Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

OXADIAZOLE: A POTENT DRUG CANDIDATE WITH VERSATILE BIOLOGICAL BEHAVIOUR

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ABSTRACT

Heterocyclic compounds possess diverse biological properties that have lead to intense study and research of these compounds. One of these compounds is Oxadiazole which has been found to exhibit various pharmacological activities. Oxadiazole having heterocyclic nucleus is a novel molecule which attract the chemist to search a new therapeutic molecule. The present review article covers various derivatives of different oxadiazole and their substitutions with diverse biological activities.

KEYWORDS

Oxadiazole, Cancer, Antimicrobial and Anti-inflammatory activity.

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INTRODUCTION

Derivatives of oxadiazole are used in the market such as Raltegravir, Nosapidil, Furamizole, etc. During recent years, there have been some interesting developments in the biological activities of oxadiazole derivatives. Literature survey reveals that the various derivatives of oxadiazole have different pharmacological activities.

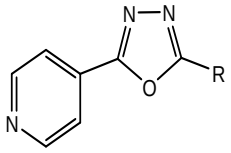
Oxadiazole nucleus are known to exhibit anti-inflammatory[1] activity, differently substituted oxadiazole moiety has been found to have other interesting activities such as analgesic[2], antitubercular[3], anticonvulsant[4], antipsychotic[5], antitumor[6], anti-protozoal[7], anti-diabetic[8], anthelmintic[9], ulcerogenic[10], anti-HIV[11], antioxidant[12], antipyretic[13], CNS depressant[14], antihypertensive[15],

muscle relaxant[16], antimicrobial[17-20], sedative-hypnotic[21] and protein binding[22] activities.

BIOLOGICALLY ACTIVE OXADIAZOLES AND ITS DERIVATIVES

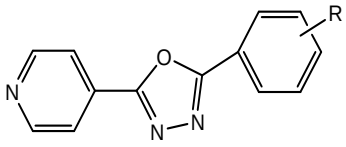
Analgesic and Anti-inflammatory

Dhansay Dewangan *et al*, Synthesized some of the Novel 2, 5- Disubstituted 1, 3, 4-Oxadiazoles and evaluated as analgesic and anti-inflammatory activities. All the synthesized compounds shown significant analgesic and anti-inflammatory activities[23].

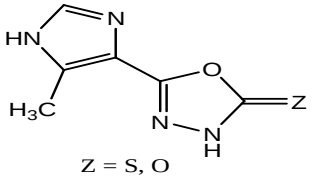


R = C_5H_4N, 2-COOH-C_6H_4

Biju CR *et al*, worked on the Design and Microwave-assisted Synthesis of 1,3,4-Oxadiazole derivatives and screened for analgesic and anti-inflammatory activities. Almost all the compounds possess good activity against the standard[24].

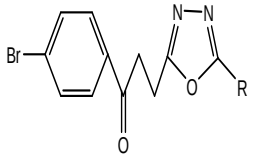


Almasirad *et al*, Synthesized new methyl-imidazolyl-1,3,4-oxadiazoles and 1,2,4-triazoles. The analgesic and anti-inflammatory profile of the synthesized compounds were evaluated by writing and carrageenan induced rat paw edema tests respectively[25].



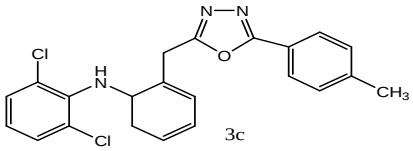
Z = S, O

A. Husain and M. Ajmal, Synthesized novel 1,3,4-oxadiazole derivatives. Title compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic and antibacterial activities. A fair number of compounds were found to have significant anti-inflammatory and analgesic activities, while a few compounds showed appreciable antibacterial activity. The newly synthesized compounds showed very low ulcerogenic action[26].

