 DOI: 10.18231/2394-2797.2018.0028

# A mini review on biological potential of 1,3,4-oxadiazole derivatives

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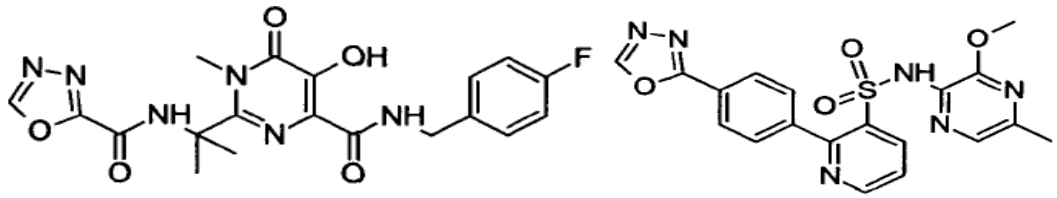
## Abstract
Among heterocyclic compounds, 1,3,4-oxadiazole has become an important synthons in development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum, including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antidepressant, anticonvulsant, and anti-diabetic properties. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important because of their privileged structure, which has an enormous biological potential.

**Keywords:** Heterocyclic compound, 1,3,4-oxadiazoles, Biological activities.

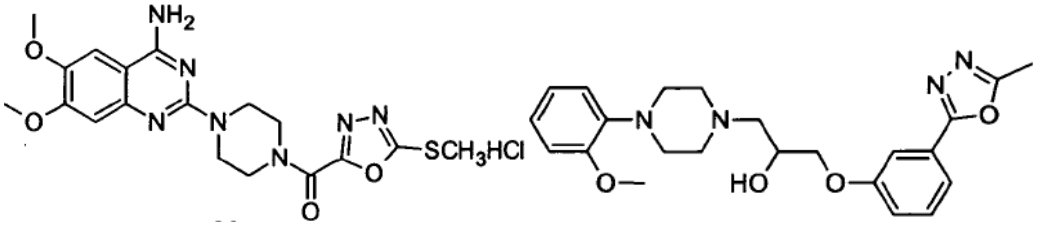
## Introduction
1,3,4-Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. Oxadiazole rings contain two carbon atoms, two nitrogen atoms, and one oxygen atom. Although 1,3,4-oxadiazoles have been known for about 80 years, it is only in the last decade that investigations in this field have been intensified. It is derived from furan by substitution of two methylene groups with two nitrogen atoms. There are four isomers of oxadiazoles: 1,3,4-oxadiazole, 1,2,4-oxadiazole, l,2,3-oxadiazole and 1,2,5-oxadiazole. However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties.[1-5]

**1,2,3-oxadiazoles 1,2,4-oxadiazoles l,2,5-oxadi:izoles 1,3.4-oxadiazoIes**

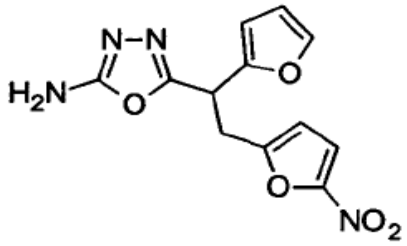
This is primarily due to the number of uses of 1,3,4-oxadiazoles in the most diverse areas, for example in drug synthesis, scintillating materials, and the dyestuffs industry. Research is also in progress to explore the various biological activities of 1,3,4-oxadiazoles. Some of the activities are mentioned here. The compounds containing 1,3,4-oxadiazole unit currently used in clinical medicine are: Raltegravir, an antiretroviral drug and Zibotentan, an anticancer agent. Oxadiazole nucleus is present in antihypertensive drugs such as Zibotentan, nesapidil and antibiotics such as furamizole.[6-8] GABA-modulating 1,2,4-oxadiazole derivatives are known for their anticonvulsant activity. 2,5-Disubstituted 1,3,4-oxadiazoles have also attracted great interest due to their applications in organic light emitting diodes, photoluminescence, polymers and material science.



**Raltegravir** **Zibotentan**

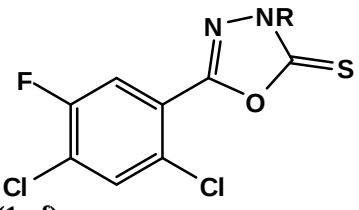


**Zibotentan** **Nesapidil**



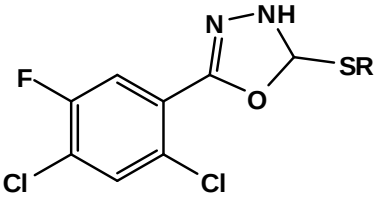
**Furamizole**

**Anticancer and Antimicrobial activity:** Some new fluorine containing 1,3,4-oxadiazoles (**1a-f**), (**2a-c**) and (**3a-c**) as potential antibacterial and anticancer agents. Most of them showed promising antibacterial activity. Also two out of nine compounds showed anticancer activity in the primary anticancer assay.[9]

