Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2021, 13(12): 1-7
(http://www.derpharmachemica.com/archive.html)

Review Article on Substituted 1,3,4-Oxadiazole Derivatives and their Biological Activities

Sachin Vishnu Patil[1]*, Seema Kashinath Bhagwat[1], Manjusha Balkrishna Suryavanshi[1], Deepak Raghorao Nagergoje[2]

[1]*Department of Chemistry, Savitribai Phule Pune University, Research Institute, H. P. T. Arts and R. Y. K. Science College, Nashik, 422005, India*
[2]*Department of Chemistry, Arts, Science and Commerce College, Mokhada, Maharastra*

***Corresponding author:** Sachin Vishnu Patil, Department of Chemistry, Savitribai Phule Pune University, Research Institute, H. P. T. Arts and R. Y. K. Science College, Nashik, 422005, India, E-mail: sachin.dhokare@yahoo.com*

ABSTRACT

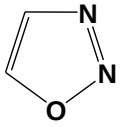
Amongst well known heterocycles 1,3,4-oxadiazole are of great interest due to their versatile biological activities such as antimicrobial, anti-tumor, ant-inflammatory, anti-convulsant, anti-oxidant, antimalarial etc. This wide range of important applications have attracted researchers for development and study of new heterocyclic compounds containing 1,3,4-oxadiazole. In this review article we have tried to summarize some of the important and major research acknowledged for different biological activities shown by 1,3,4-oxadiazole derivatives. This article will helpful to develop new molecule containing 1,3,4-oxadiazole derivatives which could play key to cure different diseases and act as leading drug molecule.

Keywords: 1,3,4-Oxadiazole; Biological activities; Antimicrobial; Anti-tumor; Anti-inflammatory; Anti-convulsant; anti-oxidant; Anti-oxidant

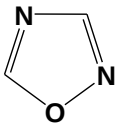
INTRODUCTION

Heterocyclic compounds have supported in the progress of society because of their importance. Our day to day life style is improved because of large numbers of heterocyclic compounds and hence now day's large efforts are given in designing and developing new compounds and study their different applications for human being.

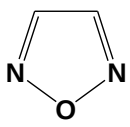
Amongst different heterocyclic molecules, five membered ring with two nitrogen and one oxygen called oxadiazole are important class of aromatic heterocyclic compounds. These are resulting from furan by the addition of two methene (-CH=) groups by two pyridine type nitrogens (-N=). 1,3,4-oxadiazoles (Figure 1) are originate to be biologically most effective out of the four types of oxadiazoles namely: 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,2,3–oxadiazoles (Figure 1).



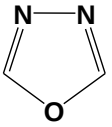
1, 2, 3-oxadiazole



1, 2, 4-oxadiazole



1, 2, 5-oxadiazole



1, 3, 4-oxadiazole

Figure 1: Types of oxadiazoles

1,3,4-oxadiazole conquers distinctive place in the pharmaceutical fieldbecause oftheir different biological activities which are summarized as follows.

RESULTS AND DISCUSSION

Biological activities of 1,3,4-oxadiazole derivatives

In heterocyclic compounds 1,3,4-oxadiazole is one of the mainpart found in many biologically active drugs such as raltagravir an integrase inhibitor,antibacterial furamizole,PDF inhibitorBB-83698, zibotentan an anticancer agent,antihypertensive agent tiozosin nesapidil,furamizole which act as antibiotic agent are based on 1,3,4-oxadiazole moiety.

1,3,4 -oxadiazole also shows low lipophilicity in drug development and because of which it is used as carbonyl bioisostere.1,3,4-oxadiazole is an important class in heterocyclic chemistry and shows a key model in medicinal chemistry due to its potent bioactivities such as anti-HIV, analgesic,anti-inflammatory,anti-cancer,antimalarial,antimicrobial and anti-tuberculosis activity (Figure 2).

