromatic acids in $POCl_3$ almost a decade ago (**Figure 6**).

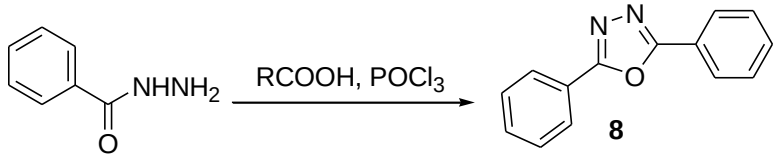


Figure 6. Synthesis of 1,3,4- oxadiazole

An imine CH functionalization of *N*-arylidene aroyl hydrazide with a catalytic amount of $Cu(OTf)_2$ has provided ready access to symmetrical and unsymmetrical 2,5-disubstituted-[1,3,4]-oxadiazole **9**. This is the most common example of amidic oxygen acting as a nucleophile in an imine CH bond oxidative coupling catalyzed by Cu catalyst [35]. These reactions may be carried out in a natural environment with air and moisture, making them extremely helpful in the preparation of organic molecules (**Figure 7**).

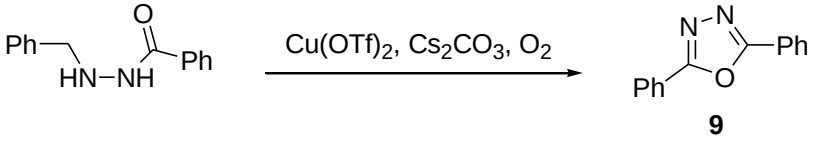


Figure 7. Synthesis of symmetrical and unsymmetrical 2,5- disubstituted-[1,3,4]-oxadiazole

Gaonkar *et al.* [36] described the oxidative cyclization of *N*-acyl hydrazones by chloramine-T under microwave irradiation to produce corresponding 5-substituted 1,3,4-oxadiazoles **10** (**Figure 8**).

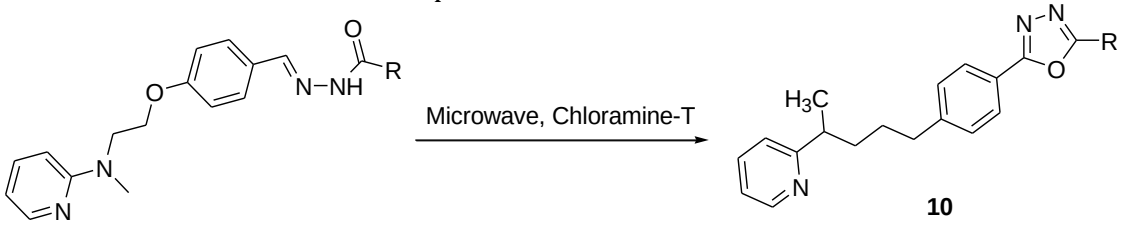


Figure 8. Synthesis of 5-substituted 1,3,4-oxadiazoles

A range of symmetrical and asymmetrical 1,3,4-oxadiazoles with aryl, alkyl, and vinyl substitutions at 2,5-positions were synthesized in a skilled and diversified method [37]. With potassium carbonate, 1,3,4-oxadiazoles **11** were synthesized utilizing substituted aryl hydrazones and stoichiometric molecular iodine, which is a viable and transition metal-

free oxidative cyclization of crude acyl hydrazones generated *via* condensation of aldehyde and hydrazide (**Figure 9**).

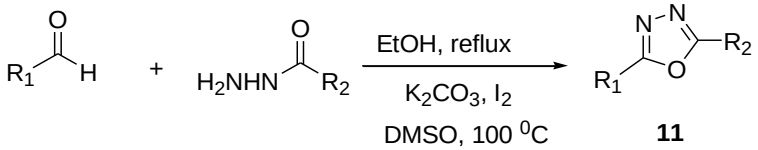


Figure 9. Synthesis of symmetrical and asymmetrical 2,5-disubstituted 1,3,4-oxadiazoles

Iodine-mediated oxidative C-O formation *via* condensation of a variety of aldehydes and semicarbazide was used to make 2-amino-substituted 1,3,4-oxadiazoles **12** [38] (**Figure 10**). This approach is a non-metal sequential procedure with aliphatic, aromatic, and cinnamic aldehydes which yields 2-amino substituted-1,3,4-oxadiazoles in a fast and versatile manner.

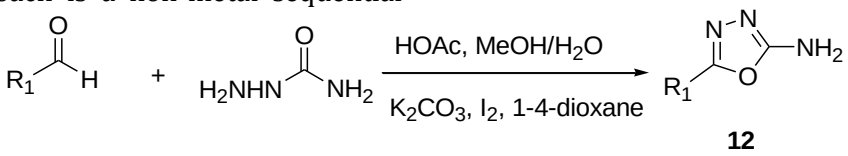


Figure 10. Synthesis of 2-amino-substituted 1,3,4-oxadiazoles

Using CBr_4 as a bromine source, an extremely effective eosin Y catalyzed oxidative hetero-cyclization of semi-carbazone was developed using visible light photo redox catalysis [39]. This methodology provided a fastest, smooth, and operational admission to substantial 5-substituted 2-amino-1,3,4-oxadiazoles **13** (**Figure 11**).

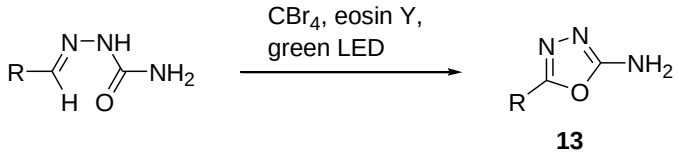


Figure 11. Synthesis of 5- substituted 2-amino-1,3,4-oxadiazoles

Through consecutive isocyanide additions into NH and OH bonds of hydrazides [40], a novel Pd-catalyzed oxidative annulations reaction was produced, allowing impactful access to beneficial 2-substituted amino-1,3,4-oxadiazole **14**, as illustrated in **Figure 12**.

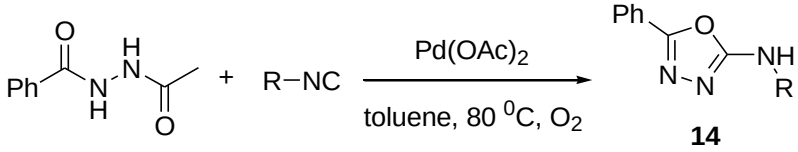


Figure 12. Synthesis of 2-substituted amino-1,3,4-oxadiazole

A simple one-pot protocol [41] for preparation of a range of 2,5-disubstituted-1,3,4-oxadiazoles **15** was described by condensing monoaryl hydrazides with acid chlorides in solvent HMPA under microwave heating, as shown in **Figure 13**. The yields were found good to excellent, the technique was fast, and there was no need for an acid catalyst or a dehydrating agent.