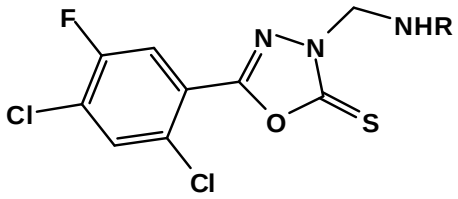


**(1a-f)**

**1a** $C_6H_5$
**1b** 4-$CH_3$-$C_6H_4$
**1c** 4-C1-$C_6H_4$-
**1d** 2.4-$Cl_2$-$C_6H_3$
**1e** 2-4 -$CI_2$-5-F-$C_6H_2$-4-Cl-
**1f** $C_6H_4OCH_2$-
**1g** 2.4-$CI_2$-$C_6H_4OCH_2$-
**1f** 2,4-$Cl_2$

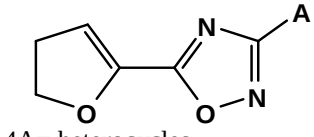


**3(a-c)** **3a** R=$CH_3$; **3b**R=$C_4H_9$ **3c**R=$C_6H_5CO$

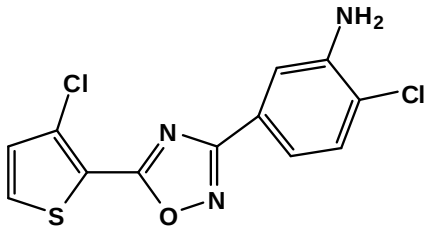


**2a-c**
**2a** R= Morpholino; **2b** R=Methyl piperazino; **2c** R=Piperidino

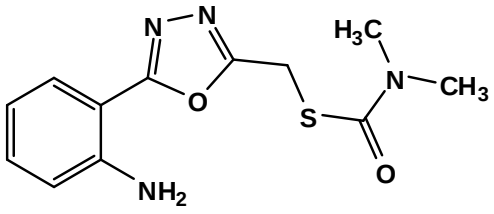
The 3,5-disubstituted-[l,2,4]oxadiazoies (4 and 5) and analogs as activators of caspases and inducers of apoptosis.[10] *In vitro* anti-proliferative activity of some novel 5-(2-amino-3-pyridy1)-2-thioxo-3/f-l,3,4-oxadiazole derivatives 6-8. One of the oxadiazoles show'ed cytotoxic activity against the cells of 4 human cell lines.[11]

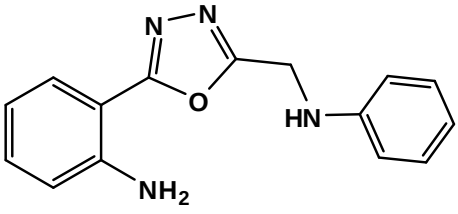


4A= heterocycles
**5**



**6**





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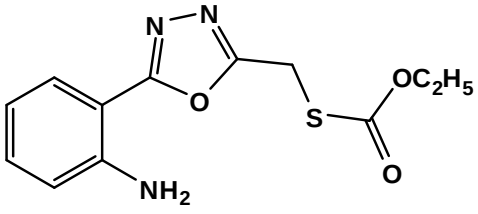
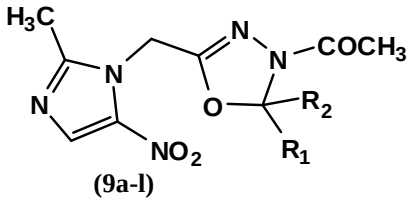


**8**

Antimicrobial activity of 1,3,4-oxadiazoles carrying imidazole moiety (9a-l). Most of the tested compounds showed promising antibacterial and antifungal activity.[12]

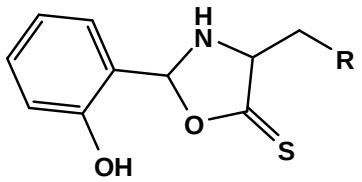
**Compounds**



**(9a-l)**

| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|
| **9a** | H | p-Toyl | **9g** | $CH_3$ | Phenyl |
| **9b** | H | p-Anisyl | **9h** | $CH_3$ | p-Anisyl |
| **9c** | H | p-Chlorophenyl | **9i** | $CH_3$ | p-Chlorophenyl |
| **9d** | H | p-Bromophenyl | **9j** | $CH_3$ | p-Bromophenyl |
| **9e** | H | p-nitrophenyl | **9k** | $CH_3$ | p-Nitrophenyl |
| **9f** | H | 3,4-methyien-dioxyphenyl | **9l** | $CH_3$ | 3,4-methylene-dioxyphenyl |

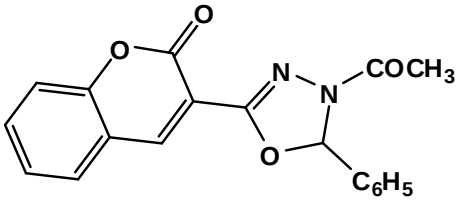
Anticancer activity of novel 5-(2-hydroxy phenyi)-3-substituted-2,3-clihydro-K3.4-oxadiazo!e-2-thione derivatives (10a-l). Some of the compounds produced a good anticancer activity [12a].



