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1,3,4-OXADIAZOLE - A LEAD MOLECULE IN MEDICINAL CHEMISTRY: A COMPREHENSIVE REVIEW

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ABSTRACT

1,3,4-oxadiazole is a five membered heterocyclic ring which is versatile lead compound used to design potent bioactive agents. 1,3,4-oxadiazole have shown significant antibacterial and antifungal activity against various strains of microorganisms such as fungi, gram positive and gram negative bacteria's. A large number of drugs used clinically contains 1,3,4-oxadiazole ring as a structural building block. A capacity of 1,3,4-oxadiazole to undergo variety of chemical reactions such as electrophilic substitution, nucleophilic substitution, thermal & photochemical reaction, which make it medicinal backbone on which number of potential molecules can be constructed. 1,3,4-oxadiazole derivatives and investigations on their chemical and biological activities have gained greater importance and vitality in recent decades for biological, medical and agricultural reasons. Present review is flooded and enriched with reports of antimicrobial activity of 1,3,4-oxadiazle derivatives published in various research papers.

KEYWORDS: 1,3,4-oxadiazole, antibacterial activity, antifungal activity, SAR of reported synthesized 1,3,4-oxadiazole containing drugs.

INTRODUCTION

The chemistry of heterocyclic compounds has been an interesting field of study since a long time.[1]

Heteroaromatic ring system is the pivotal part of any biologically active drug molecule. Heteroaromatic rings are essential because they provide similarity with respect to the biologically active compounds within our body for e.g. all the nucleic acids, hormones,

neurotransmitters etc. which constitutes one or the other heteroaromatic ring. Among many heteroaromatic rings present, fused and pendent [1,3,4]-oxadiazoles are also ubiquitous feature of many pharmaceutical products. Compounds having five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles or furodiazoles in the older literature.[2]

1,3,4-oxadiazole have occupied a unique place in the field of medicinal chemistry due to its wide range of exhibited activies.[3] The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial.[4,5] Anti HIV.[6] Antitubercular.[7] antimalarial.[8] Anti-inflammatory.[9,10] Anticonvulsant.[11] and Antitumor.[12]

2,5-Disubstituted-1,3,4-oxadiazole and its derivatives constitute an important family of heterocyclic compounds. Due to their remarkable unique properties, 1,3,4-oxadiazole and its derivatives have been frequently employed in drug synthesis, various commercial and industrial applications. In fact, 1,3,4-oxadiazole ring carrying substitution in an appropriate position and substituent with a nucleophilic center are excellent precursors for further synthesis of heterocyclic compounds.[13]

Oxadiazoles have gained great importance in medicinal chemistry owing to their broad spectrum and metabolic profile.[14] Many studies have confirmed that oxadiazole derivatives possess antifungal activity.[15-22] Among oxadiazole derivatives, 1,3,4-oxadiazolin-2-thiones have received a great deal of attention in heterocyclic chemistry as versatile intermediates due to the fact that the thiol group on oxadiazole ring undergoes nucleophilic substitution reactions readily.[23]

The treatment of infectional diseases still remains a challenging factor because of the increase in a number of multi-drug-resistant microbial pathogens and new infectious diseases such as severe acute respiratory syndrome and avain influenza. 1,3,4-oxadiazole have shown significant anti-microbial activity against a wide variety of micro-organism like fungi, Gram-positive, Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtillis* and *Staphylococus aureus* etc.[24]

1,3,4-oxadiazoles designed as analogues of the anti-fungal natural product pimprinine, and evaluated for their anti-fungal activities against *Phytophthora infestans*, *Septoria tritici*, *Uromyces-viciae-fabae*, *Pythium dissimile*, *Alternaria solani*, *Botryotinia fuckeliana*,

Gibberella zeae. Several of the synthesized compounds exhibit higher anti-fungal activity than pimprinine, the natural product, which inspired synthesis of drugs containing 1,3,4-oxadiazole moiety.[25]