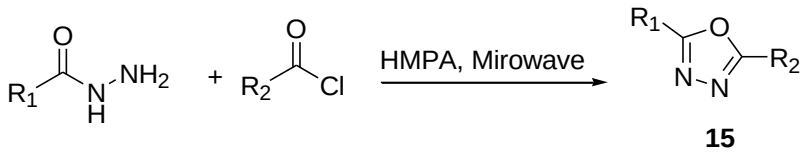


Figure 13. Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles

The ready formation of 5-substituted 2-(*N*-alkyl/aryl)-1,3,4-oxadiazoles **16** was accounted for using a simple and broad convention [42]. In this case, hydrazide was acylated with the appropriate isothiocyanate to produce thiosemicarbazide, which was subsequently treated with tosyl chloride/pyridine for intervening cyclization to obtain 5-substituted 2-(*N*-aryl/alkyl)-1,3,4-oxadiazoles **16** (**Figure 14**).

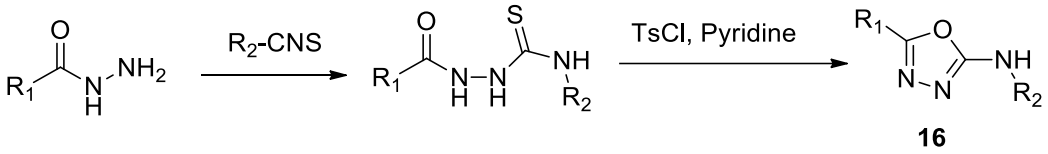


Figure 14. Synthesis of 5-substituted 2-(*N*-alkyl/aryl)-1,3,4-oxadiazoles

Ramazani *et al*. [43] reported a one-pot synthesis of the 2,5-disubstituted 1,3,4-oxadiazole derivative **17** in CH_2Cl_2 at room temperature with high yields utilizing (*N*-isocyanimino) triphnylphosphorane, a 2^0 amine, a carboxylic acid, and an ArCHO (**Figure 15**).

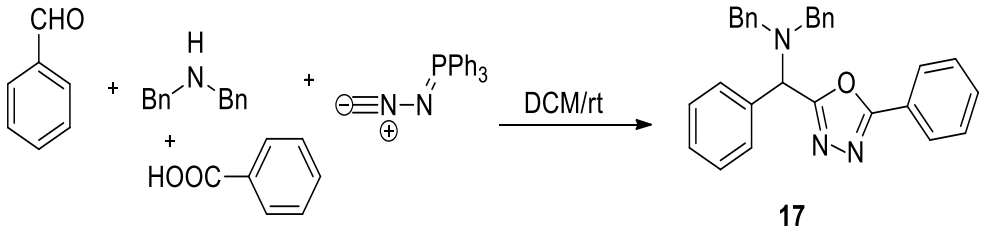


Figure 15. Synthesis of 2,5-disubstituted 1,3,4- oxadiazole derivative

Brain *et al.* [44] developed a novel methodology for generating 1,3,4-oxadiazoles **18** from 1,2-diacylhydrazines reacting with Burgess reagent under microwave conditions (**Figure 16**).

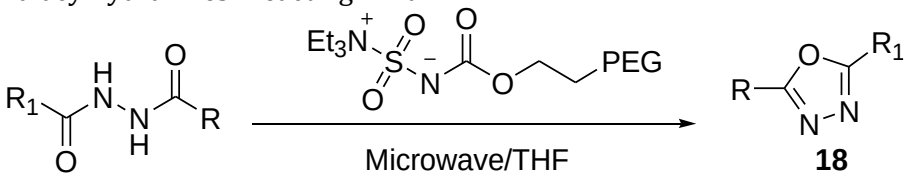


Figure 16. Synthesis of 1,3,4-oxadiazoles

3. Pharmacological activities and recent advances

A wide range of biological actions have been discovered in 1,3,4-oxadiazole derivatives such as antibacterial, anticancer, anti-inflammatory, anticonvulsant, pesticide, monoamine oxidase inhibitors (MOA), antihypertensive, and other properties, etc.

3.1. Antimicrobial activities

5-(5-methylisoxazole-3-yl)- 3-substituted aminomethyl-2-thio-1,3,4-oxadiazoles **19**, 4-acetyl-2-thio-1,3,4-oxadiazoles (5-methylisoxazole-3-yl) 2-aryl-5-9 and -5-substituted 1,3,4-oxadiazoles **20** (5-methylisoxazole-3-yl)-1,3,4-oxadiazoles **21** were synthesized using the Mannich reaction [45], and their anti-bacterial activation against *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis* was evaluated by cup plate

procedure at 100 g/mL. 4-Acetyl-2-phenyl-(5-methylisoxazole-3-yl) 2-aryl-5-9-substituted 1,3,4-oxadiazoles and 5-substituted 1,3,4-oxadiazoles (5-methylisoxazole-3-yl) were found to be the most active candidates in this family of 1,3,4-oxadiazoles (**Figure 17)**.

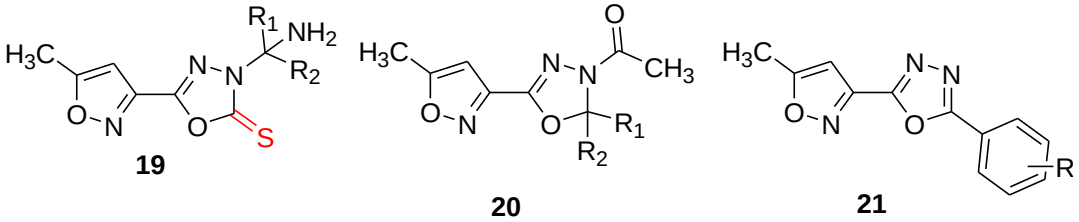


Figure 17. Family of 1,3,4-oxadiazoles exhibiting antimicrobial activity

Some new 1,2,4 triazolo-1,3,4-oxadiazole derivatives **22**, oxa-di-azolo [1,3,5]-triazine **23**, and triazolo-1,3,4-oxadiazole **24** were tested (**Figure 18**) for their anti-bacterial activity *in vitro* on Gram-negative bacteria (*S. typhi* and *E. coli*.) and Gram-positive bacteria (*S. aureus*) by Mulwad and Chaskar [46]. Tube dilution techniques were used to determine the minimum inhibitory concentration (MIC) of ciprofloxacin, cloxacillin, and gentamicin. The majority of the compounds in this class have been found to have considerable biological action.