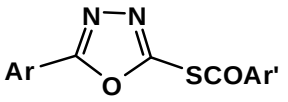
**10a-l**

| | | | |
|---|---|---|---|
| **10a** | 1-Moipholine | **10g** | NH-$C_6H_4$(4-$OCH_3$) |
| **10b** | 1-Phenyl piperazine | **10h** | NH-$C_6H_4$(2-$OC_2H_5$) |
| **10c** | NH-$C_6H$= | **10i** | NH-$C_6H_4$(2-C1) |
| **10d** | NH-$C_6H_4$(3-$CH_3$) | **10j** | NH-$C_6H_4$(3-Cl) |
| **10e** | NH-$C_6H_4$(4-$CH_3$) | **10k** | NH-$C_6H_4$(4-Cl) |
| **10f** | NH-$C_6H_4$(2-$OCH_3$) | **10l** | NH-$C_6H_4$(4-Br) |

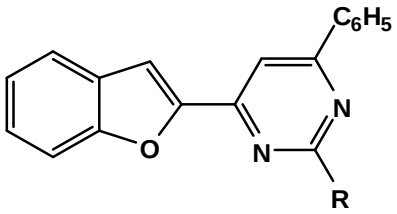
Antibacterial activity of coumarin incorporated 1,3,4-oxadiazoles 11. Most of the compounds showed moderate antibacterial activity[13]and evaluated the antibacterial activity of 5-aryl-2-arylthio-1,3,4-oxdiazoles 12**.**[14] The antifungal activity of new 1,3,4-oxidiazolo [3,2-b]-s-triazine-5-ones and their thione anaiogoues 13a-c. Antifungal activities of the prepared compounds have been compared with Dithane M-45 against *Phytophthara infestans* and *Collectotricum falcatiun* and the results correlated with their structural features.[15]



**11**

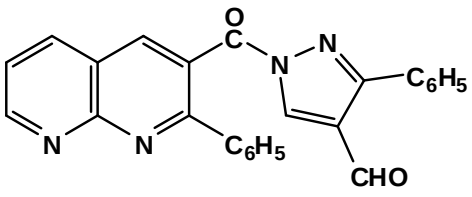


**12**

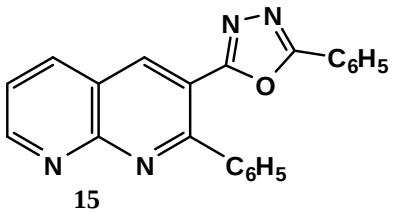


**13a**R=NH2, **13b**R=SH, **13c** R=OH

Antibacterial activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-l,8-napth>ridine compounds 14 and 15 have been tested for their antibacterial activity using streptomycin as a reference compound.[16]

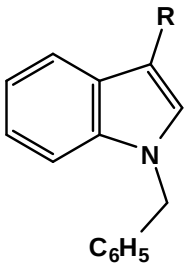


**14**

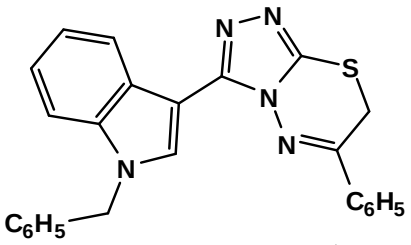


**15**

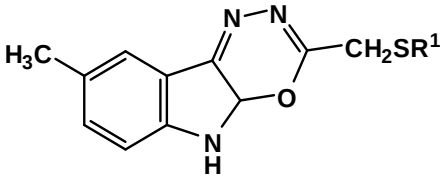
Antimicrobial activity of some new indoiyl 1,3,4-oxadiazole, triazoie and pyrazole derivatives (16a-b) and 17.[17] The antibacterial activities of some 1,3,4-oxadiazole and pyvazoline derivatives containing i.3-Naphthyridine moiety.[18] The antihistaminic, antimuscarinic and antimicrobial activity of some new 2-substituted-[l,3,4]-oxadiazino [5,6'b] indole 18. The compounds has shown $H_I$-antihistaminic and higher antibacterial activity than the respective standards pheniramine maleate and ampicillin.[19]



