Review Article

A Comprehensive Review on 1,3,4-oxadiazole Derivatives

Mamta Soreng*, Lata Khani Bisht, D Visagaperumal, Vineeth Chandy
Department of Pharmaceutical Chemistry, T.John College of Pharmacy, Gottigere, Bannerghatta road, Bangalore 560083, India.
***Corresponding author's E-mail:** mamtasorengranchi@gmail.com

Received: 15-09-2019; **Revised:** 28-10-2019; **Accepted:** 05-11-2019.

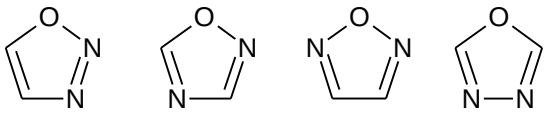
ABSTRACT

Furadiazole or 1,3,4-oxadiazole is a five membered heterocylic nucleus and it is derived from the furan ring by replacement of two methane group (-CH=) by pyridine type nitrogen. 1,3,4-oxadiazole derivatives have a number of biological activities like antibacterial, antifungal, anti-inflammatory, anti-cancer, genotoxic, hypolipidemic, cytotoxic, ulcerogenic activities etc. Antimicrobial agents are clinically useful agents against significant species of bacteria which is having global problem. In this review we have collected information about the 1,3,4-oxadiazole nucleus and its antimicrobial activity for further research and development. Oxadiazoles are formed by cyclization of diacylhydrazines which is influenced by the different reaction conditions maintained.

Keywords: Oxadiazole, antimicrobial activity, antimicrobial agents.

INTRODUCTION

Oxadiazoles form an important class of heterocyclic aromatic compounds of azole family with extensive medicinal properties.



(1) (2) (3) (4)

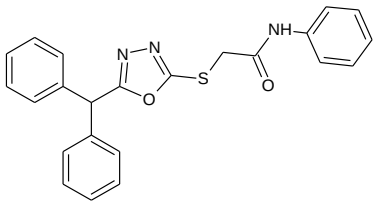
It can exist in four isomeric forms i.e, 1,2,3-oxadiazole (1), 1,2,4-oxadiazole (2), 1,2,5-oxadiazole (3) and 1,3,4-oxadiazole (4).

The isomers 1,2 and 3 are unstable and ring opening reaction occurs to form diazoketone tautomer.[1] It is similar to furan and formed by replacing by two pyridine type nitrogen(-N=). This will reduce the aromaticity of oxadiazole ring, and make it a weak base due to inductive effect of extra heteroatom. Oxadiazole ring is seen in different variations of pharmaceutical medicines like butalamine, oxolamine, raltegravir, pleconaril and fasiplon.[2] Electrophillic substitution reaction in oxadiazole ring is very difficult to perform at carbon position due to the low density of electrons on carbon atom which can be allocated to the electron withdrawal effect of pyridine type nitrogen. The 1,3,4-oxadiazole undergoes electrophilic substitution reactions on electron rich nitrogen. It improves reactivity if the oxadiazole ring is substituted with electron-releasing groups. Halogen-substituted oxadiazoles undergo nucleophilic substitution reaction with replacement of halogen by nucleophiles.[3] The 1,3,4-oxadiazole moiety possesses good pharmacokinetic properties due to presence of –N=C-O- group which increases its lipophilicity and thus capacity to reach the target. Moreover 2,5-disubstituted 1,3,4-oxadiazoles are also found to exhibit better structure for the antimicrobial and antifungal properties compared to the standard drugs.

Antimicrobial Activity

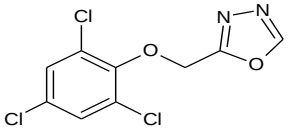
1,3,4-oxadiazole derivatives have been investigated for antibacterial, antioxidant, anticonsvlsant, analgesic, anti-inflammatory, antiemetic, antimicrobial, antifungal and host of other biological activities. Oxadiazole derivatives possess broad spectrum antimicrobial activity. A number of methods have been reported for synthesis of 1,3,4-oxadiazoles. The most common method is reaction between acid hydrazides (or hydrazine) with acid chlorides (or carboxylic acids) followed by direct cyclization of diacylhyrazines using a variety of dehydrating agents like phosphorus oxychloride[4], Thionyl chloride[5], Phosphorus pentoxide[6],

Mohd Amir *et al* (2011), synthesized a series of 2-[(5-diphenylmethyl-1,3,4-oxadiazoles-2-yl) sulfanyl-N-(substituted phenyl)-acetamides as antiinflamatory agents using paw edema model in wister rats. Halogen substituted derivatives in aryl ring showed significant anti-inflammatory activity.