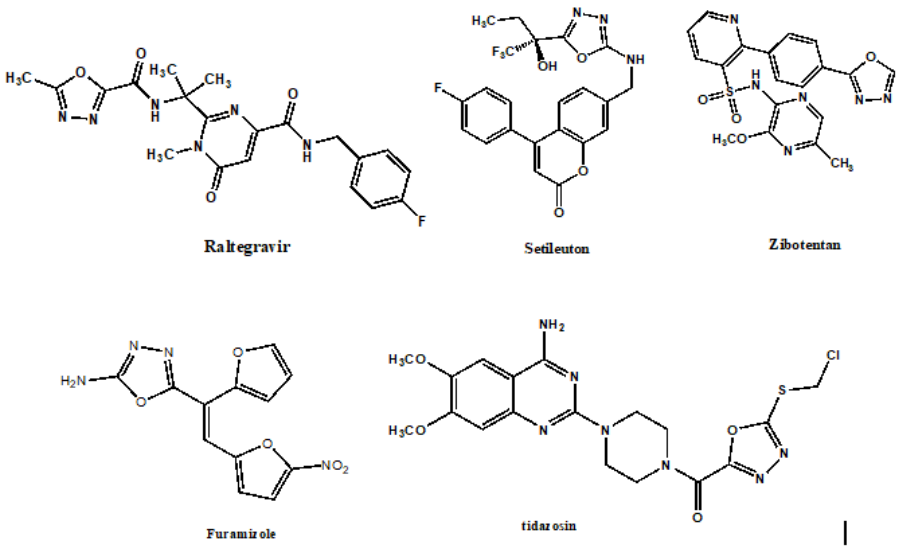


Figure 2: 1,3,4-oxadiazole derivatives

Antimicrobial activity

New compound synthesized by Unnikrishnan et al [1] which contain π conjugated polymer linkage were evaluatedfor antimicrobial activities. Compound [1] found to show good antimicrobial activity against staphylococcus and E.coli bacteria.

Different 2,5,-disubstituted-1,3,4-oxadiazoles were reported by Poojary et al [2] and found that compound (2) and (3)exhibited pronounced antimicrobial and antibacterial activity against gram positive and gram negative bacteria using amoxicillin and streptomycin as a reference standard drug.Theoretical study like molecular docking for synthesized compounds also showed good binding properties. (5-substituted -1,3,4-oxadiazole -2-yl)-1-(4-methoxyphenyl)butan-2-one derivatives were synthesized and tested for biologicalactivities by Suman bala et al [3] and it was notice that compound [4]displayed potential antibacterial activity against bacterial strain. Compound (5) with p-chloro and (6) with m-methoxy and p-hydroxy substituent showed best activity (Figure 3).

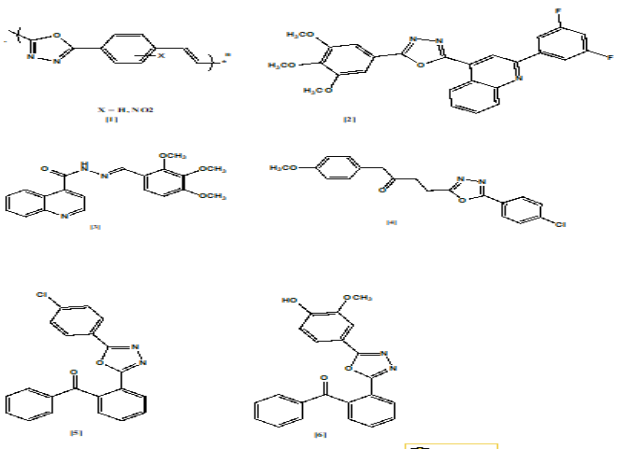


Figure 3: 2,5,-disubstituted-1,3,4-oxadiazoles

A set of 2-5 substituted 1,3,4-oxadiazole derivatives were reported by Kikkeri et al [4] and verified for antimicrobial and antifungal activities using standard drug nystatin. Compound (7) and (8) showed significant activity as compared with the standard drug bacteriomycin and gentamycin. The compound with methoxy group as electron donating group (7) showed significant antimicrobial activity. It was noted that electron withdrawing group like fluorine also enhanced antimicrobial activity.

Kaur et al [5] presented thiophene containing 1,3,4-oxadiazole and encountered for their antimicrobial activity. The combination of thiophene and oxadiazole ring boosted the antimicrobial activity. The compound (9) showed potent inhibitory potential with MIC ranging from 2-7µg/ml. Parikhet al [6] synthesized new compounds containing triazole and oxadiazole. The compound (10) was found to shown noteworthy antibacterial activity against p. aeruginosa and compound (11) showed highest antifungal activity against c. albicans. A new series of 1,3,4-oxadiazole derivatives bearing dibenzosuberane were described by Manjunath et al [7] and all were evaluated for antibacterial and antifungal activity. The results revealed that fluoro group on phenyl at para position attached to 1,3,4- oxadiazole rises the antibacterial and antifungal activity of compound. It was found compound (12) between all reported compounds showed highest antibacterial activity using standard drug nitrofurazone.