**16a R**=$CONHNH_2$,
**16b** R=$CHC_6HN(CH_3)_2$-4

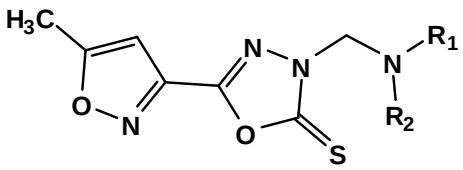


**17**

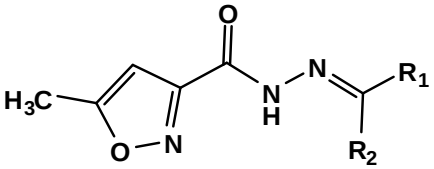


**18** $R^1$ = 2-ben2imidazoyl

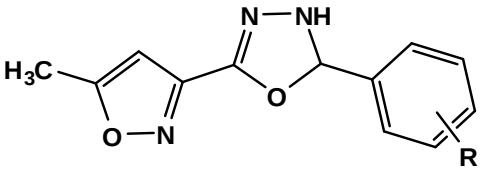
Some oxadiazoles bearing 2-arylamino-5-mercapto-I,3.4-[hiadiazole niiclei as possible antimicrobial agents.[20]



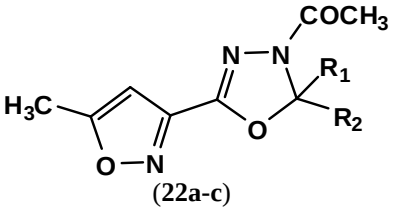
(**19a-e**)



(**20a-c**)



(**21a-c**)

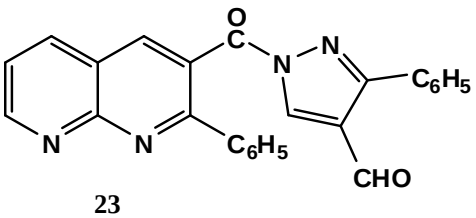


(**22a-c**)

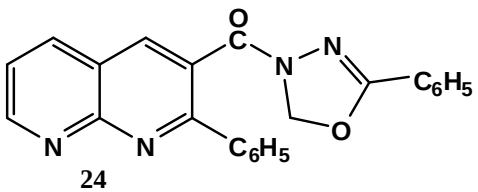
| Compounds | $R_1$ | $R_2$ |
|---|---|---|
| **19a** | Morpholinyl | Morpholinyl |
| **19b** | H | $C_6H_5$ |
| **19c** | H | 4-$C1C_6H4$ |
| **19d** | H | 4-$BrC_6H_5$ |
| **19e** | H | 4-$O_2NC_6H_4$ |
| **20a** | $CH_3$ | $C_6H_5$ |
| **20b** | H | 4-Cl $C_6H_4$ |
| **20c** | H | $C_6H_5$ |
| **21a** | 4-H | |
| **21b** | 4-Cl | |
| **21c** | 4-Br | |
| **22a** | $CH_3$ | $C_6H_5$ |
| **22b** | H | 4-Cl $C_6H_4$ |
| **22c** | H | $C_6H_5$ |

Antibacterial activities of 1,3,4-oxadiazole derivatives containing 5-methyl isoxazole moiety (19a-e)-(22a-c).[21]

Antibacteriai activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-1.8-napthyridine compounds 23 and 24 have been tested for their antibacterial activity using streptomycin as a reference compound.[22]

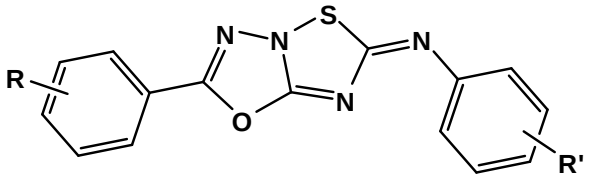


**23**



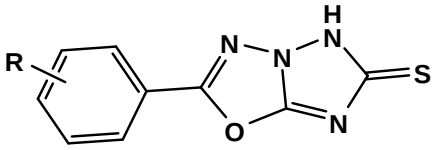
**24**

Evaluated the fungi toxicity of fluorinated-1,2,4'triazolo and thiadiazolo [3,2-b]-l,3,4-oxadiazoles (25-i) and (26a-c). The compounds have been tested *in vitro* for their fungicidal activity against *Cephalosporium tacharri, Aspergillus niger* and *Fusariurn oxyspoitrrn* and the results are compared with their parent thioureas. The structural features of the tested compounds have been correlated with their fungicidal activity.[23] Antimicrobial study of heterocycle substituted S-triazoles, 1,3.4-thiadiazoles, oxadiazoles 27 and related heterocycles.[24]



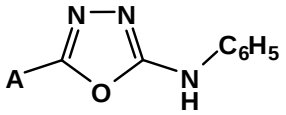
(**25a-i**)

| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|
| **25a** | 2-F | 2-Cl | **25f** | 3-F | 4-Cl |
| **25b** | 4-F | 2-Cl | **25g** | 2-F | 4-$CH_3$ |
| **25c** | 3-F | 2-Cl | **25h** | 4-F | 4-$CH_3$ |
| **25d** | 2-F | 4-Cl | **25i** | 3-F | 4-$CH_3$ |
| **25e** | 4-F | 4-Cl | | | |