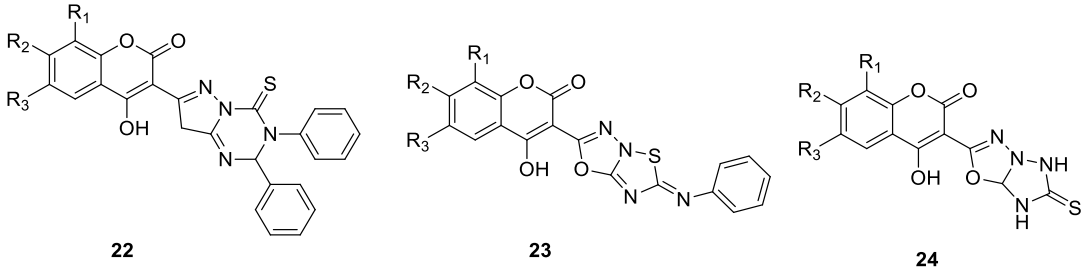


Figure 18.

The preparation of 5-(2,4-dichloro-5-fluorophenyl) -3-[(substituted-amino)methyl]-1,3,4-oxadiazole-2(3H)-thione **27** and 2-oxadiazole-2(3*H*)-thione (2,4-dichloro-5-fluorophenyl) -5-(substituted-sulfanyl) -1,3,4-oxadiazole **28** has been reported [47] and evaluated for antibacterial property on *S. aureus*, *E. coli*, and *K. pneumonia* by a serial dilution technique using nitrofurazone as the reference drug. The majority of tested chemicals were active in a similar range to the standard [48]. It's possible that the presence of 2,4-dichloro-5-fluorophenyl and 4-chloroaryloxy methyl groups explains the reason for the activity (**Figure 19**).

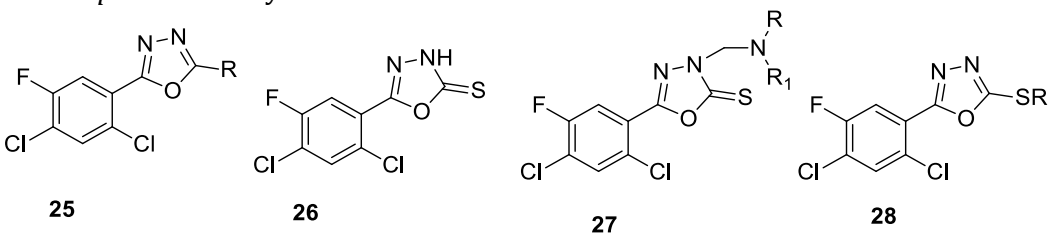
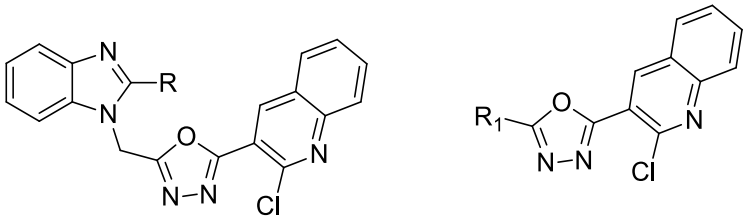


Figure 19.

3.2. Anti-cancer activities

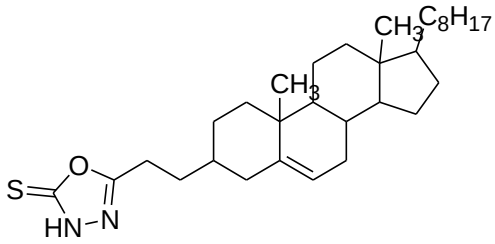
2-Chloro-3-{5-[(2-substituted-1-*H*-benzimidazol-1-yl)methyl]-1,3,4-oxadiazol-2-yl}quinoline **29** and 2-chloro-3-(5-substituted-phenyl-1,3,4-oxadiazol-2-yl)quinoline **30** (**Figure 20**) were prepared [49] and screened for anti-cancer property against to 60 cancer cell line at a dose of 10^{-5} Molar on different broad cell lines.



29 30

Figure 20. Family of 1,3,4-oxadiazoles exhibiting anti-cancer activity

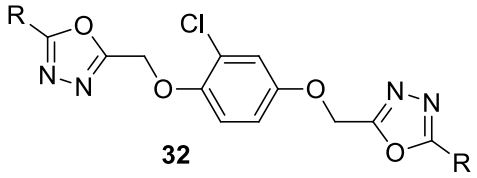
Steroidal derivatives of 3b-[5′-mercapto-1,3,4-oxadiazole-2-yl] methoxycholest-5-ene **31** (**Figure 21**) were prepared and tested for anti-cancer property over human leukemia (HL-60) cell line using MTT assay [50] and found IC_{50}at 17.



31

Figure 21.

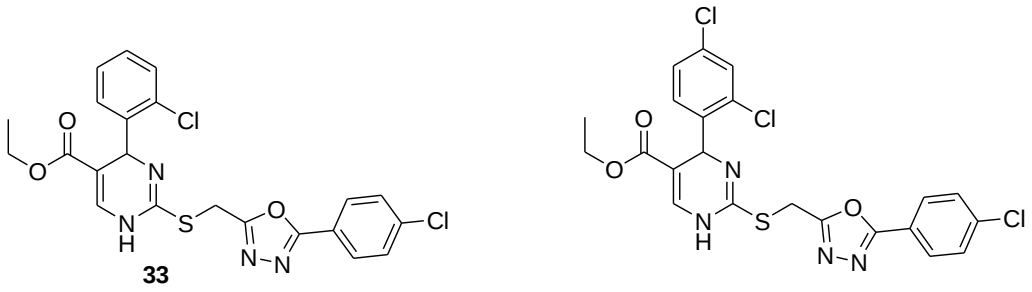
The 2-chloro-1,4-bis-(5-substituted-1,3,4-oxadiazol-2pheylmethyleneoxy)phenylene derivative **32** was synthesized (**Figure 22**) and tested *in vitro* on NCI-60 cancer cell lines of various cancer types, as well as leukaemia, CNS, colon, melanoma, lung, renal prostate, ovarian, and breast cancer. Most cancer cell lines demonstrated substantial action against the molecules with R= 2,4-dicholoro $C_6H_3OCH_2$ and 4-$ClC_6H_4NHCH_2$ [51].