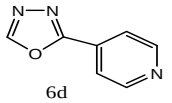


R = C_6H_5 -, 2-ClC_6H_4 -, 4-ClC_6H_4 -, 2-HOC_6H_4-, 4-$NO_2C_6H_4$-, 4-FC_6H_4-, 4-CH $3C_6H_4$ -, 4-$OCH_3C_6H_4$ -, 3,4-$(OCH_3)_2C_6H_3$-, $C_6H_5CH_2$-,$C_6H_5OCH_2$-, 2-$C_6H_5COC_6H_4$-, 1-$C_{10}H_7OCH_2$-, 2-$C_{10}H_7OCH_2$-

R. R. Somani *et al*, worked on the Synthesis and Evaluation of Anti-inflammatory, Analgesic and Ulcerogenic Potential of NSAIDs Bearing 1,3,4-Oxadiazole Scaffold. These compounds were further subjected to anti-inflammatory, analgesic and acute ulcerogenic activity. Compound 3c and 6d exhibited good anti-inflammatory activity and compounds 3c, 3e, 6c, 6d, 6e were found to be non ulcerogenic[27].

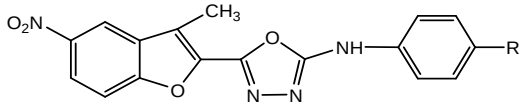


3c



6d

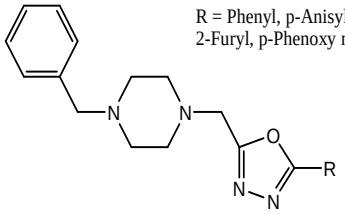
K. M. Basavaraja worked on the Analgesic and anti-inflammatory activity of 3-methoxy-5-nitro-2-(1',3',4'-oxadiazolyl,1',3',4'-thiadiazolyl and 1',2',4'-triazolyl)benzofurans. The title compounds have shown encouraging analgesic activity. Their analgesic potency has been found to be equal to that of a standard drug. The analgesic activity of remaining compounds is found to be moderate. The anti-inflammatory activity results indicate that some compounds are equally active and comparable with standard phenylbutazone. Other compounds have been found to be either moderately or poorly active[28].



R = OCH_3, Br, Cl

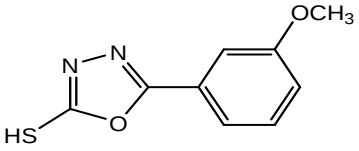
Anticancer activity

Shyamkumar Immadi *et al* synthesized some of the 1-[(5-substituted-1,3,4 oxadiazol-2-yl) methyl]-4-benzylpiperazines. All the title compounds (VIa-j) were screened for anticancer activity using HBL-100 cell lines by MTT method and antibacterial activity against *B. subtiliis*, *S.aureus*, *E.coli* and *P.vulgaris*[29].

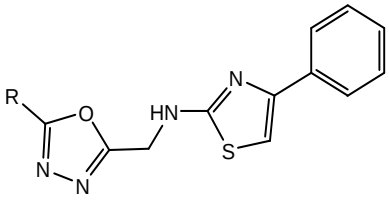


R = Phenyl, p-Anisyl, o-Tolyl, p-Tolyl, p-Chlorophenyl, 3-Pyridyl, 2-Furyl, p-Phenoxy methyl, p-Cresyloxymethyl, o-Cresyloxymethyl

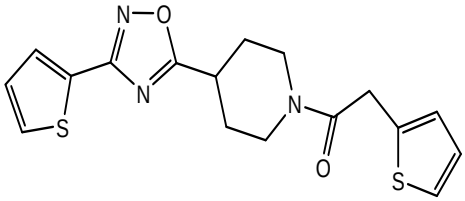
Kiran *et al*, worked on the Molecular docking studies of 2-mercapto-5-(3-methoxyphenyl) 1, 3, 4 oxadiazole thiones with focal adhesion kinase. Thus the bioactive compound interacting with the target can be used as a potent inhibitor to block the action of FAK protein. The selected ligand can be verified at wet laboratory validations and made into an effective anticancer drug[30].



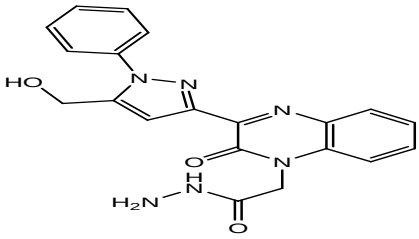
Jisha Mol. V. *et al*, worked on the Synthesis, characterization and *in-vitro* anticancer screening of novel thiazole-1,3,4-oxadiazole hybrid analogues and screened for *in-vitro* anticancer activity on human breast cancer cell line MCF-7 and lymphoma cancer cell line DLA . The derivatives showed moderate activity on both cell lines[31].