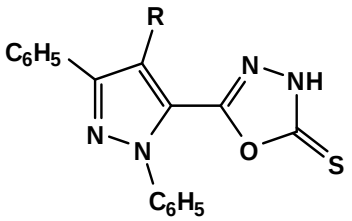
(**26a-c**)

| | R |
|---|---|
| **26a** | 2-F |
| **26b** | 4-F |
| **26c** | 3-F |



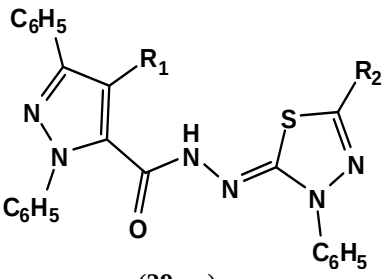
**27** A= Heterocycle

Antimicrobial activity of 5-(pyrazol-5-yl)-l,3,4-oxadia2ole-2(3H)-thiones (28a-c) and (29a-c).[25]



(**28a-c**)

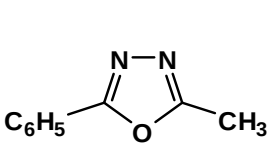
| R |
|---|
| $C_6H_5$ |
| 4-$CH_3C_6H_4$ |
| 4-$ClC_6H_4$ |



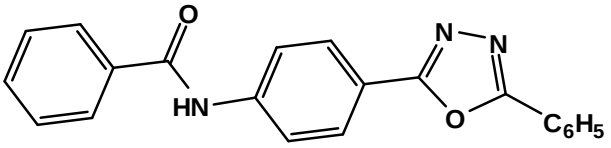
(**29a-c**)

| $R_1$ | $R_2$ |
|---|---|
| $C_6H_5$ | $C_6H_5$ |
| 4-$CH_3C_6H_4$ | $C_2H_5O_2C$ |
| 4-$ClC_6H_4$ | $CH_3CO$ |

The synthesis and antimicrobial activity of some novel oxadiazole, thiadiazole and triazole derivatives.[26] The chloramine-T-mediated syntliesis of 1,3,4-oxadiazoie along with their antimicrobial activity. Among the compounds tested, few compounds have displayed significant anti fungal activity.[27] Various rearrangements and dehydration reactions of 1,3,4-oxadiazoles were worked out extensively. Polyphosphoric acid influenced dehydration of l-acetyl-2-ary!-hydrazine and their rearrangements to afford 2-methyl-5-aryl-1,3,4-oxadiazoles 30.[28] The synthesis and antimicrobial activity of benzamido phenyl oxadiazole 31, most of the compounds possess bactericidal and fungcidal activity.[29]

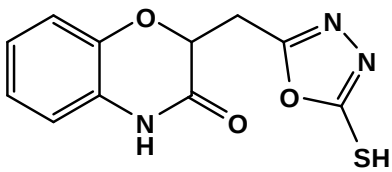


**30**

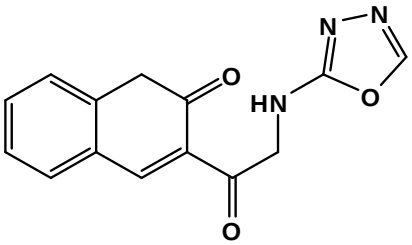


**31**

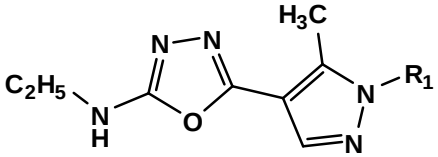
Synthesized and evaluated the antimicrobial activities of oxadiazole, 1, 5-disitbstituted-2-mercapto-l, 3, 4-tritiz,ole and 2, 5-disubstitited-2-mercapto-1, 3, 4-thiadiazole derivatives.[30] Synthesized eight 2-(3,4 dihydro-3-oxo-2H-1,4-benzoxazin-2-yl-methy!)-5-ajkyl/arylthio)-1.3,4-oxadiazoles 32 from their respective hydrazides. All the compounds were screened for antimicrobial activity against *B. suhtilis, B. polymyxia, E. coli,* A, *niger. F. oxysporiuin* and *P. grixeofiilviuin.*[31] Further, condensation of 3-bromoacetyl coumarin and 2~amino-4-phenyl oxadiazole, various oxadiazolyl derivatives 33 showed moderate antimicrobial activity.[32] A series of 1,3,4-oxadiazoles 34 by the cyclisation of respective hydrazides. They were screened for their antibacterial, antifungal and antirnycobacterial activities.[33]