(5)

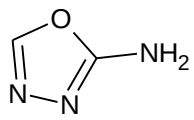
In the year 2007, he synthesized derivatives of 2-substituted aryl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4-oxadiazole for anti-inflammatory and ulcerogenecity using pylorus ligation method.[7]



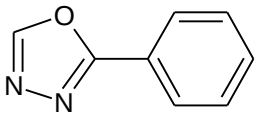
(6)

Mudasir R Bandy *et al* (2010) was successful in synthesizing 5-(alkenyl)-2-amino-1,3,4-oxadiazoles and 2-(alkenyl)-5-phenyl-1,3,4 oxadiazole. These compounds obtained were screened for antibacterial and antifungal activities. These compounds revealed broad spe

ctrum of activity and showed promising results.[8]

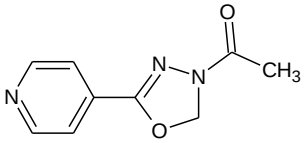


(7)

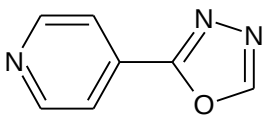


(8)

Dhansay Dewangan *et al* (2010) explored 2,5-disubstituted-1,3,4-oxadiazole derivative for analgesic and anti-inflammatory activity by acetic acid induced method and carrageenan induced rat paw edema respectively.



(9)

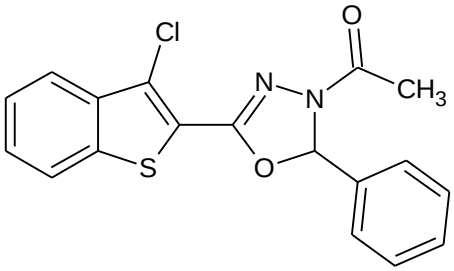


(10)

Compound 9, 10	R
a	2-OH-C_6H_4
b	4-OCH_3-C_6H_4
c	3-OCH_3, 4-OH-C_6H_4
d	2-C_4H_3O
e	-C_6H_5
f	-C_8H_8
g	-C_5H_4N
h	2-NH_2-C_6H_4
i	4-NH_2-C_6H_4
j	2-COOH-C_6H_4

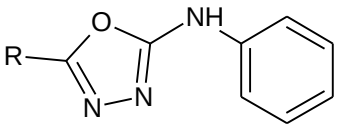
Analgesic activity was shown by 9b, 10f, and 10j while significant anti-inflammatory activity was seen in 9c, 10g, 10j.[9]

Rakesh Chawla *et al* (2010) synthesizes 3-acetyl-5-(3-chloro-1-benzo[b] thiophen-2-yl)-2-substituted phenyl-2,3-dihyro-1,3,4-oxadiazoles and 2-(3-chloro-1-benzo[b] thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles to investigate for antimicrobial activity.[10]

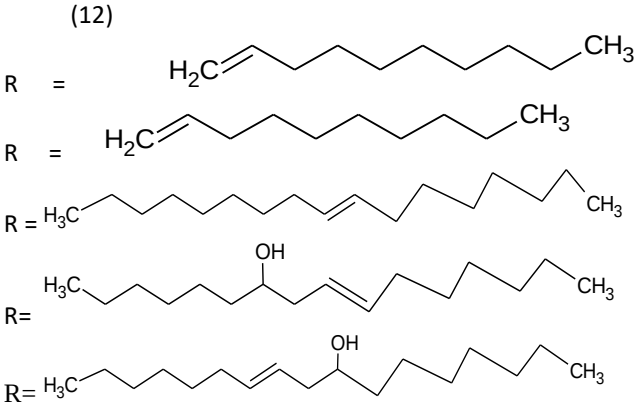


(11)