A new series of 1,3,4- oxadiazole derivatives and were evaluated for in vitro antibacterial activity against gram positive and gram negative bacteria by Chikhalia et al [8]. They found that the electron withdrawing substituent raises the activity as compared to electron donating groups. Five compounds from the series displayed significant in vitro antimicrobial activity. Compound (13) and (14) exhibits excellent activity which is close to standard fluconazole.

Bobade et al [9] reported a thiosubstituted oxadiazole derivative with coumarin and biological evaluation report showed that fluoro group enhanced antibacterial and antifungal activity while electron donating group decreased antimicrobial activities and compound (15) showed significant activity (Figure 4).

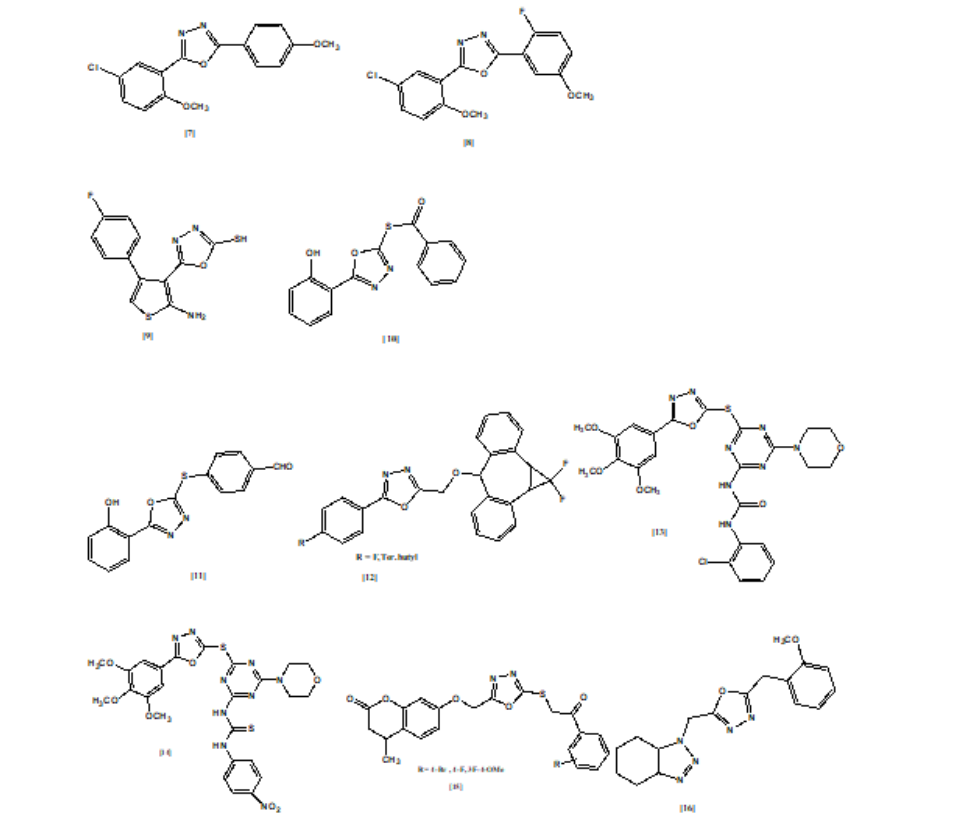


Figure 4: Oxadiazole derivatives

Antitumor activity

A sequences of 2,5-substituted 1,3,4-oxadiazole derivatives were presented by Hai-liang zhu et al [10] and were tested for their antitumor activity. Between all synthesized compounds, potential antitumor activity against MCF-7 cells was shown by (16). Other compounds also displayed the good antitumor activity against HeLa cells in comparison to the activity of cis platin.