**32**

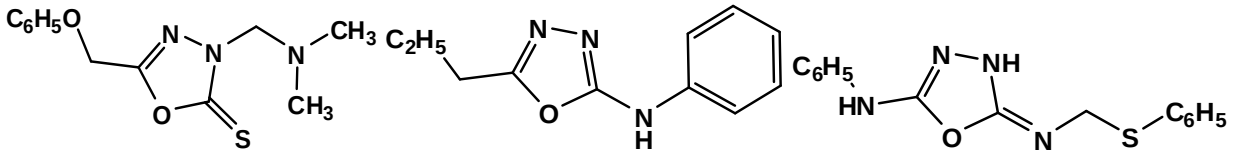


**33**



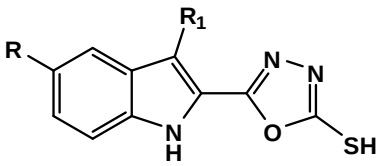
**34** R= Pyridyl

Mannich bases synthesized from 1,3,4-oxadiazoles were screened for biological activities, 3-(2-isopropyl-1,5-dimethyl) phenoxymethyl '4~amino-5-mercapto-1,3.4-oxadiazoles 35 were synthesized starting from thymol. Various amino derivatives were obtained by the reaction of formaldeliyde and the oxadiazole-thione.[34] The synthesis and antibacterial activity of some novel substituted oxadiazoles from p-aryl propiony! hydrazines 36, All the compounds showed effective anti bacterial activity.[35] A series of 2-(phenyhimino)-5-phenyl-thio/phenyl sulfonyi) methyl-1,3,4-oxadiazole 37. These derivatives were screened for antibacterial activity against *E. coil, K. pneumonia* and *S. aureus.*[36]



**35** **36** **37**

The 2-(5-'thioxo-1',3',4-oxadiazol-2'-yl)indoles (38a-c) by the reaction of indole-2-carboxy hydrazides with CS; and KOH. On screening, these compounds showed moderate activity against *S. aureus. E. Coli. P. vulgaris* and *B. Subtilis.*[37]

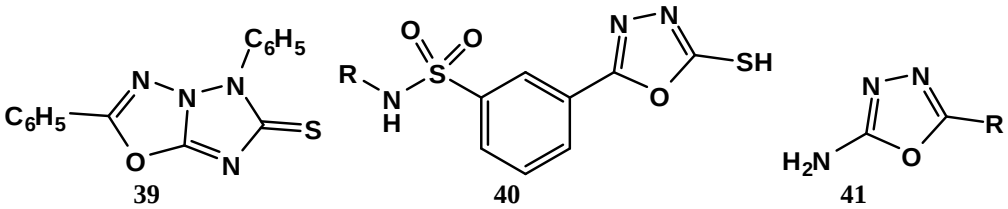


| R | $R_1$ |
|---|---|
| O | H |
| $CH_3$ | C |
| O | $H_3$ |
| $C_2H_5$ | $C_6$ |
| Cl | $H_5$ |

(**38a-c**)

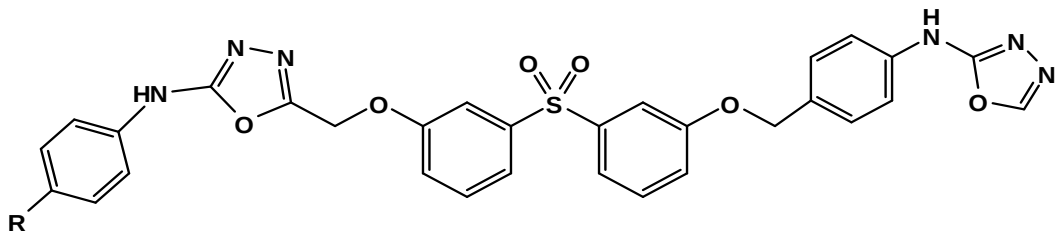
In view of achieving pharmacological compounds of high potency, fusion of 1,3,4-oxadiazoles with various heterocyclic rings by the oxidation cyclisation of the corresponding N-phenyl-N'-(5-aryl-1,3,4 oxadiazol -2-yl) thioureas with pyridine resulting in the synthesis of several 2-ary]-5-phenyl-1,2,4-triazolo(3,2-b)l,2,4 oxadiazol-6-thione 39. These compounds were screened *in vitro* for fungitoxicity against A. *niger and F. oxysporiiim.*[38]

Synthesis of 2-carboxymethyl thio-5-(3 -arylamino sulfophenyl)-1,3,4-oxadiazole 40, the reaction of 2-mercapto-l,3,4-oxadiazole with chloroacetic acid gave the product. The product was screened for antibacterial and antifungal activity against *S. aureus, E. coli, A. niger* and C *albicans.* Moderate activity was obtained.[39] Antibacterial and antianioebic activity of substituted amino aryl-1,3,4-oxadiazoles 41. They showed excellent activity.[40]



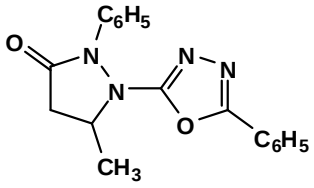
**39** **40** **41**

The antibacterial and antifungal activity of p,p'-bis (2-arylamino)-l,3,4-oxadiazol-5'yl-metlioxy diphenyl sulphones 42.[41]