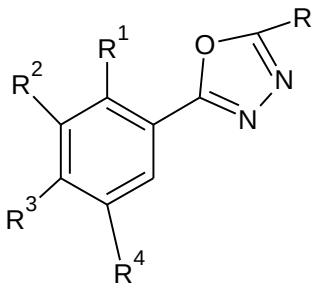
Farshori *et al* (2010) synthesized and also investigated compounds for antimicrobial and antifungal activity. He synthesized 5-alkenyl/hydroxyl-alkenyl-2-phenyl amine-1,3,4-oxadiazole derivatives.[11]



(12)

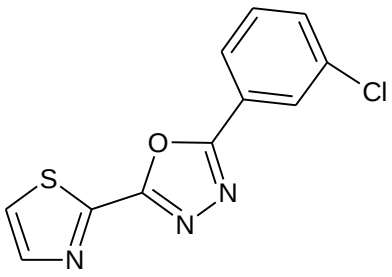


B. Chandrakantha *et al* (2010) tested a series of 1,3,4-oxadiazole derivatives with 2-fluoro-4-methoxy which has been synthesized for antimicrobial activity against *Escherichia coli* and *Pseudomonas aeruginosa,* and antifungal activity against *C.Albicans.*[12]

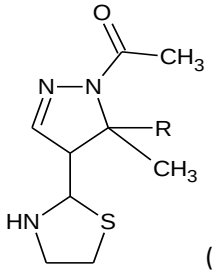


(13)

Kumar *et al* (2010) synthesized some novel 1,3,4-oxadiazoles derivatives using 2-substituted-5-[isopropylthiazole] and investigated them for antibacterial and antifungal activity. The standard drugs used were ciprofloxacin, norfloxacin, and fluconazole.[13]

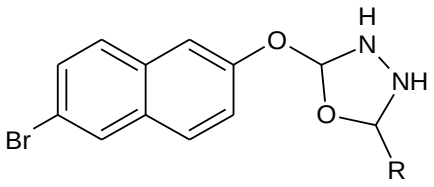


(14)

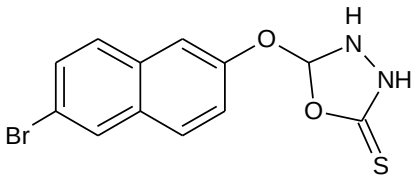


(15)

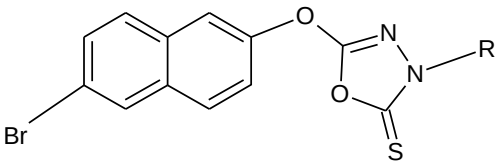
H. S. Yathirajan *et al* (2010) synthesized 2-[(6-bromo-2-naphthyl)oxy] acetohydrazide derivatives of 1,3,4-oxadiazole using mannich reaction for antimicrobial activity.[14]



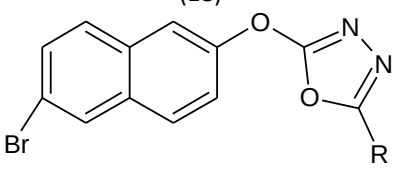
(16)



(17)

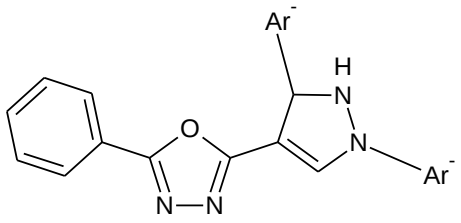


(18)



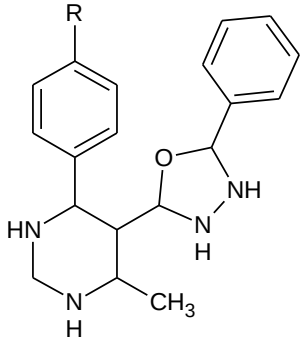
(19)

Prakash *et al* (2010) synthesized novel unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles for antibacterial and antifungal activities. The compounds were compared with ciprofloxacin as standard drug.[15]



(20)

Manish Kumar Mishra *et al* (2010) synthesized 6-methyl-4-aryl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-one. The derivatives were effective against gram +ve *(Streptococcus pneumonia*) and gram –ve (*E.coli*) bacteria.[16]

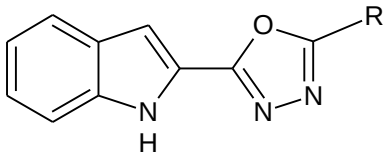


(21)