32

Figure 22.

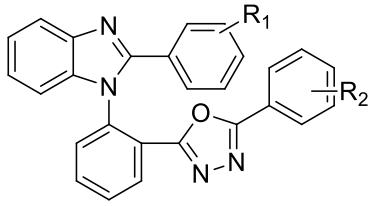
As monastrol analogues, a novel series of dihydropyrimidine derivatives containing the 1,3,4-oxadiazole moiety was created. 4-(3-Chlorophenyl)-2-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-6-methyl-1,4-dihydropyrimidine-5-carboxylateb **33** and ethyl 2-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate **34** were discovered active among all [52]. MOLT-4 (IC50 80 nM) and leukaemia HL-60TB (IC50 56 nM) were the most sensitive cell lines and were found to be more potential than monastrol (IC_{50}=215 and 147 nM, respectively) (**Figure 23**).



33 34

Figure 23.

Kapoor *et.al.* [53] synthesized a series of 2-(substituted phenyl)-5-(2-(2-(substituted phenyl)-*1H*-benzo[d]imidazol-1-yl) phenyl)-1,3,4-oxadiazoles **35 (Figure 24)** and tested for anti-tumor activity against breast cancer cell lines (MCF-7) by MTT assay. The substitutions with R_1=4-OCH_3, and R_2=4-OCH_3 compound exhibited excellent cytotoxic activity.

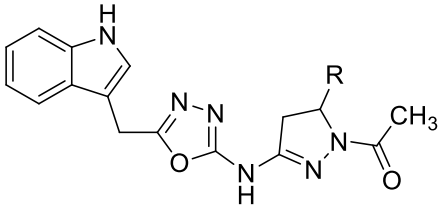


35

Figure 24.

3.3. Anti-inflammatory activities

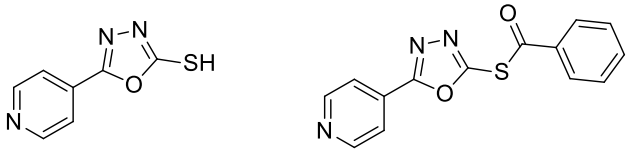
1-{5-(4-Hydroxy-phenyl)-3-[5-(1*H*-indol-3-ylmethyl)-4H-pyrazol-3-ylamino]-4,5-dihydro-pyrazol-1-yl}-ethanone (R=*p*-OHC_6H_5) **36** was synthesized [54] and tested, and also their anti-inflammatory activity with inhibition at a dose at 50 mg kg^{-1} (**Figure 25**).



36

Figure 25. Family of 1,3,4-oxadiazoles exhibiting anti-inflammatory activity

5-Pyridyl-1,3,4-oxadiazole-2-thiol **37** and *S*-benzoyl-5-(4-pyridyl)-1,3,4-oxadiazole-2-thiol [55] **38** analogs were synthesized and evaluated for anti-inflammatory activity against indomethacin as standard with 40.7 and 39.2% inhibitions, respectively (**Figure 26**).



37 38

Figure 26.

A series of 2,5-disubstituted-1,3,4-oxadiazole compounds, 5-(2,4,6-trichlorophenoxy methyl)-2-mercapto-1,3,4-oxadiazole **39**, 2,4-dichlorophenyl- 5-(2,4,6-trichlorophenoxy methyl)-1,3,4-oxadiazole **40,** and 1-(4-isobutylphenyl) ethyl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4-oxadiazole **41** were synthesized [56] and tested *in vivo* for their anti-inflammatory activity (**Figure 27**).

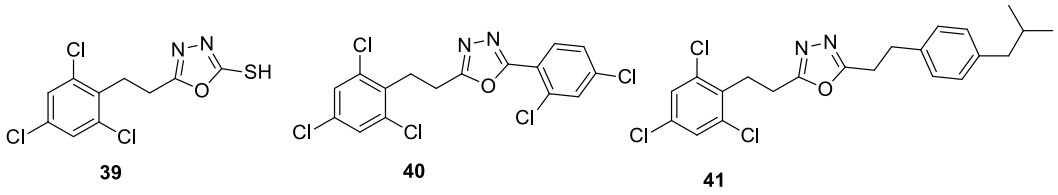


Figure 27.

3.4. Anti-tubercular activities

Aryl sulfonamido-5-[2′-(benzimidazol-2″-yl)]-1,3,4-oxadiazoles **42** and 2-benzoylamino-5-[2′-(benzimidazol-2″-yl)phenyl]-1,3,4-oxadiazoles **43** were prepared (**Figure 28**) and studied for anti-tubercular property against H37Rv in BACTEC 12B medium using BACTEC 460 radiometric system [57].

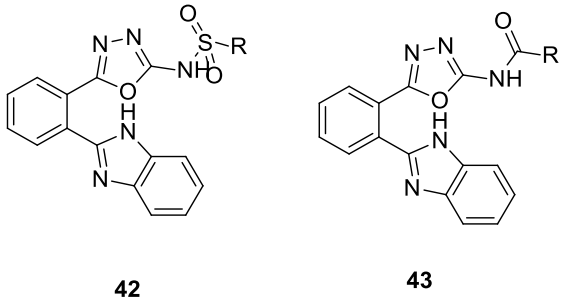


Figure 28. Family of 1,3,4-oxadiazoles exhibiting anti-tubercular activity

A new sequence of substituted sulfanyl-1-[5-substituted-1,3,4-oxadiazol-2-yl]-derivatives of 1*H*-benzimidazole **46** were created with the goal of discovering a more effective anti-inflammatory and antitubercular property. Middle brook 7H9 agar media was used to screen all of the compounds for anti-tubercular activity against the H37Rv strain. The anti-tubercular action of compounds containing R=phenyl, 2-hydroxyphenyl, and 4-aminophenyl has been found good [58] (**Figure 29**).

The novel series of 2,5-disubstituted-1,3,4-oxadiazoles **45** were produced and tested for anti-tubercular activity against the H37Rv strain using middle brook 7H9 agar media. Compounds with R with 4-aminophenyl and Ar with phenyl substituent indicated promising anti-tubercular activity (**Figure 29**).