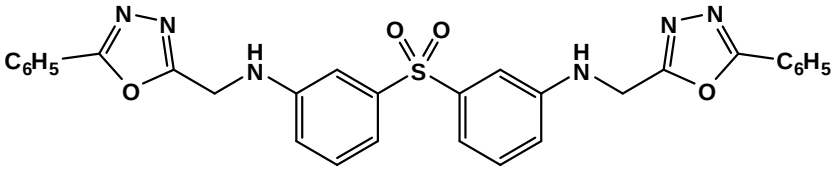


**42**

The antibacterial activity of substituted 5-aryl'1,3,4-oxadiazoles 43.[42] The synthesis and antimicrobial activity of p,p‘-bis (5-aryl-l,3,4-oxadiazole-2-yl-methylaraino) diphenyl sulfones 44.[43]

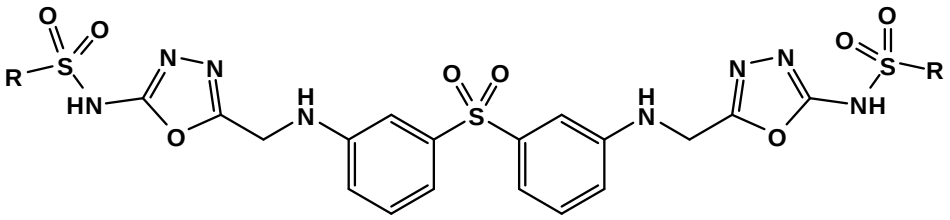


**43**



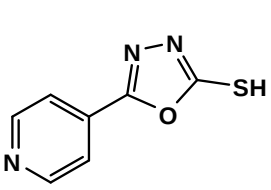
**44**

The antimicrobial activity of p,p’-bis[[(2-arylsuifonamido)-l,3,4-oxadiazol-5--yl)methyl]amino] diphenyl suifones 45. The synthesized compounds were tested for bactericidal and fungicidal activity, most of them showed moderate activity.



**45**

The antimicrobial activity of 5-(p-methylbenzoylacetyl)-3-phenyl-1,3.4-oxadiazole. The anti tubercular activity of some new 2-substituted thio 5-(4'-pyridyl)-1,3,4-oxadiazoles. Compounds 46 and 47 inhibited the growth *of Mycobaaeriim* completely at concentration of 20-40 mg/ml of culture medium.



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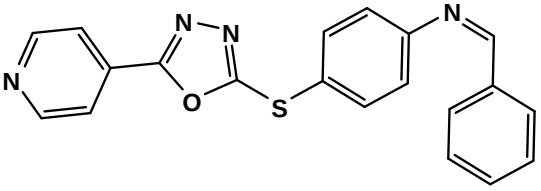
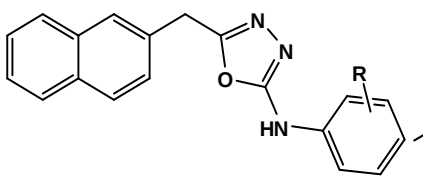


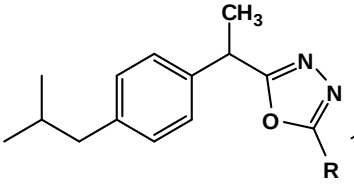
**47**

The synthesis and antimicrobial activity of some novel 3,5-disubstituted oxadia2ole-2-thiones.

**Anti-inflammatory activity:** The synthesis and anti-inflammatory activity of Naphathylmethyl oxadiazoies 48. The tested compounds showed !5,58% to 70.13% inhibition at l00 mg/kg dose compared to ibuprofen which shows 61.04% inhibition at 100 mg/kg dose in carrageenen induced edema in rats. The synthesis and anti-inflammatory activity of substituted 1,3,4-oxadiazole derivatives 49-52.



**48**



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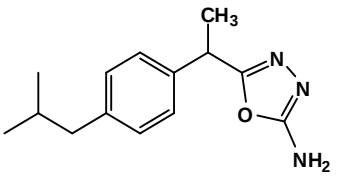
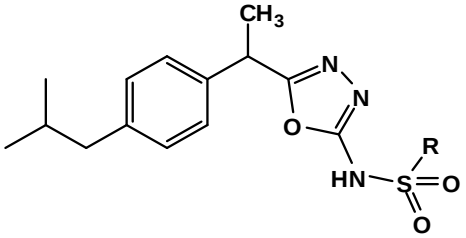


**50**



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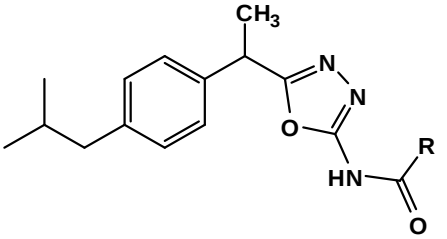
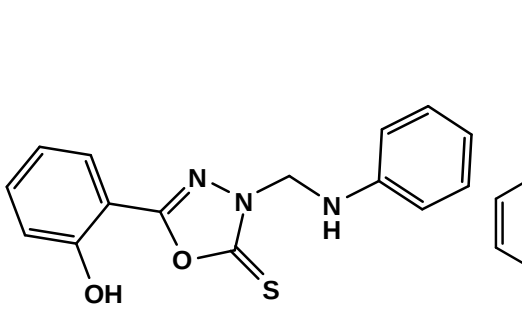
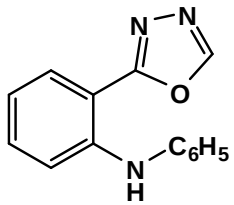