Nitin Bhardwaj *et al* (2009) was successful in synthesizing indole substituted 1,3,4-oxadiazoles and evaluated them for antimicrobial activity using norfloxacin and fluconazole as standards. The compounds were found to be effective at higher concentrations with respect to standard drug.[17]

R= H

R= C_6H_4Cl

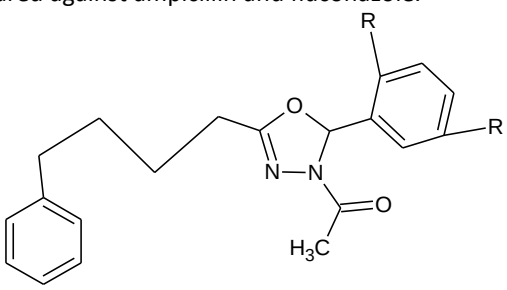


R= C_6H_4OH

R= C_6H_5

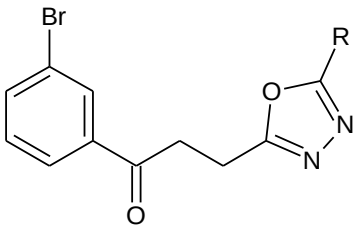
(22)

Neeraj Kumar Fuloria *et al* (2009) synthesized novel compounds series of 1-(2-aryl-5-phenethyl-1,3,4-oxadiazole-3(2H)-yl)ethanones and evaluated them for antibacterial and antifungal activity. The results were compared against ampicillin and fluconazole.[18]



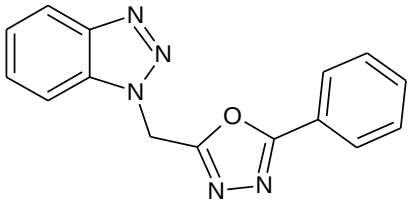
(23)

Asif Husain *et al* (2009) investigated antibacterial activity in both Gram +ve (*Staphylococcus aureus*) and Gram-ve (*E.coli*) bacteria by synthesizing a novel series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)1,3,4-oxadiazoles.[19]



(24)

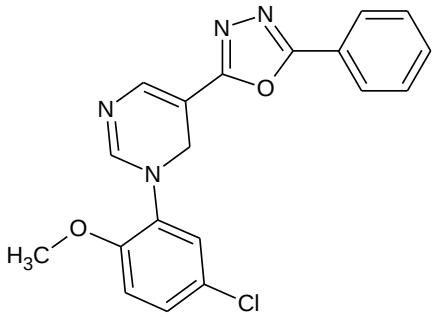
Rakesh saini *et al* (2009) investigated 2,5-disubstituted -1,3,4-oxadiazole derivatives for anti-bacterial activity against *E.coli* and *S.aureus*. The ortho-chloro benzene substituted derivative was found to be most effective. [20]



(25)

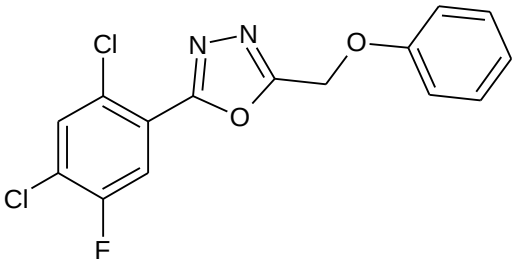
Rai *et al* (2009) tested antibacterial activity on 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1H-pyrazol-4-yl]-5-

(substituted phenyl)-1,3,4-oxadiazole using Ampicillin as standard.[21]



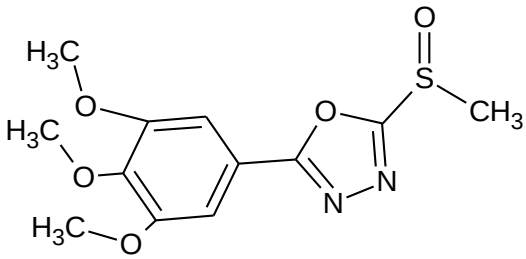
(26)

Karthikeyan *et al* (2008) tested 2,4-dichloro-5-fluorophenyl containing oxadiazoles for antimicrobial and antifungal activity.[22]