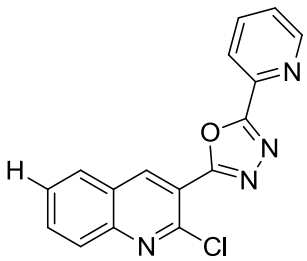
Chemistry of oxadiazole moiety

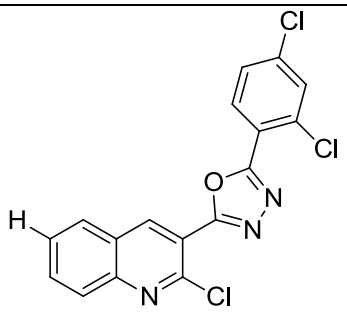
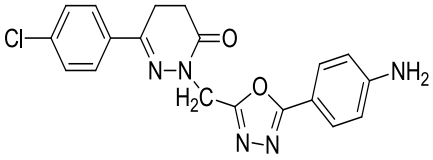
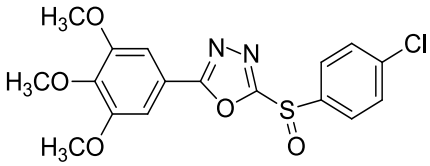
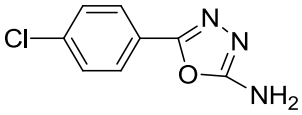
1,3,4- Oxadiazole is a versatile heterocyclic nucleus, which has attracted a wide attention of the medicinal chemists for development of new drugs. Oxadiazole is a cyclic compound containing one oxygen and two nitrogen atoms in a five member ring having general formula $C_2H_2ON_2$. There are four isomers of oxadiazoles. 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-oxadiazole ARE known, but 1,2,3 is unbalanced and reverse to the diazoketone tautomers. Oxadiazole is derived from furan by substitution of two methylene groups with two pyridine type nitrogen. The 1,3,4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical reactions.

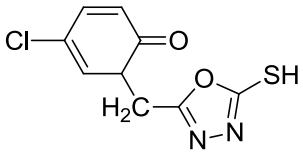
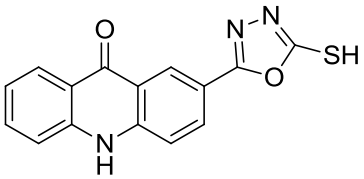
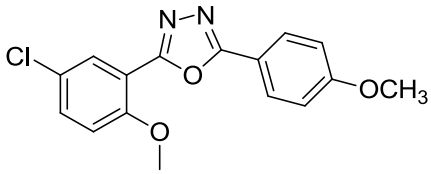
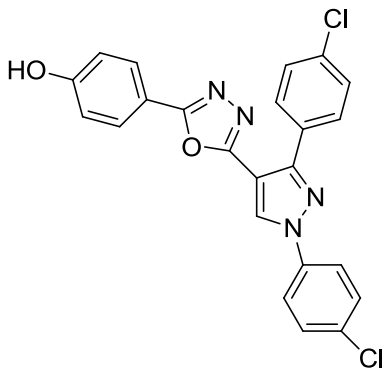
The oxadiazoles are classified into four different groups, depending on the position of nitrogen and oxygen atoms in the ring. These are 1,2,3-oxadiazole, 1,2,5 oxadiazole, 1,2,4 oxadiazole and 1,3,4 oxadiazole.

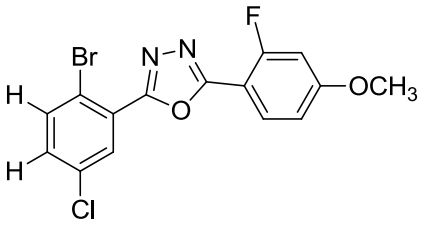
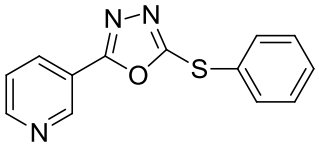
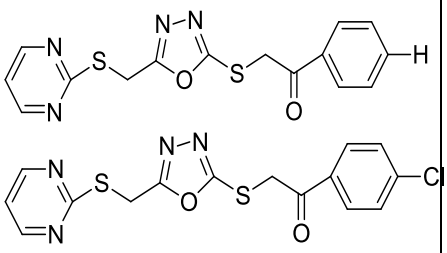
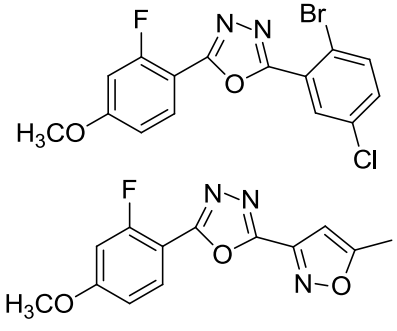
			