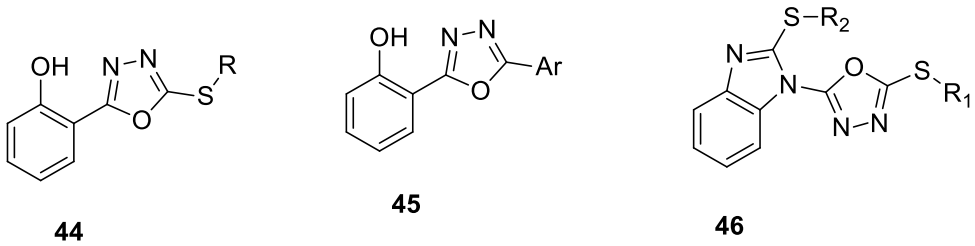
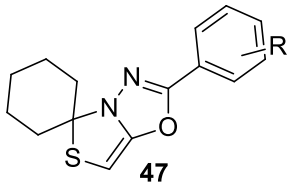


Figure 29.

3.5 Molluscicidal activities

Nizamuddin and Singh presented the preparation of 2-phenyl-spiro(cyclohexane)-1′,5-[1,3,4] oxadiazolo[3,2-c]thiazoline

analogue **47** **(Figure 30**) tested for molluscicidal activity against *Lymnaea acuminata* and found greater activity among others [59].

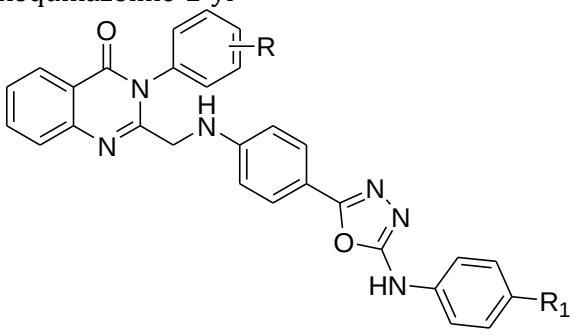


47

Figure 30. Family of 1,3,4-oxadiazoles exhibiting anti-molluscicidal activity

3.6 Hypoglycemic activities

Hussain and Jamali synthesized [60] 2-arylamino-5-[*p*-(3-aryl-4-oxoquinazoline-2-yl methyl amino)phenyl]1,3,4-oxadiazoles **48** and evaluated for hypoglycemic property (**Figure 31**).

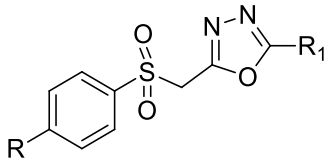


R=-OCH_3, *p*-NO_2, CH_3 R1=CH_3, OCH_3, Cl, Br

48

Figure 31. Family of 1,3,4-oxadiazoles exhibiting anti-hypoglycemic activity

5-alkyl-2-aryl sulfonamido-l,3,4-oxadiazoles **49** derivatives were synthesized and tested for hypoglycemic activity. Among that, R= *p*-amino group were found as a prerequisite for excellent hypoglycemic property (**Figure 32**).

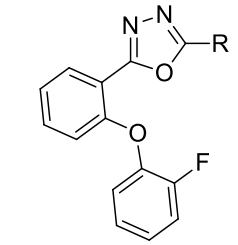


49

Figure 32.

3.7 Anticonvulsant activities

Almasirad *et al.* [61] presented the preparation of a sequence of novel 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles **50** and the evaluation of their anticonvulsant properties. In both the PTZ and the maximal electroshock seizure (MES) models, the compound containing an -NH_2 substituent at the 2nd position on oxadiazole ring exhibits the highest anticonvulsant effect (**Figure 33**). In a PTZ test, the effect was blocked by flumazenil, a benzodiazepine antagonist, indicating that benzodiazepine receptors are involved in this impact [62].

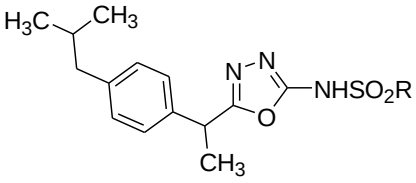


R= NH_2, SH, SCH_3, OH

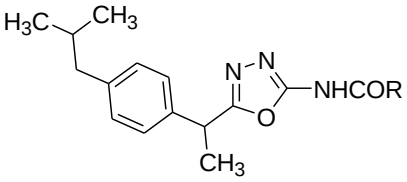
50

Figure 33. Family of 1,3,4-oxadiazoles exhibiting anti-convulsant activity

2-Arylsulphonamido-5-(α-methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles **51** and substituted benzamido-5-(α-methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles **52** were synthesized and screened for anticonvulsant property by MES and subcutaneous pentylenetetrazole (scPTZ) approaches [63].



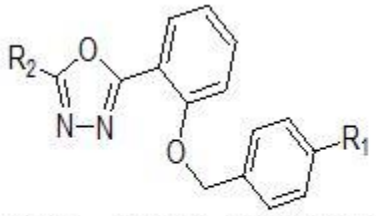
51



52

Figure 34.

The anticonvulsant property of a sequence of 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles **53** was investigated. In both the PTZ and MES designs, the molecule with an amino substituent at the 2nd position of the oxadiazole ring and a fluoro substituent at the *p*- position of the benzyloxy group exhibited encouraging results (**Figure 35**). The activity was stopped when the fluoro substituent was replaced with a bigger electron-withdrawing group, such as chlorine.

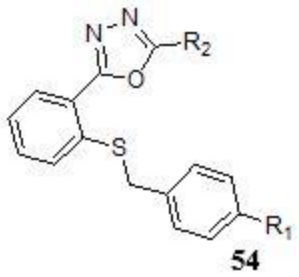


R_1: H, F, Cl R_2: NH_2, SH, SCH_3, SC_2H_5

53

Figure 35.

Anticonvulsant drugs have been devised and synthesized using a sequence of novel 2-substituted-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles **54**. The insertion of an amino group at the 2nd position of 1,3,4-oxadiazole ring and a fluoro substituent at the *p*-position of the benzylthio group provided the best anticonvulsant action in electroshock and pentylenetetrazole-induced convulsion tests [64] (**Figure 36**).

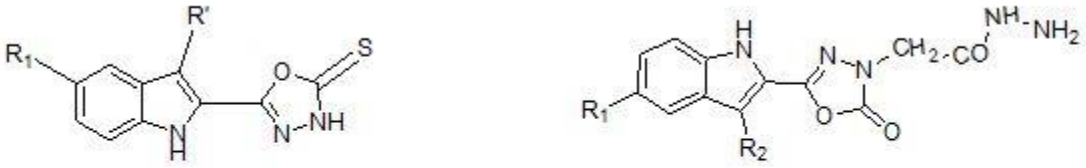


54

Figure 36.