Aboraia et al [11] presented a set of 1,3,4-oxadiazole derivatives of mannich base of salicylate containing thione and estimated for anticancer activity. Seven compounds displayed potent in-vitro anticancer activity against human cancer cell. Compound (17) and (18) showed the maximum anticancer activity as compared to standard drug 5-fluoraciland cyclophosphamide. Gudipati et al [12] synthesized isatin derivatives containing 1,3,4-oxadiazoleand screened them for biological activity. The compound (19) which has electron withdrawing substituent at C5 position showed the highest activity against all cancer cell lines. A set of 2,5-disubstituted -1,3,4-oxadiazole were presented by Pidugu et al [13] and encountered them for biological activity. It was found that compound (20) showed promising anticancer activity to vorinostat (SAHA) and substantial HDAC8 inhibitory activity. Slawinski et al [14] presented a set of benzene sulfonamide with1,3,4-oxadiazole and all were evaluated for anticancer activity. It

was found that presence of styryl group at 5 position of 1,3,4-oxadiazole showed highest anticancer activity against HCT-116, MCF-7 and HeLacancer cell lines. It was also noted that compound (21) showed highest anticancer activity. Some new carboxy methyl derivatives of 1,3,4-oxadiazole -2-thiones were designed and developed by Sengupta et al [15] and noticed that the compounds showed good anticancer activity. It was further notified that compound (22) showed highest cancerous cell growth inhibition activity.

Rubina et al [16] reported a batch of new benzthiazolyl 1,3,4-oxadiazole derivatives and screened them for their oral anti-hyperglycemic activity and noticed that compound (23), (24) and (25) showed better activity comparable to the reference drug glibenclamide. Presence of group with electron withdrawing effect (Cl) enhanced antidiabetic action as showed by compound (23) and (25). A new 1,3,4-oxadizole bearing 1,2,4-oxadizole were presented by Polothi et al [17] and verified for anticancer activity against human cancer cell. Between all synthesized compounds, compound (26) displayed potential anticancer activity compared to doxorubicin as a standard drug (Figure 5).

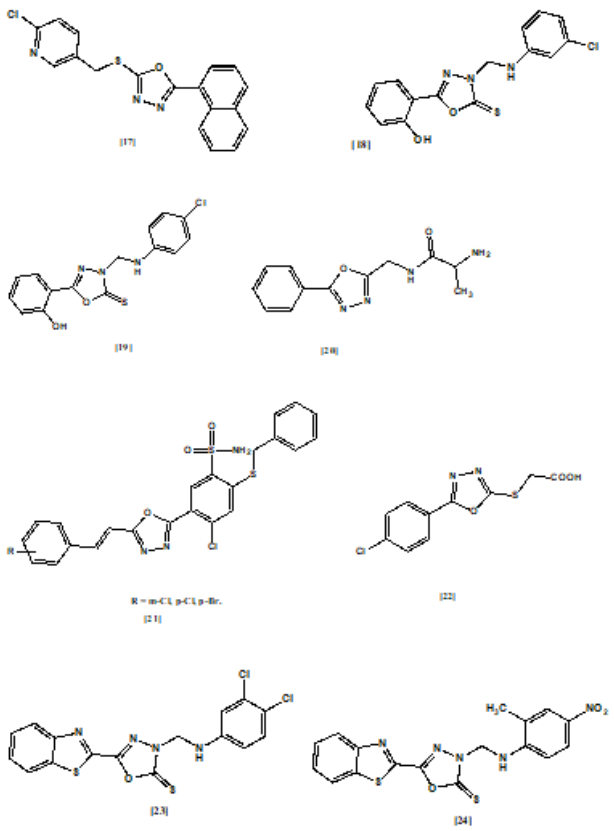
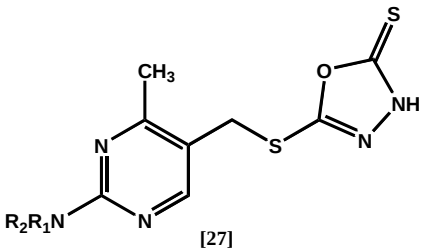


Figure 5: New benzthiazolyl 1,3,4-oxadiazole derivatives

Anti-inflammatory activity

A series of 1,3,4-oxdiazole-2-thione derivatives were exposed by Burbulience et al [18] and evaluated for anti-inflammatory activity and observed that compound (27) exhibits a potent activity compared to the ibuprofen as a standard reference (Figure 6).