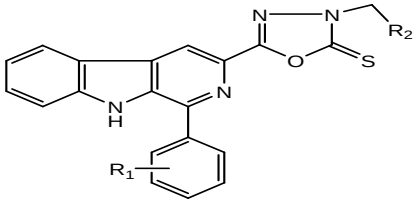
Durust *et al*, worked on the Synthesis of novel triazoles bearing 1,2,4-oxadiazole and phenylsulfonyl groups by 1,3-dipolar cycloaddition of some organic azides and their biological activities. In addition, anticancer activities of the cycloadducts against MCF-7 cells were also investigated[32].



Omaima O. M. Farahat and Kamal F. M. Atta, Synthesized a Novel 1, 3, 4-Oxadiazolyl- and Pyrazolylquinoxalines. Anti-tumor evaluation of the synthesized compounds in vitro against three cell lines HCT-116 (colon carcinoma), HEPG2 (liver carcinoma) and MCF-7 (breast carcinoma) revealed that they possess high anti-tumor activities[33].

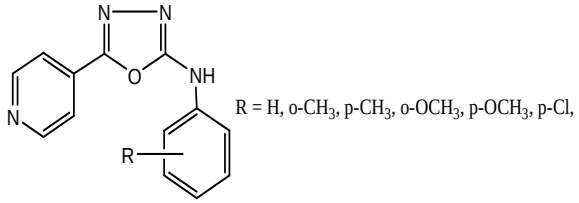


Savariz *et al* synthesized a Novel 1-Substituted Phenyl-3-[3-alkylamino (methyl)-2-thioxo-1,3,4-oxadiazol-5-yl] b-Carboline Derivatives. Antitumor activity evaluation of several novel Mannich bases 2-7(a-c), by the introduction of different alkylamino(methyl) groups in the 1,3,4-oxadiazole unity of 1a-c[34].

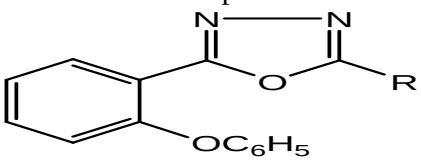


Anticonvulsant activity

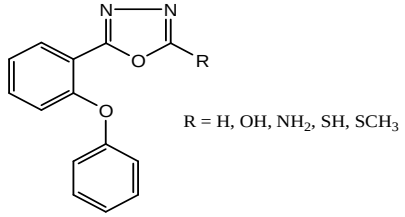
Mohammad Shahar Yar and Mohammad Wasim Akhter, Synthesized the substituted oxadiazole and thiadiazole derivatives by the reaction between isoniazid and various substituted isothiocyanates and were tested for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsometer[35].



Tabatabai A *et al*, worked on the Design, Synthesis and Anticonvulsant Activity of 2-(2-Phenoxy) phenyl-1,3,4-oxadiazole Derivatives. Anticonvulsant activity of the synthesized compounds, determined by pentylenetetrazole-induced lethal convulsion test, showed that the introduction of an amino substituent in position 5 of 1,3,4- oxadiazole ring generates compound 9 which has a respectable effect[36].

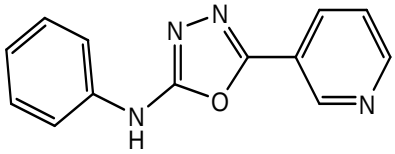


Sayyed Abbas Tabatabai, worked on the Design, Synthesis and Anticonvulsant Activity of 2-(2-Phenoxy) phenyl- 1,3,4-oxadiazole Derivatives. Anticonvulsant activity of the synthesized compounds, determined by pentylenetetrazole-induced lethal convulsion test, showed that the introduction of an amino substituent in position 5 of 1,3,4- oxadiazole ring generates compound 9 which has a respectable effect[37].