3.8 Anti-protozoal activities

New 5-(3,5-disubstituted-1H-indol-2-yl)-1,3,4-oxadiazole-2(3H)-thione and 2-[5-(3,5-disubstituted-1H-indol-2-yl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl]acetohydrazides were synthesized and evaluated for potential anti-helmintic property on *Pheratimaposthuma* using piperazine citrate 2 mg ml^{-1} as standard. 3-Ethyl-5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazole-2(*3H*)-thione **55** and 3-benzyl-5-(5-methyl-3-phenyl-*1H*-indol-2-yl)-1,3,4-oxadiazole-2(*3H*)-thione **56** were two tested molecules with better activity among the most common compounds in this series [65] (**Figure 37**).



R_1= CH_3, Br, OCH_3 R'= Phenyl CH_3 R_1= CH_3, Br, OCH_3 R_2= Phenyl, Ethyl, CH_3

55 **56**

Figure 37. Family of 1,3,4-oxadiazoles exhibiting anti-protozoal activity

4. Conclusions

In this review, the authors successfully described the significant syntheses of 1,3,4-oxadiazole derivatives that have been published during the last decade. Oxadiazole derivatives reveal a wide range of biological activity and drug discovery programs. We believe oxadiazole research is still in the early stage, and huge potential remains unexploited in many fields, further study will open a new era of scientific development particularly novel reactions and applications in organic synthesis methodologies by creative chemists will certainly allow the access to challenging targets in an extremely efficient manner.

Acknowledgment

The authors are thankful to Acharya Nagarjuna University for constant support and encouragement.

Orcid:

Hari Babu Bollikolla
https://www.orcid.org/0000-0003-1308-391X

Ravi Varala
https://orcid.org/0000-0002-6466-9454

References

[1]. C. Ainsworth, *J. Am. Chem. Soc.*, **1965**, *87*, 5800-5801. [Crossref], [Google Scholar], [Publisher]
[2]. E.P. Nesynov, A.P. Grekov, *Russ. Chem. Rev.*, **1964**, *33*, 508-514. [Google Scholar], [Publisher]
[3]. F. Tok, M. Kaya, H. Karaca, B. Koçyiğit-Kaymakçıoğlu., *Synth. Commun.,* **2022**, *52*, 926-

935. [Crossref], [Google Scholar], [Publisher]
[4]. M. Luczynski, A. Kudelko, *Appl. Sci.*, **2022**, *12*, 3756-3775. [Crossref], [Google Scholar], [Publisher]
[5]. S. Nayak, S.L. Gaonkar, E.A. Musad, A.M.A. Dawsar, *J. Saudi Chem. Soc.*, **2021**, *25*, 101284. [Crossref], [Google Scholar], [Publisher]
[6]. K.D. Patel, S.M. Prajapati, S.N. Panchal, H.D. Patel. *Synth. Comm.*, **2014**, *44*, 1859-1875. [Crossref], [Google Scholar], [Publisher]
[7]. M.M. Alam, *Biointerface Res. Appl. Chem.*, **2022**, *12*, 5727-5744. [Crossref], [Google Scholar], [Publisher]
[8]. M. Luczynski, A. Kudelko, *Appl. Sci.*, **2022**, *12*, 3756-3774. [Crossref], [Google Scholar], [Publisher]
[9]. B. Ahmad, Z. Safeena, U.M. Ehsan, N.A. Muhammad, S.H. Syeda, A. Tashfeen, Ihsan-ul-Haq, S. Amina, M.K. Khalid, *Lett. Drug Des. Discov.*, **2018**, *15*, 1346-1355. [Crossref], [Google Scholar], [Publisher]
[10]. H. Vaghani, S. Patel, S. Patel., 1,3,4-Oxadiazole and its potency: A review, *Indian J.Pharm. Sci. Res.*, **2021**, *12*, 5292-5299. [Crossref], [Publisher]
[11]. S. Bala, S. Kamboj, A. Kajal, V. Saini, D.N. Prasad, *BioMed Res. Int.*, **2014**, *2014*, 172791. [Crossref], [Google Scholar], [Publisher]
[12]. A.I. Hameed, M.M. Alam., Carib. *J. Sci. Tech.*, **2019**, *7*, 050-057. [Crossref], [Google Scholar], [Publisher]
[13]. D. Tiwari, R. Narang, S. Lal khokra, *World J. Adv. Res. Rev.*, **2021**, *09*, 086-096 [Crossref], [Google Scholar], [Publisher]
[14]. M.N. Ahmed, B. Sadiq, N.A. Al-Masoudi, K.A. Yasin, S. Hameed, T. Mahmood, K. Ayub, M. N. Tahir, *J. Mol. Struct.*, **2018**, *1155*, 403-413. [Crossref], [Google Scholar], [Publisher]
[15]. G. Verma, G. Chashoo, A. Ali, M.F. Khan, W. Akhtar, I. Ali, M. Akhtar, M.M. Alam, M. Shaquiquzzaman, *Bioorg. Chem.*, **2018**, *77*, 106-124. [Crossref], [Google Scholar], [Publisher]
[16]. H.S. Abd-Ellah, M. Abdel-Aziz, M.E. Shoman, E.A.M. Beshr, T.S. Kaoud, A.S.F.F. Ahmed, *Bioorg. Chem.*, **2017**, *74*, 15-29. [Crossref], [Google Scholar], [Publisher]
[17]. M.A. Tantray, I. Khan, H. Hamid, M.S. Alam, A. Dhulap, A. Kalam, *Bioorg. Chem.*, **2018**, *77*, 393-401. [Crossref], [Google Scholar], [Publisher]
[18]. B. Yadagiri, S. Gurrala, R. Bantu, L. Nagarapu, S. Polepalli, G. Srujana, N. Jain, *Bioorg. Med. Chem. Lett.*, **2015**, *25*, 2220-2224. [Crossref], [Google Scholar], [Publisher]
[19]. Z. Hajimahdi, A. Zarghi, R. Zabihollahi, M. R. Aghasadeghi, *Med. Chem. Res.*, **2013**, *22*, 2467-2475. [Crossref], [Google Scholar], [Publisher]
[20]. V. Modi, P. Modi, *J. Saudi Chem. Soc.*, **2012**, *16*, 327-332. [Crossref], [Google Scholar], [Publisher]
[21]. S. Giovanni, T. Alessio, *Int. J. Mol. Sci.*, **2019**, *20*, 3483-3500. [Crossref], [Google Scholar], [Publisher]
[22]. R. Gudipati, R.N.R. Anreddy, S. Manda, *Saudi Pharm. J.*, **2011**, *19*, 153-158. [Crossref], [Google Scholar], [Publisher]
[23]. R.A. Rane, P. Bangalore, S.D. Borhade, P.K. Khandare, *Eur. J. Med. Chem.*, **2013**, *70*, 49-58. [Crossref], [Google Scholar], [Publisher]
[24]. S. Ningaiah, U.K. Bhadraiah, S.D. Doddaramappa, S. Keshavamurthy, C. Javarasetty, *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 245-248. [Crossref], [Google Scholar], [Publisher]
[25]. S. Valente, D. Trisciuoglio, T. De Luca, A. Nebbioso, D. Labella, A. Lenoci, C. Bigogno, G. Dondio, M. Miceli, G. Brosch, D. Del Bufalo, L. Altucci, A. Mai, *J. Med. Chem.*, **2014**, *57*, 6259-6265. [Crossref], [Google Scholar], [Publisher]
[26]. S.J.M. Rao, M.B. Ramana, M.M. Alam, M.S.N. Reddy, B. Hari Babu, *Indian J. Het. Chem.*, **2021**, *31*, 505-509. [Publisher]
[27]. B.R. Mutchu, S.N.R. Mule, K.M. Mannam, Bollikolla H.B., *Rasayan J. Chem,*, **2019**, *12*, 2052-2057. [Crossref], [Google Scholar], [Publisher]
[28]. B.R. Mutchu, V. Kotra, S.R. Onteddu, S.N. Boddapati, H.B. Bollikolla, *Chemistry Africa*, **2019**, *2*, 15-20. [Crossref], [Google Scholar], [Publisher]
[29]. SNR Mule, SK Battula, G Velupula, DR Guda, H.B. Bollikolla, *RSC Advances*, **2014**, *4*, 58397-58403. [Crossref], [Google Scholar], [Publisher]
[30]. M.S.N. Reddy, B.S. Kumari, B. Hari Babu, *Lett. Drug Des. Discov.*, **2012**, *9*, 942-946. [Crossref], [Google Scholar], [Publisher]
[31]. N.R. Rivera, J. Balsells, K.B. Hansen, *Tetrahedron Lett.*, **2006**, *47*, 4889-4891. [Crossref], [Google Scholar], [Publisher]
[32]. M. Koparir, A. Çetin, A. Cansiz,. *Molecules*, **2005**, *10*, 475-480. [Crossref], [Google Scholar], [Publisher]