[27]

Figure 6: 1,3,4-oxdiazole-2-thione derivatives

Dhansay et al [19] synthesized new pyridine containing 1,3,4-oxadiazole in which pyridine is at 5-possition.All the newly derived compounds were tested for anti-inflammatory activity. The compound (28) shown promising activity compared with Indomethacin as a standard drug.Gaonkar et al [20] reported a set of 2-{4-[2-(5-ethylpyridin-2-yl) ethoxy]phenyl}- 5-substituted-1,3,4-oxadiazoles derivatives from which compound (29) containing chlorine atom showed enhanced anti-inflammatory activity. Chawla et al [21] synthesized and evaluated a series of 1,3,4-oxadiazole derivatives and displayed their in vivo anti-inflammatory activity. The results showed that compound (30) with unsubstituted aryl ring showed less anti-inflammatory activity than the halogen substituted aryl ring. It was further noticed that compound (31) with fluorine group on aryl ring displayed highest anti-inflammatory activity. A new series of schiffs bases of diclofenac acid and S-substituted 1,3,4-oxadiazole derivatives were displayed by Bhandari et al [22] and found that most of the compounds exhibited noteworthy anti-inflammatory activity. It was observed that

compound (32) amongst all synthesized compounds showed promising anti- inflammatory activity compared to reference drug diclofenac (Figure 7).

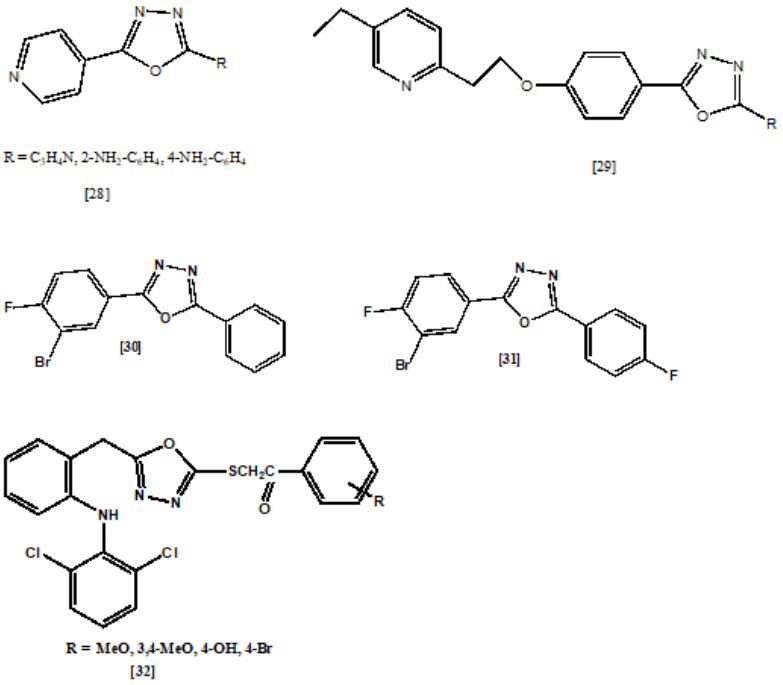


Figure 7: New pyridine containing 1,3,4-oxadiazole

Anticonvulsant activity

A set of new 2-5 substituted 1,3,4-oxadiazole was produced and reported for anticonvulsant activity by Zarghi et al [23] and it was noted that the fluoro and amino group present on benzylthio and oxadiazole respectively enhanced the activity. It was further revealed that the compound (33) showed the potent anticonvulsant activity. A compound with Phthalamide attached with 1,3,4-oxadiazole were synthesized by Bhat et al [24] and were screened for anticonvulsant and neurotoxicity studies. They found that the group with electron donating effect enhanced the activity of compounds. Between all synthesized compounds, the compound with methoxy substituent on aryl group [34] showed the significant anticonvulsant activity with low neurotoxicity. Shahzad et al [25] synthesized 1,3,4-oxadiazolyl 2-thione derivatives and tested for their antitumor activity and the compound (35) showed significant antitumor activity (Figure 8).

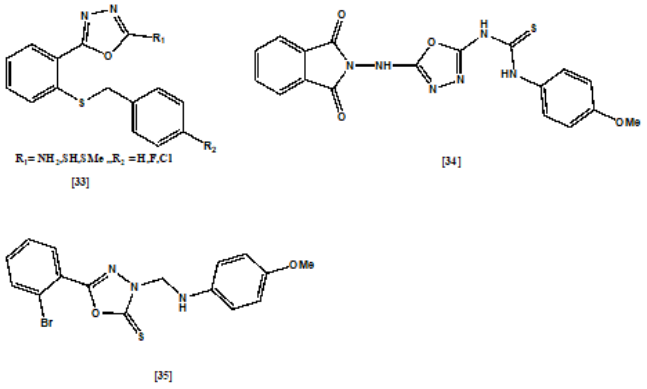


Figure 8: New 2-5 substituted 1,3,4-oxadiazoles

Antioxidant activity

A new set of 2-N-phenylpiperazino-5-mercapto-1,3,4-oxadiazole derivatives was derived by Bharatiya et al [26] through one pot method and evaluated for antioxidant activity. Between all synthesized molecules compound [36] showed the significant antioxidant activity. Abdelmonemet al [27] synthesized and evaluated the pyrazolyl oxadiazole derivative for their antioxidant activity and noticed that among the reported derivatives the compound (37) showed potent antioxidant activity (Figure 9).