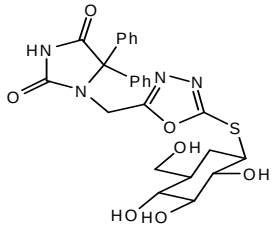
R = H, OH, NH_2, SH, SCH_3

Ramanji Naik, Synthesized the 1, 3, 4-oxadiazole and 1,3,4- thiadiazole derivatives for their potential anticonvulsant activity by autodock software[38].

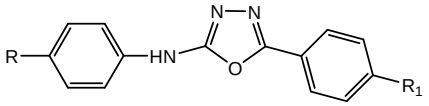


Antimicrobial activity

Omar M. Ali *et al*, Synthesized new [(oxadiazolyl) methyl] phenytoin derivatives. Antimicrobial activity of the prepared compounds was evaluated against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Aspergillus niger* and *Candida albicans*. The dithiohydrazone as well as oxadiazole thiole derivatives, sugar hydrazones and acyclic nucleoside analogs were the highly active compounds[39].

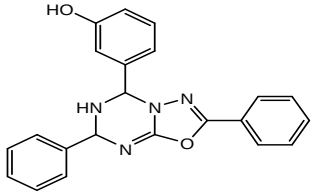


Yogesh Murti *et al*, worked on the Design, Synthesis and Biological Evaluation of Some Novel 2,5-Disubstituted-1,3,4-Oxadiazole Derivatives. The results of biological activities revealed that all the synthesized 2,5-disubstituted-1,3,4-oxadiazoles are potential lead compounds in search of new chemical entities *viz*. antimicrobial and analgesic agents[40].

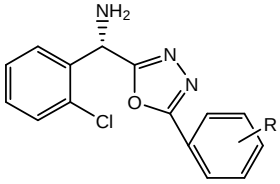


R = H, Cl, Br, NO_2, OCH_3, H, Cl, Br, OCH_3
R_1 = Cl, Cl, Cl, Cl, Cl, Br, Br, Br, Br, Br

Deepak Kumar Basedia *et al*, Synthesized novel 2,5-substituted aryl-7-phenyl-1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazine derivatives. Antimicrobial activity of synthesized compounds was carried out by cup-plate method. All the synthesized compounds show a moderate biological activity. The compound 1c, 1e, 1i, 2b, 2d, 2i and 1b, 1e, 1j, 2a, 2d shows better significant antibacterial and antifungal activity respectively[41].

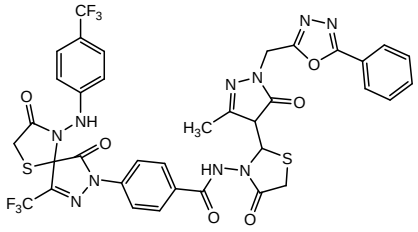


Mistry *et al*, worked on the Comparative studies of novel oxadiazole derivative having chiral center. The newly synthesized compounds indicate that some of them show better antibacterial and antifungal activity than compared to their reference drug[42].

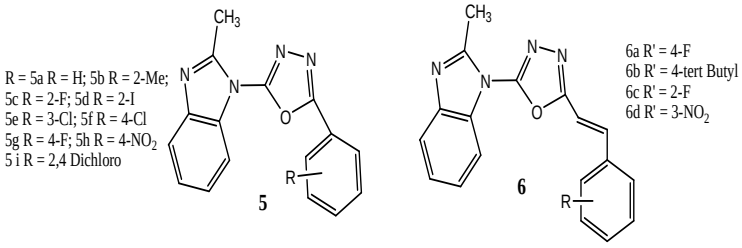


R = -H, 3-CH_3, 2-OH, 4-OH, 2,4-di-Cl, 2-NO_2, 4-NO_2, 4-NH_2, 3-NH_2 2-OH, 3,5 di-NH_2

P. Nagarjuna Reddy *et al*, worked on the Synthesis, characterization and anti-microbial evaluation of novel 1,3,4-oxadiazole containing pyrazolones and 2-thiazolidinone ring systems. Most of the compounds exhibited moderate antibacterial activity against both bacteria. The presence of chloro, bromo and nitro in the structure has shown increased effect on their antibacterial activity[43].