**52**

The synthesis and anti-inflammatory activity of some novel 5-(3,5-substituted hydroxyphenyl)1.3,4-thiazoles, 1,3,4-oxiadiazoles and 1,2,4-triazoles. Synthesized 5-(2-hydroxyphenyl)-3-(aryl aminomethyl)1,3,4 -oxadiazole-2-(3H)-thiones 53 and screened for their anti-inflammatory activity by paw edema method in rats. The synthesis of a series of 5-(2-anilinophenyl)-1,3,4-oxadiazoles 54-56 and their effective anti-innammatory activity. The spasmolytic and hypotensive activity of 2-(substituted acetyl)amino-5-alkyl-l.3,4-oxadiazoles 57.



**53**



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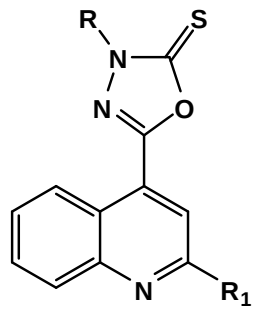

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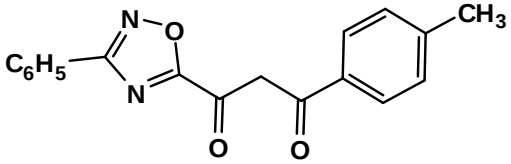
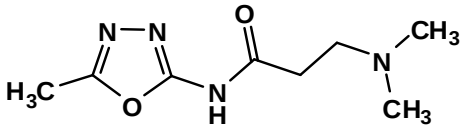
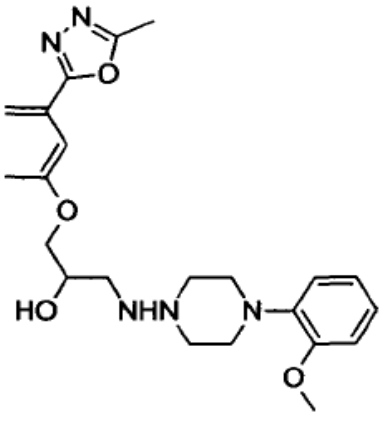


**56**

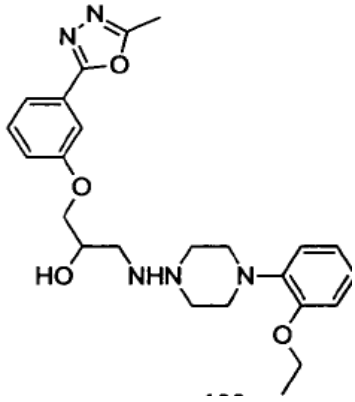


**57**

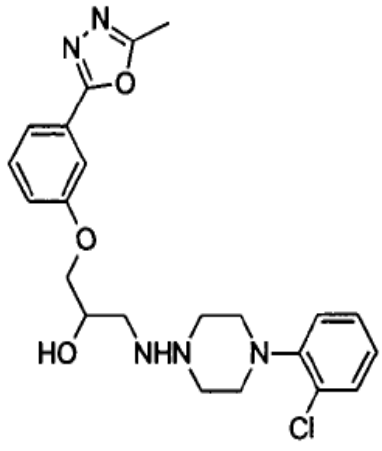
Biologically active molecules containing the oxadiazole moiety include the HIV integrase inhibitor[44] and the antituberculosis agents.[45] The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry is evident from the following examples. 2-Amino-1,3,4-oxadiazoles exhibit muscle relaxants (58-60) and show anti-mitotic activity.



**58**

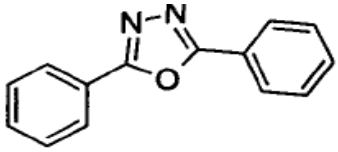


**59**



**60**

The 2,5-Diaryl-l,3,4-oxadiazoles (61) are platelet aggregation inhibitors. 5-Aryl-2-hydroxymethyl-l,3,4-oxadiazole (62) display diuretic, analgesic, anti-inflammatory, anticonvulsive, and antiemetic properties.



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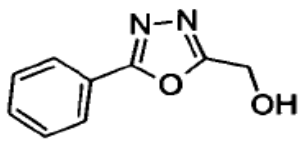

**62**

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**How to cite this article:** Asif M, Abida. A mini review on biological potential of 1,3,4-oxadiazole derivatives. *Int J Pharm Chem Anal* 2018;5(4):179-187.