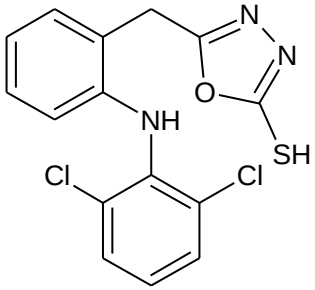
(27)

Liu *et al* (2008) investigated sulfoxide derivatives of trimethoxy phenyl-1,3,4-oxadiazole for antifungal activity.[23]



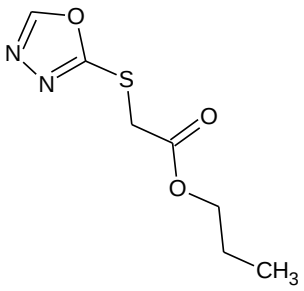
(28)

Shashikant V Bhandari *et al* (2008) studied anti-inflammatory activity and ulcerogenicity of 5-[2-(2,6-dichloroaniline)benzyl]2-mercapto-1,3,4 oxadiazole.[24]

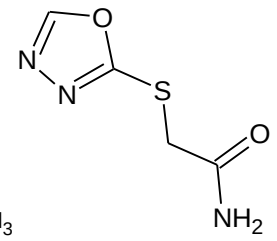


(29)

Mohammed zareef *et al* (2008) synthesized 5-substituted-2-mercapto-1,3,4-oxadiazoles derivatives to screen them for anti-microbial and antifungal activity using agar well diffusion method and agar plate technique respectively. The corresponding S-esters and S-amides were also synthesized. The meta chloro benzene of S-esters was found to exhibit moderate activity.[25]

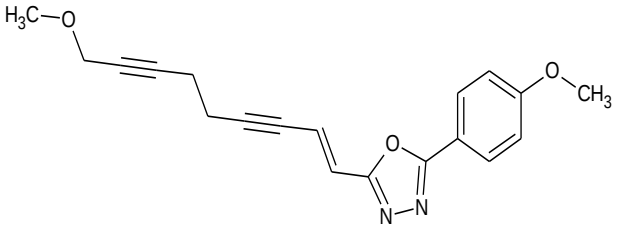


(30)



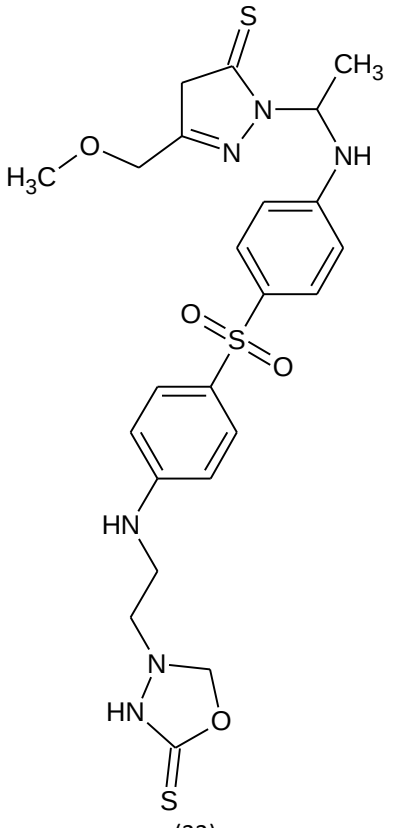
(31)

Shaharyar *et al* (2007), synthesized some novel 1,3,4-oxadiazole derivatives as an anti-tubercular drugs. The compound 2-(2'naphthyloxymethyl)-5 phenoxymethyl 1,3,4-oxadiazole showed highest activity among the synthesized derivatives[26]



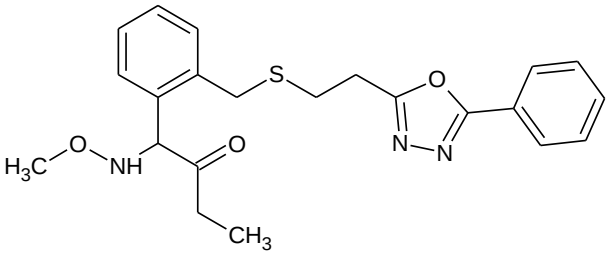
(32)