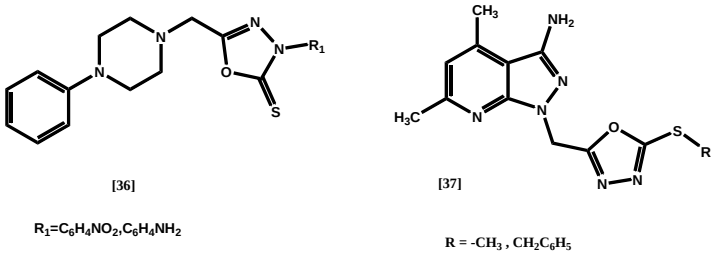


Figure 9: 2-N-phenylpiperazino-5-mercapto-1,3,4-oxadiazole

Antimalerial activity

Thakkar et al [28] reported set of substituted 1,3,4-oxadiazole derivatives with mercapto group. Evaluation of the synthesized compounds were done for genotoxicity studies against s.pombe cells and also for their in vitro antimalerial activity. The compound (38) showed significant antimalerial activity against plasmodium falciparum strain (Figure 10).

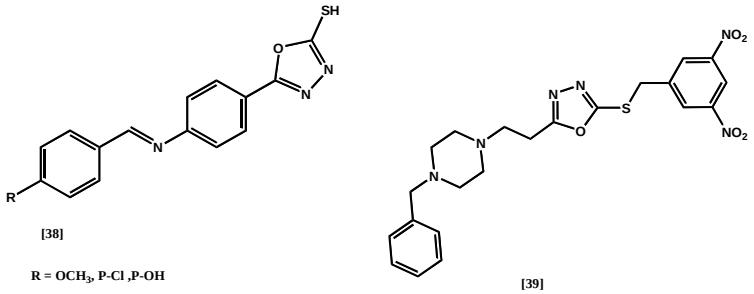


Figure 10: Substituted 1,3,4-oxadiazole derivatives with mercapto group

A series of N-benzylpiperazine–substituted 1,3,4-oxadiazole derivatives were presented byJ.Roh et al [29] and are evaluated for biological activities. The compounds (39), (40) and (41) showed highest activity against the M.tb. strain compared to the anti-TB drug INH. The compound (41) showed the highest activity against mycobacterial strains higher than INH (Figure 11).

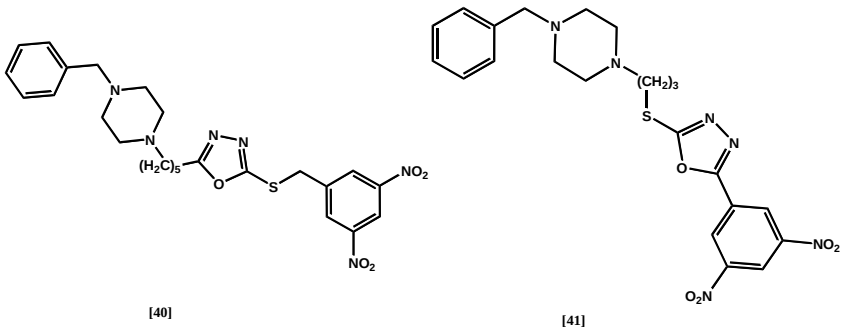


Figure 11: N-benzylpiperazine–substituted 1,3,4-oxadiazole derivatives

CONCLUSION

From all above literature it is crystal clear that 1,3,4-oxadiazole derivatives are the main key in deciding the role of drug molecule. On the basis of all above literature survey we came to the statement that compounds containing 1,3,4-oxadiazole heterocyclic nuclei is versatile and it is the molecule with multifunction's and retain therapeutic effects such as antimicrobial activity, antitumor activity, anti-inflammatory activity, anticonvulsant activity, antioxidant activity and antimalarial activity etc. From all above information it can be concluded that a new heterocyclic molecule containing 1,3,4-oxadiazole could be promising heterocyclic nuclei in the effective drug design which could be leading drug molecule in the dictionary of pharmaceutical medicines.