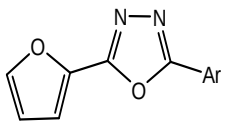


Vivek D. Bobade *et al*, worked on the Synthesis and antimicrobial studies of 2-(5-substituted)-1, 3, 4-oxadiazole-2-yl)-H-imidazo [1, 2, α] pyridine derivatives. All the synthesized compoundswere tested for their antibacterial and antifungal activity of which compound 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 6a, 6c and 6d exhibited good antimicrobial activity[44].



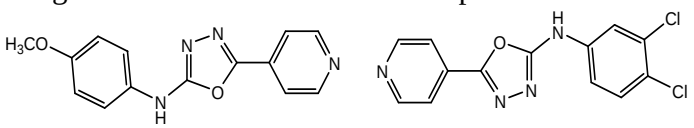
Antitubercular activity

Alex Martin synthesized 2, 5-Disubstituted-1, 3, 4-Oxadiazoles. The synthesized compounds were screened for their anti-tubercular activity. The anti-tubercular activity was carried out against M. tuberculosis H37RV strain. The MIC values for the *in-vitro* anti-tubercular studies of the compound. The anti-tubercular activity revealed that all the compounds showed activity at concentrations 100µg/ml and 50µg/ml[45].

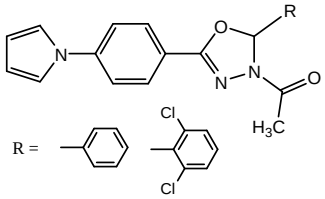


Ar = 4.a) p-chlorobenzoic acid, 4.b) p-nitrobenzoic acid, 4.c) 3,5-dinitrobenzoic acid, 4.d) Benzoic acid 4.e) o-aminobenzoic acid, 4.f) p-hydroxybenzoic acid. 4.g) Salicylic acid.

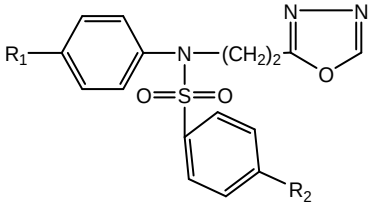
M. Asif, synthesized Some of the 2-isonicotinoylhydrazinecarboxamide, 5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine, *N´*-(*E*)-heteroaromatic-isonicotino-hydrazide and 1-(7-chloroquinolin-4-yl)-2-(heteroaromatic)methylene hydrazone derivatives. The synthesized compounds were screened for their anti-tubercular activity. Several compounds were non-cytotoxics and exhibited significant MIC value (3.12, 2.50, 1.25, or 0.60 µg/mL) compared with ethambutol (3.12 µg/mL) and rifampicin (2.0 µg/ml). These results can be considered an important point for the rational design of new leads for anti-TB compounds[46].



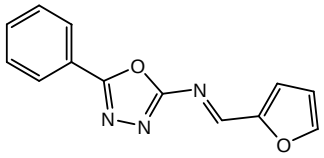
S.D. Joshi *et al*, Synthesized new 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems. Compounds were evaluated for their preliminary in vitro antibacterial activity against some Gram-positive and Gram-negative bacteria and compounds were screened for anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method. Some compounds showed very good antibacterial and antitubercular activities[47].



Shobha R. Desai *et al*, worked on the Synthesis and Pharmacological Activities of Some New 5-Substituted-2-mercapto-1,3,4-oxadiazoles. Only two compounds 4b (73%) and 4e (54%), have shown moderate antituberculosis activity. All the compounds have shown moderate anti-inflamatory activity and least ulcerogenecity. Most of the compounds have shown significant analgesic activity (64.20-120.72%) in comparison with the standard, Aspirin (49.39%) In the MES method, however only compound 4a, exhibited a protection of 33.33%, and others failed to protect[48].