[33]. W.A. El-Sayed, O.M. Ali, H.A. Hendy, A.A. Abdel-Rahman, *Chinese J. Chem.*, **2020**, *30*, 77-83. [Crossref], [Google Scholar], [Publisher]
[34]. K.K. Jha, A. Samad, Y. Kumar, M. Shaharyar, R. L. Khosa, J. Jain, V. Kumar, P. Singh, *Eur. J. Med. Chem.*, **2010**, *45*, 4963-4967. [Crossref], [Google Scholar], [Publisher]
[35]. S. Guin, T. Ghosh, S.K. Rout, A. Banerjee, B. K. Patel, *Org. Lett.*, **2011**, *13*, 5976-5979. [Crossref], [Google Scholar], [Publisher]
[36]. S.L. Gaonkar, I. Nagashima, H. Shimizu, *Org. Chem. Int.*, 2012, ***2011***, 1-5. [Crossref], [Google Scholar], [Publisher]
[37]. W. Yu, G. Huang, Y. Zhang, H. Liu, L. Dong, X. Yu, Y. Li, J. Chang, *J. Org. Chem.*, **2013**, *78*, 10337-10343. [Crossref], [Google Scholar], [Publisher]
[38]. P. Niu, J. Kang, X. Tian, L. Song, H. Liu, J. Wu, W. Yu, J. Chang, *J. Org. Chem.,* **2014**, *80*, 1018-1024. [Crossref], [Google Scholar], [Publisher]
[39]. R. Kapoorr, S.N. Singh, S. Tripathi, L.D.S. Yadav, *Synth. Lett.*, **2015**, *26*, 1201-1206. [Crossref], [Google Scholar], [Publisher]
[40]. T. Fang, Q. Tan, Z. Ding, B. Liu, B. Xu, *Org. Lett.*, **2014**, *16*, 2342-2345. [Crossref], [Google Scholar], [Publisher]
[41]. S.H. Mashraqui, S.G. Ghadigaonkar, R.S. Kenny, R.S., *Synth. Commun*., **2003**, *33*, 2541-2545. [Crossref], [Google Scholar], [Publisher]
[42]. S.J. Dolman, F. Gosselin, P.D. O'Shea, I.W. Davies, *J. Org. Chem.*, **2006**, *71*, 9548-9551. [Crossref], [Google Scholar], [Publisher]
[43]. A. Ramazani, A. Rezaei, *Org. Lett.*, **2010**, *12*, 2852-2855. [Crossref], [Google Scholar], [Publisher]
[44]. C.T. Brain, J.M. Paul, Y. Loong, P.J. Oakley, *Tetrahedron Lett.*, **1999**, *40*, 3275-3278. [Crossref], [Google Scholar], [Publisher]
[45]. X.P. Hui, C.H. Chu, Z.Y. Zhang, Q. Wang, Q. Zhang, *Indian J. Chem.*, **2002**, *41B*, 2176-2179. [Crossref], [Google Scholar], [Publisher]
[46]. V.V. Mulwad, A.C. Chaskar, *Indian J. Chem.*, **2006**, *45B*, 1710-1715. [Google Scholar], [Publisher]
[47]. K.S. Bhat, M.S. Karthikeyan, B.S. Holla, N.S. Shetty, *Indian J. Chem.*, **2004**, *43B*, 1765-1769. [Google Scholar], [Publisher]
[48]. S. Salahuddin, A. Mazumder, M. Shahar Yar, *Med. Chem. Res.*, **2015**, *24*, 2514-2528. [Crossref], [Google Scholar], [Publisher]
[49]. Shamsuzzaman, T. Siddiqui, M.G. Alam, A.M. Dar, *J. Saudi Chem. Soc.*, **2015**, *19*, 387-391. [Crossref], [Google Scholar], [Publisher]
[50]. B.S. Holla, K.N. Poojary, K.S. Bhat, M. Ashok, B. Poojary, *Indian J. Chem.*, **2005**, *44B*, 1669-1673. [Google Scholar], [Publisher]
[51]. F.A.F. Ragab, S.M. Abou-Seri, S.A. Abdel-Aziz, A.M. Alfayomy, M. Aboelmagd, *Eur. J. Med. Chem.*, **2017**, *138*, 140-151. [Crossref], [Google Scholar], [Publisher]
[52]. S. Sharma, V.K. Srivastava, A. Kumar, *Indian J. Chem.*, **2002**, *41B*, 2647-2654. [Google Scholar], [Publisher]
[53]. A. Kapoor, N. Dhiman, *Der Pharm. Lett.*, **2016**, *8*,149-156. [Google Scholar], [Publisher]
[54]. M.Y.S. Khan, G. Chawla, M.A. Mueed, *Indian J. Chem.*, **2004**, 43B, 1302-1305. [Google Scholar], [Publisher]
[55]. M. Amir, S.A. Javed, H. Kumar, *Indian J. Chem.*, **2007**, *46B*, 1014-1019. [Google Scholar], [Publisher]
[56]. P.R. Kagthara, N.S. Shah, R.K. Doshi, H.H. Parekh, , *Indian J. Chem.*, **1999**, *38B*, 572-576. [Google Scholar], [Publisher]
[57]. N.S. Dighe, R.B. Saudagar, D.A. Jain, *Int. J. Pharma Bio. Sci.*, **2013**, *4*, 484-496. [Publisher]
[58]. S.R. Pattan, P.A. Rabara, J.S. Pattan, A.A. Bukitagar, V.S. Wakale, D.S. Musmade, *Indian J. Chem.*, **2009**, *48B*, 1453-1456. [Google Scholar], [Publisher]
[59]. A. Singh, *Indian J. Chem.*, **2004**, *43B*, 901-905. [Google Scholar], [Publisher]
[60]. M.I. Husain, M.R. Jamali, *Indian J. Chem.*, **1988**, *27B*, 43-47.
[61]. A. Almasirad, S.A. Tabatabai, M. Faizi, A. Kebriaeezadeh, N. Mehrabi, A. Dalvandi, A. Shafiee, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 6057-6059. [Crossref], [Google Scholar], [Publisher]
[62]. K. Ladva, P. Patel, P. Upadhyay, H. Parekh, *Indian J. Chem*., **1996**, *35B*, 1062-1066. [Google Scholar], [Publisher]
[63]. Z. Afshin, S.A. Tabtabai, M. Faizi, A. Ahadian, P. Navabi, V. Zanganeh, A. Shafiee, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 1863-1865. [Crossref], [Google Scholar], [Publisher]
[64]. H. Rajak, B.S. Thakur, A. Singh, K. Raghuvanshi, A.K. Sah, R. Veerasamy, P.C. Sharma, R. Pawar, M.D. Kharya, *Bioorg. Med. Chem. Lett.*, **2013**, *23*, 864-868. [Crossref], [Google Scholar], [Publisher]
[65]. R. Patil, J.S. Biradar, *Indian J. Chem*., **1999**, *38B*, 76-82. [Google Scholar], [Publisher]