ACKNOWLEDGEMENT

The authors thank to the Department of Chemistry, HPT Arts and RYK Science College, Nashik for a kind support.

REFERENCES

[1] Kaippamangalath N and Gopalakrishnapanicker U. wiley online library Polym int, **2016**. 65: p. 1221-1231.
[2] Bharadwaj SS, Poojary B, Kumar SM et al., New J chem, **2017**, 41: p. 8568-8585.

[3] Bala S, Kamboj S, Kajal A et al., BioMed Research International, **2014**. p. 1-18.
[4] Basavapatna NPK, Kikkeri NM, Lingappa M et al., Int J Med Chem. **2013**, p. 1-6.
[5] Singla N, Singh G, Bhatia R et al., Wiley online library, chemistry select. **2020**, 5: p. 3835-3848.
[6] Parikh PK, Marvaniya HM and Sen DJ. Int J Drug Dev and Res, **2011**, 3(2): p. 248-255.
[7] Moger M, Satam V, Govindaraju DRC et al., J Brazillian Chemical Society. **2014**, 25(1): p. 104-111.
[8] Chikhalia KH, Vashi DB and Patel MJ. J Enzyme Inhib Med Chem. **2009**, 24(3): p. 617-622.
[9] Bobade VD, Patil SV, Gaikwad ND. J Chemical Research. **2012**, p. 25-28.
[10] Yin Luo, Zhi-Jun Liu, Guo Chen et al., Med Chem Comm. **2016**, 7: p. 263-271.
[11] Aboraia AS, Rahman HM, Mahfouz NM et al., Bioorg Med Chem. **2006**. 14(4): p. 1236-46.
[12] Gudipati R, Anreddy RNR, Manda S. Saudi Pharm J, 2011. 19(3): p. 153–158.
[13] Pidugu VR, Yarla NS, Pedada SR et al., Bioorg Med Chem. **2016**, 24(21): p. 5611–5617.
[14] Slawinski J, Szafranski K, Pogorzelsk A et al., Eur J Med Chem, **2017**, 132: p. 236-248.
[15] Sengupta P, Dash DK, Yeligar VC et al., Indian J Chem. **2008**, 47B: p. 460-462.
[16] Bhutani R, Pathak DP, Kapoor G et al., Bioorganic chemistry. **2018**, 77: p. 6-15.
[17] Polothi R, Raoji GSB, Kuchibhotla VS et al., Synthetic communication, **2019**, 49(13): p. 1603-1612.
[18] Burburlience MM, Jakubkiene U, Mekuskiene G et al., IL farmaco. **2004**, 59: p. 767-774.
[19] Dewangan D, Panday A, Sivakumar T et al., Int J Chem Tech Res. **2010**, 2(3): p. 1397-1412.
[20] Gaonkar SL, Rai KML, Prabhuswamy B. Eur J Med Chem. **2006**, 41: p. 841-846.
[21] Chawla G, Kumar U, Bawa S et al., J Enz. Inhibition and med chem. **2012**, 27(5): p. 658-665.
[22] Bhandari SV, Bothara KG, Raut MK et al., Bioorg Med Chem. **2008**, 16: p. 1822-1831.
[23] Zarghi A, Faizi M, Shafaghi B et al., Bioorg Med Chem Lett. **2005**, 15: p. 3126-3129.
[24] Bhatt MA, Al-omar NA and Siddiqui N. Pharma Chem. **2010**, 2: p.1-10.
[25] Shahzad SA, Yar M, Bajda M et al., Bioorg Med Chem. **2014**, 22(3): p.1008-1015.
[26] Bharatiya N and Gharu CP. Indian J Appl Res. **2014**, 4: p. 88-90.
[27] Abdelmonem YK, EI-Essaway FA, EI-Enein SAA et al., Int J Org Chem. **2013**, 3: p. 198-205.
[28] Thakkar SS, Thakor P, Doshi H, et al., Bioorg Med Chem. **2017**, 25: p. 4064-4075.
[29] Roh J, Karabanovich G, Vlckova H et al., Bioorg Med Chem., **2017**, 25: p. 5468-5476.