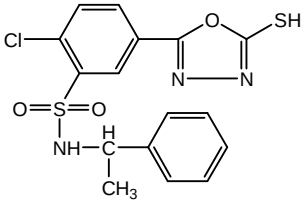


B. Mathew *et al*, worked on the Design, Synthesis, Toxicity Estimation and Molecular Docking Studies of N‑(furan‑2‑yl)‑1‑(5‑substituted) phenyl‑1,3,4‑oxadiazol‑2‑yl) methanimine. The mechanism of action of the titled derivatives was predicted by docking on the *Mycobacterium tuberculosis* Enoyl‑ACP reductase enzyme. The antitubercular studies showed that the both Fa and Fb possessed significant activity with the MIC as low as 3.125 µg/ml[49].

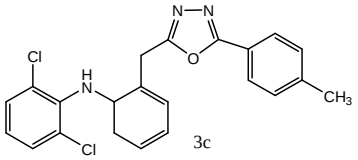


Miscellaneous

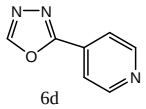
R. Iqbal *et al,* worked on the Synthesis, Antimicrobial and Anti-HIV Activity of Some Novel Benzenesulfonamides Bearing 2,5-Disubstituted-1,3,4-oxadiazole Moiety. Some of the synthesized compounds have been screened in vitro for their antimicrobial and anti-HIV activity; the results were in accordance with SAR[50].



R. R. Somani *et al,* worked on the Synthesis and Evaluation of Anti-inflammatory, Analgesic and Ulcerogenic Potential of NSAIDs Bearing 1,3,4-Oxadiazole Scaffold. These compounds were further subjected to anti-inflammatory, analgesic and acute ulcerogenic activity. Compound 3c and 6d exhibited good antiinflammatory activity and compounds 3c, 3e, 6c, 6d, 6e were found to be non ulcerogenic[51].

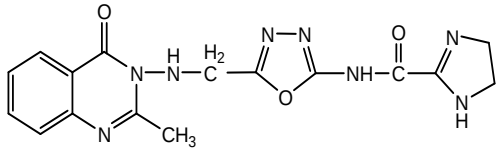


3c

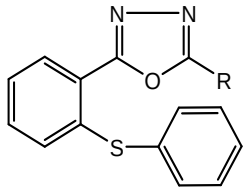


6d

Mirdula Tyagi, worked on the 2-{2"-carbomyl-5"-[3'-amino-2'-methylmono/Dihalosubstituted Quinazolin-4'(3'h)-onomethylene]-1",3",4"-oxadiazol-2"-yl}-4,5-dihyd and evaluated for their cardiovascular activity. The most active compound of this series is 2-{2"-carbomyl-5"-[3'-amino-2'-methyl-6-bromoquinazolin-4'(3'H)-onomethylene]-",3",4"-oxadiazol-2"- yl}-4,5-dihydroimidazolines i.e. compound VIc[52].

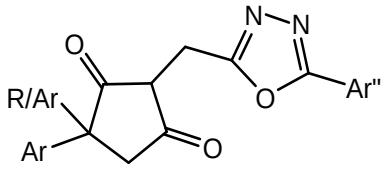


Shafiee *et al,* Synthesized A series of Substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazoles. Compounds were evaluated *in vivo* for their anticonvulsant and muscle relaxant activities using PTZ and rotarod tests, respectively. Only compound 3-amino-5-[2-(phenylthio) phenyl]-4*H*-1,2,4-triazole (5) showed weak anticonvulsant activity. However, most of the compounds were active in rotarod test and the most effective compound was 5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole-2(3*H*)-one (13) which had comparable activity with diazepam[53].



R = NH_2, SH, SCH_3, OH

Dinesh Rishipathak *et al,* worked on the Design and Molecular Docking Studies of Some 1,3,4-Oxadiazole Derivatives and found that the derivatives hiving good protein binding activity[54].



CONCLUSION

This review thus gives an overview of therapeutic and diverse biological properties of the 1,3,4- oxadiazole ring and the availability of varied drugs in the market containing the heterocyclic ring. Therefore, These observations have been guiding for the development of 1,3,4-oxadiazole nucleus, which can be a lead nucleus for future developments to get safer and effective compounds. Thus this paper proves to be significant for further research work on the bioactive oxadiazole ring.

ACKNOWLEDGEMENT

The authors are grateful to Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Guntur for providing facilities to perform the research work.

CONFLICT OF INTEREST

None declared.

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