Baby Ramana M:, She completed her M.Sc. in Organic Chemistry Specialization in the year 2011 through Andhra University and joined in Acharya Nagarjuna University to pursue her M.Phil. and completed it successfully in 2016. Later, she continued her research leading to Ph.D. and succeeded in 2019. Her research interests are developing novel methodologies for the construction of biologically important Synthetic Organic compounds. She published around 12 papers in reputed journals.

Mothilal M: He pursued his M.Sc from Loyola College, Chennai, India in 2021 after completion of his B.Sc. with distinction in the year 2019. He had done his internship program on "Various synthetic approaches for 1,3,4-oxadiazole derivatives and its biological activities" in Csir-Neist, Jorhat, Assam, under the guidance of Dr. B. Hari Babu, Associate professor in the department of Chemistry, of Archarya Nagarjuna University, Guntur, A.P.-India. He also did a project in M.Sc. relating to synthesis and spectral characterization of some heterocyclic compounds and their molecular docking studies under the guidance of Dr. John Maria Xavier, Assistant, professor in the department of chemistry, Loyola college, Chennai, India.

Maheswara Rao G: He completed his M.Sc. in 2006 from Acharya Nagarjuna University, AP-India and Ph.D. from Csir-Neist, Hyderabad. His postdoctoral from Prof. Hunter, University of Cape Town, South Africa. He is having over all 16 year research experience. His research interests centre on the new methodology development of heterocyclic compounds and total synthesis of natural products and their application biology and medicinal chemistry field. He has more than 50 publications in reputed journals.

Mannam Krishna Murthy: He is now working as Director A N University Research Center at SVRM College, Nagaram, Andhra Pradesh. He has about 40 years of teaching experience; worked as a faculty of University P.G. Center, Nuzvid and Executive Dean of 'Varsity Education Management Limited', Hyderabad. He is Secretary, South Zone of Association of Chemistry Teachers (ACT, Mumbai). He has about hundred research publications to his credit. He is author/editor of about 30 books and book chapters.

Ravi Varala: He pursued his Ph.D. from Csir-Neist, India during 2000-2006 and went on postdoctoral research in Portugal during 2007-2009. From 2010 to till date, he had gained vast experience in both academic and research fields. During 2015-2016, he was '*Invited Researcher'* (Visiting Scientist) to University of Sao Paulo, Brazil. He has got 90 published research articles of international and national repute. Attended or participated in more than 130 national and international conferences. He has published two books, seven book chapters and ten reviews/perspectives, up to date. He has research collaborations with KSA and Malaysia. Presently, he is working as Scientist in Scrips Pharma, Hyderabad. His fields of research interests are: organic synthesis and catalysis.

Hari Babu Bollikolla: He completed his Ph.D. from Acharya Nagarjuna University, AP-India in 2006 and currently working as an Associate Professor in the Dept. of Chemistry. He also working as HOD, Dept. of Nanotechnology. He has 18 years of research experience and 19 years of teaching experience. His main research areas are Synthetic organic chemistry and Chemical Biology. He published around 170 articles in various national and international journals and published three Patents. He received Andhra Pradesh State Best Teacher Award in 2019. He also nominated as Associate Fellow of Andhara Pradesh Akademi of Sciences. 34 Ph.D's and 12-M.Phills were awarded under his esteemed guidance.