1,2,3-oxadiazole	1,2,5-oxadiazole	1,2,4-oxadiazole	1,3,4-oxadiazole

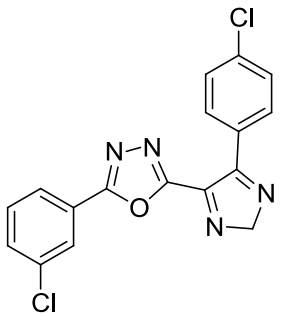
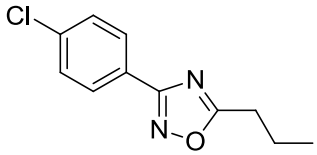
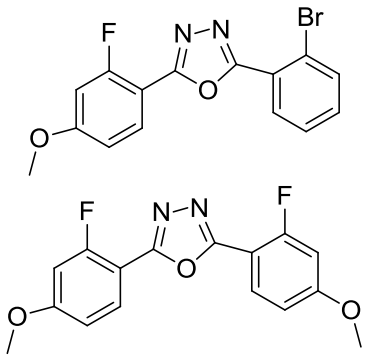
Table 1: Synthetic drugs / derivatives / analogues containing 1,3,4-oxadiazole reported in various research papers along with their SAR data.

Sr. No.	Chemical structures	SAR	References
1		The activity of these compounds may be attributed to the presence of the pyridine ring along with two other rings 1,3,4-oxadiazole and quinoline. Due to the two electron withdrawing (chlorine group) substituent present at 2nd and 4th position of the phenyl ring linked with	Ajmer Singh Grewal, Sonika Redhu International Journal of PharmTech Research Vol.6, No.7, pp 2015-2021, November 2014

		quinoline and 1,3,4-oxadiazole.	
2		This compound shows Antibacterial, Antifungal activity and Active against M.tuberculosis.	Ram VJ. Synthesis, spectral, thermal analyses, molecular modeling, and antimicrobial activities of Cu (II)-complexes with 1,3,4-oxadiazole Schiff-base derivatives. *Indian J. Chem*. (1988) 35B: 980.
3		This compound is showing Antifungal activity due to presence of methoxy group attached to phenyl ring and oxadiazole ring.	M. S. Y. Khan, R. M. Khan, and S. Drabu, "Anticonvulsant and antibacterial activity of some new 1,3,4-oxadiazole derivatives," *Indian Journal of Heterocyclic Chemistry*, vol. 11, no. 2, pp. 119–122, 2001.
4		Improved antifungal activity against candida albicans and lesser toxicity.	Manish Srivastav, Ashish Singh, Deepak Singh kushwah, P.D.Gokulan,synthesis and Biological Evaluation of 1,3,4-Oxadiazole Derivatives, Journal of Pharmaceutical Research 14-2010,20-24.