Mohamed Ashraf Ali *et al* (2007) investigated oxadiazole derivatives formed using mannich reaction between 1,3,4-oxadiazole, dapsone and aldehydes for antitubercular activity. Compound 3-{2-furyl[4(4-{2-furyl[5-(2-naphthyl oxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazole-3yl] mothylamino}phenyl sulfonyl) anilino] methyl}-5-(2-naphthyloxmethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione have shown good activity.[27]



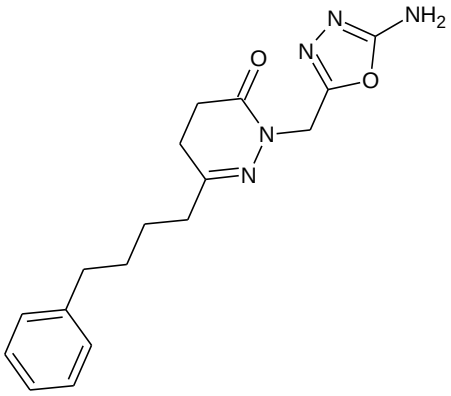
(33)

Yan Li *et al* (2006) synthesized novel (E)-a-(methoxyimino)-benzeneacetate derivatives to evaluate fungicidal activity against *Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae* e.t.c. It shows potent fungicidal activity against *R. Solani*.[28]

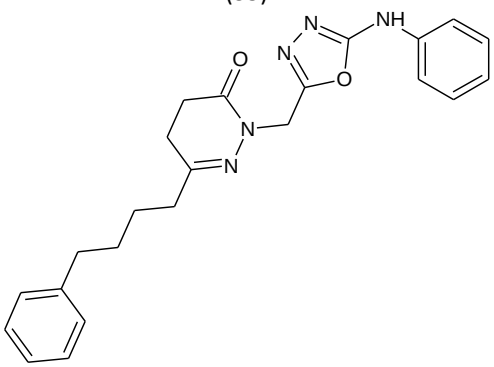


(34)

Mojahidul Islam *et al* (2006) synthesized novel series of 5-{3'-oxo-6'-(substitutedaryl)-2',3',4',5'- tetrahydropyridazin -2i-ylmethyl}-2-substituted 1,3,4-oxadiazole for antibacterial activity.[29]

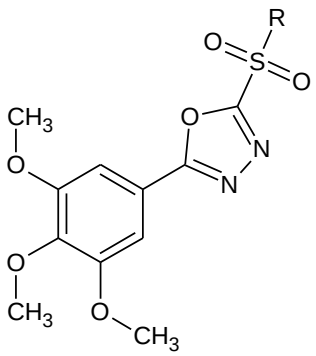


(35)



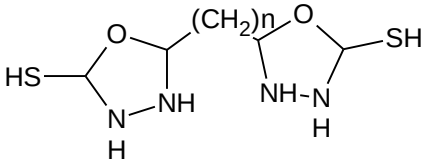
(36)

Chen *et al* (2006) synthesized 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives for antifungal activity.[30]

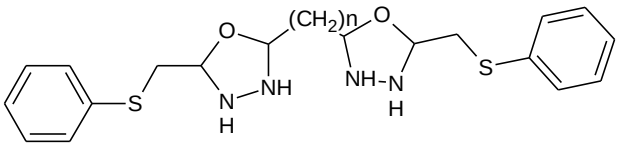


(37)

Ahmed O. Maslat *et al* (2002) synthesized mercapto derivates to investigate their antibacterial and antifungal property against *S.aureus* and *B.subtilis*. They synthesized 5,5'-dimercapto-bis [1,3,4-oxadiazole-2-yl] propane;5,5'-dimercapto-bis-[1,3,4-oxadiazole-2-yl] butane-5,5'-dimercapto-bis[1,3,4-oxadiazole-2-yl] soctane and 5,5'-dibenzyl thio-bis-[1,3,4-oxadiazole-2-yl] butane.[31]



(38)



(39)

CONCLUSION

This review highlights the broad spectrum of antimicrobial activity associated with 1,3,4-oxadiazoles along with anti-inflammatory, anti-tumour, analgesic, anti-convulsant, antioxidant, anti-viral activity and a host of other activitives. This puts impetus on the need to explore 1,3,4-oxadiazole moiety for further research and screening.

REFFERENCES

1. Bachwani M, Sharma V. Antimicrobial activities of 1,3,4-oxadiazole: A review Int J Res Ayurveda Pharm, 2(6), 2011 Nov 16, 1738-1742.

2. Oxadiazole from Wikipedia, the free encyopedia[cited Aug 26 2011. Available from, en.wikipedia.org/wiki/oxadiazole.

3. Nagaraj, Chaluvaraju KC, Niranjan Kiran.S 1, 3,4 oxadiazole, a potent drug candidate with various pharmacological activities Int J Pharm Pharm Sci, 3(3), 2011, 9-16.

4. Kadi AA,Synthesis, antimicrobial and anti-inflammatory activities of Novel 2-(1-adamantyl)-5-substituted 1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. European Journal of med chem., 42(2), 2007, 235-242.

5. Mickevicius V, syn of substituted 1,3,4-oxadiazole ders chem of heterocyclic compounds, 45(2), 2009, 215-218.

6. Bentin F, A new syn of symmetrical 2,5-disubstituted 1,3,4-oxadiazoles. Journal of heterocyclic chemistry, 36(4), 1999, 437-443.

7.Amir M, Saifullah K, Akhter W. Design, Synthesis and Pharmacological evaluation of 1,3,4-oxadiazole derivatives of aryl acetic acid as anti-inflammatory and analgesic agents. Indian Journal of Chemistry Aug, 50(B), 1107-1111.

8. Banday MR, Mattoo RH, Rauf A, Synthesis, characterization and anti-bacterial activity of 5-(alkenyl)-2-amino- and 2-(alkenyl)-5-phenyl-1,3,4-oxadiazoles. J. Chem.Sci., 122(2), 2010 March, 177-182.

9. Dewangan D, Pandey A, Sivakumar T, Rajavel R, Dubey RD. Synthesis of some Novel 2, 5- Disubstituted 1,3,4-Oxadiazole and its Analgesic, Anti-inflammatory, Anti-Bacterial and Anti-

Tubercular Activity. International Journal of Chem Tech Research, 2(3), 2010 Sept, 1397-1412, ISSN-0974-4290.

10. Chawla Rakesh, Arora Anshu, Parameshwaran Manoj Kumar, Sharma Prabodh Chander, Michael Sukumar, Thengungal Kochupappy Ravi, Synthesis of novel 1,3,4-oxadiazole derivatives as potential antimicrobial agents. Acta Poloniae Pharmaceutical and Drug Research, 67(3), 2010, 247-253.

11. Farshori NN, Banday Ahmad A, Khan AU, Rauf A. Synthesis, Characterization, and in vivo Antimicrobial Activities of 5-alkenyl/Hydroxyalkenyl-2 phenylamine-1,3,4-oxadaizoles and Thiadiazoles. Bioorg. Med. Chem. Lett, 20, 2010, 1933-1938.

12. Chandrakantha B, Shetty Prakash, Nambiyar Vijesh, Isloor Arun M. Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety. European Journal of Medicinal Chemistry, 45, 2010, 1206-1210.

13. Kumar GVS, Rajendraprasad Y, Mallikarjuna BP, Chandrasheker SM, Kistayya C. Synthesis of some novel 2-substituted-5-[isopropylthiazole]clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents Eur.J.Med. Chem, 45, 2010, 2063-2074.

14. Yathirajan HS, AnilMayekar N, Narayana B, Sarojini BK, Suchetha Kumari N. Synthesis and Antimicrobial Studies on New Substituted 1,3,4-oxadiazole Derivatives Bearing 6-Bromonaphthalene Moiety. International Journal of Chemistry, 2(1), 2010, 38-54.

15. Prakash O, Kumar M, Sharma C, Aneja KR. Hypervalent iodine (3) mediated synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4-oxadaizoles as antibacterial and antifungal agents. Eur. J. Med. Chem, 45(9), 2010, 4252-4257.

16. Mishra Manish Kumar, Gupta AK, Negi S, Bhatt Meenakshi, Synthesis of 6- Methyl – 4 – aryl – 5 – (5- phenyl -1, 3, 4 – oxadiazole -2- yl) -1, 2, 3, 4-tetrahydropyrimidine-2(1*H*)-one. International Journal of Pharma Sciences and Research, 1(3), 2010, 172-177.