5		Shows antifungal activity against candida albicans and candida neoformans.	HasanTashtoush, Mamhmud AL Talib, Synthesis, Antibacterial, Antifungal and genotoxic activity of Bis-1,3,4-Oxadiazole Derivatives., Polish Journal of Pharmacology, 2002,54,55-59.
6		Shows anti-fungal activity against (Gibberela, Cercospora arachidicola, Physolosporapiricola and Fusarium oxysporum)	Desai NC, Bhatt N, Somani H, Trivedi A. Synthesis, antimicrobial and cytotoxic activities of some novel thiazole clubbed 1,3,4-oxadiazoles. Eur J Med Chem 2013;67:54-9.
7		Showed good antifungal activity against Fusariumoxysporum due to presence of electon donating methoxy group.	Basavapatna N. Prasanna Kumar,Kikkeri N. Mohana, Lingappa Mallesha, and Kikkeri P. Harish Hindawi Publishing Corporation International Journal of Medicinal Chemistry Volume 2013, Article ID 725673, 6 pages http://dx.doi.org/10.1155/2013/725673
8.		Having inhibitory action against two strains of fungus	Ajjanna M. Sridhara, Kallam R. Venugopala Reddy, Jathi Keshavayya, Palusa Sanath Kumar Goud, Bankavadi C. Somashekar, Prosenjit Bos, Sanenahalli K. Peethambar, Satish Kumar Gaddam. "Synthesis and antimicrobial activity of 2-substituted[4-(1,3,4-oxadiazol-2-yl methyl)] phthalazin-1(2H)-one

			derivatives". European Journal of Medicinal Chemistry 45 (2010) 4983e4989.
9		Shows antifungal activity against candida albiacns due to presence of electron withdrawing fluorine and electron donating methoxy group with phenyl moety attached with 1,3,4-oxadiazole	B. Chandrakantha, Prakash Shetty, Vijesh Nambiyar, Nishitha Isloor, Arun M. Isloor, European Journal of Medicinal Chemistry, (2010), 45, 1206–1210.
10		This compound has shown promising antifungal,antibacterial activity against candida albicans and S.aureus,A.Niger etc.	Shashikant apttan,Deepak musmane.sonali pawar,aarti dhaitankar,nikita wable,sanjay bhawar,indian journal of chemistry,vol-52B.February,2013-293-299.
11		These compounds are having strongest antifungal activity against candida albicans strains and It can be attributed to + π effect of Phenyl and chlorophenyl groups.	Zafer Asim Kaplancikli Molecules 2011, 16, 7662-7671; doi:10.3390/molecules 16097662
12		These compunds were twice as potent as fluconazole against C. albicans	Cledualdo Soares de Oliveira , Bruno Freitas Lira , José Maria Barbosa-Filho , Jorge Gonçalo Fernandez Lorenzo and Petrônio Filgueiras de Athayde-Filho "Molecules" 2012, 17, 10192-10231; doi:10.3390/molecules 170910192

13.		It may conclude that this compounds which contain 2-chlorophenyl substituent on the 5th position of the oxadiazole ring may increase the antimicrobial profile of the compound.	Shridhar Malladi , Arun M. Isloor , S.K. Peethambar , Hoong Kun Fun Arabian Journal of Chemistry (2014) 7, 1185–1191
14		This compound shows good antimicrobial activity against candida albicans.	Srivasta, R. M., Analice de, A. L., Osnir, S. V., Marcelo J. da, C. S., Maria, T. J. A . "Antiinflammatory Property of 3-Aryl-5-(n-propyl)-1,2,4-oxadiazoles and Antimicrobial Property of 3-Aryl-5- (n-propyl)-4,5-dihydro-1,2,4 oxadiazoles: Their Synthesis and Spectroscopic Studies." Bioorg. Med. Chem. 2003, 11, 1821–1827.
15		These compounds showed significant antibacterial activity against Escherichia coli and Pseudomonas aeruginosa and antifungal activity against Candida albicans	Chandrakantha, B., Shetty, P., Nambiyar, V., Isloor, N., Isloor, A. M. "Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety" Eur. J. Med. Chem. 2010, 45(3),1206-1210.

CONCLUSION

This review, has summarized the antimicrobial activities for 1,3,4-oxadiazole derivatives reported in the literature during the past ten years. Oxadiazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions, which are discussed in brief in this article. This article mainly focused on the various derivatives of 1,3,4-oxadiazole showed various important

pharmacological activities, among them only antifungal and antibacterial were discussed along with their SAR and salient features.

Thus by studying all the derivatives showing variety of activities can say that 1,3,4-oxadiazole ring have been explored in past years and is still be used for future development of new drugs against many more pathological conditions.

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