17. Bhardwaj Nitin, Saraf, Sharma Pankaj SK, Kumar Pradeep. Synthesis, Evaluation and Characterization of some 1,3,4-oxadiazoles as Antimicrobial Agents. E-Journal of Chemistry, 6(4), 2009, 1133-38.

18. Fuloria Neeraj Kumar, Singh Vijender, Shanharyar Mohammad, Ali Mohammad. Synthesis and Antimicrobial Evaluation of Some New Oxadiazoles Derived from Phenylpropionohydrazides. Molecules, 14, 2009, 1898-1903.

19. Husain Asif, Ajmal Mohammed, Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties. Acta Pharm, 59, 2009, 223-33.

20. Saini R, Rai AK, Kesari AN, Yar MS. Synthesis and Biological Evaluation of 2, 5 Di-substituted 1,3, 4-oxadaizole. Asian J. Research Chem, 2(1), 2009 Feb 22, 34-36.

21. Rai NP, Narayanaswamy VK, Shashikanth S, Arunachalam PN. Synthesis, characterization and antibacterial activity of 2-[1-(5-chloro-2-methoxy-phenyl)-5-methy-1H-pyrazol-4-yl]-5-(substituted-phenyl)-[1,3,4]oxadiazoles. Eur. J. Med. Chem, 44, 2009, 4522-4527.

22. Karthikeyen MS, Parsad DJ, Mahalinga M, Holla BS, Kumari NS. Synthesis of 2,4-dichloro-5-flourophenyl containing Oxadiazoles. Eur. J. Med. Chem, 43, 2008, 25-31.

23. Liu F, Luo X, Song B, Bhadury PS, Yang S, Jin L, Xue W and Hu D. Synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-thiadiazole and 1,3,4-oxadiazole moiety. Bioorg. Med. Chem, 16, 2008, 3632-3640.

24. Bhandari SV, Bothara KG, Raut MK, Patil AA, Sarkate AP, Mokale VJ. Design, Synthesis and Evaluation of Anti-inflammatory, Analgesic and Ulcerogenicity studies of Novel S-Substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of Diclofenac acid as Nonulcerogenic Derivatives. Bioorganic & Medicinal Chemistry, 16, 2007 Nov 19, 1822-1831.

25. Zareef M, Iqbal R, Mirza M, Khan KM, Manan A, Asim F, et al. Synthesis and antimicrobial activity of some derivatives of acylhydrazine including novel benzenediazasulfonamides. Arkivoc, 2, 2008, 141-152.

26. Yar MS, Siddiqui AA, Ali MA. Synthesis and anti tuberculostatic Activity of novel 1,3,4-oxadiazole Derivatives. Journal of the Chinese Chemical Society, 54, 2007, 5-8.

27. Ashraf Ali Mohamed, Shaharyar Mohammad, Oxadiazole mannich bases, Synthesis and antimycobacterial activity. Bioorganic & Medicinal Chemistry Letters, 17, 2007, 3314-3316.

28. Li Yan, Liu Jie, Zhang Hongquan, Yanga Xiangping and Liu Zhaojie, Stereoselective synthesis and fungicidal activities of (E)-a-(methoxyimino)-benzeneacetate derivatives containing 1,3,4-oxadiazole ring Bioorganic & Medicinal Chemistry Letters, 16, 2006, 2278-2282.

29. Islam Mojahidul, Siddiqui Anees, Rajesh Ramadoss, Bakht Afroz and Goyal Sunil, Synthesis and antimicrobial activity of some novel oxadiazole derivatives. Acta poloniae pharmaceutica-Drug research, 65(4), 2006, 441-447.

30. Chem CJ, Song BA, Yang S, Xu GF, Bhadury PS, Jin LH, Hu DY, Li QZ, Liu F, Xue W, Lu P Chen Z. Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives. Bioorg. Med. Chem, 15, 2007, 3981-3989.

31. Maslat Ahmed o, Abussaud Mahmud, Tashtoush Hasan, Talib Mahmoud AL, Synthesis Antibacterial, Antifungal and Genotoxic activity of bis-1, 3, 4-oxadiazole derivatives. Pol.j. Pharmacology, 54, 2002, 55-59.

Source of Support: Nil, **Conflict of Interest:** None.