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REVIEW ARTICLE

Significance of 1,3,4-Oxadiazole Containing Compounds in New Drug Development

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Abstract: ***Background*:** Oxadiazole core displays various pharmacological properties among five membered nitrogen heterocyclic compounds, specially 1,3,4-oxadiazole containing molecules that have occupied a particular place in the field of synthetic medicinal chemistry as surrogates (bioisosteres) of carboxylic acids, carboxamides and esters. Moreover, they are having widespread kind of applications in numerous zones as polymers, as luminescence producing materials and as electron-transporting materials and corrosion inhibitors.

***Methods*:** This study contains comprehensive and extensive literature survey on chemical reactivity and biological properties associated with 1,3,4-oxadiazole containing compounds.

***Results*:** This review summarises 1,3,4-oxadiazole moiety in numerous compounds with reported pharmacological activity such as antiviral, analgesic and anti-inflammatory, antitumor, antioxidant, insecticidal and anti-parasitic, etc.. Nevertheless, ring opening reactions of the 1,3,4-oxadiazole core have also made great attention, as they produce new analogues containing an aliphatic nitrogen atom and to other ring systems.

***Conclusion*:** In relation to the occurrence of oxadiazoles in biologically active molecules, 1,3,4-oxadiazole core emerges as a structural subunit of countless significance and usefulness for the development of new drug aspirants applicable to the treatment of many diseases. It concludes that 1,3,4-oxadiazole core compounds are more efficacious and less toxic medicinal agents with respect to new opinions in the search for rational strategies.

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1. INTRODUCTION

Compounds containing nitrogen as heteroatom exhibit an imperative character in drug discovery and development [1]. Nitrogenous core frequently occurs in the chemical structure of many drugs with different ring sizes, aromatic and non-aromatic skeleton, bicyclic and fused ring systems. Nitrogen containing heterocycles are present in diverse therapeutic zones such as cardiovascular disorders, metabolism diseases, brain disorders, analgesic and anti-inflammatory, anticancer, anti-infective drugs, etc. '59% of small-molecular drugs which are distinctive in nature and approved by the Food and Drug Administration, USA, contain a nitrogen heteroatom' said the authors of an incredible review which has published by Njardarson's group [2], from the University of Arizona, Tucson.

Oxadiazole core displays various pharmacological properties among five membered nitrogen heterocyclic compounds specially 1,3,4-oxadiazole containing molecules have occupied a particular place in the field of synthetic medicinal chemistry as surrogates (bioisosteres) of carboxylic acids, carboxamides and esters. Moreover, they are having widespread kind of applications in numerous zones as polymers [3], as luminescence producing materials [4], as electron-transporting materials [5] and as corrosion inhibitors [6]. An imperative characteristic feature of oxadiazole ring is that it is stable in aqueous medium which certifies the development of biologically active molecules containing this moiety. An additional significant feature of oxadiazole compounds is their ability to act as a hydrogen bond acceptor, owing to the presence of non-ligand electron pairs of the heteroatoms in their structural organization [7]. Oxadiazole nuclei are usually employed as a bioisosteric replacement for compounds containing carbonyl groups for example amide, ester, carbamate and hydroxamic ester in drug discovery. These groups are generally unstable in biological medium, which poses as a hurdle for their usage in the structure of drug applicants [8]. Simultaneously, their spatial geometry is analogous to the oxadiazole bioisostere, thus new compounds can bind similarly at the same bioactive sites [9].

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2. CHEMISTRY OF 1,3,4-OXADIAZOLES

Oxadiazole core is made up of carbon (two atoms), nitrogen (two atoms) and oxygen (one atom). Tiemann and Krüger [10] discovered oxadiazoles first in 1884 and coined the term as furo[ab]diazoles. On account of the inductive effect of extra heteroatom in the ring, oxadiazole is a very weak base and it can be compared with furan [11] isosterically, by the fact that replacement of two methine (−CH=) groups in furan by two pyridine type nitrogen (–N) can be made. In this way, a reduction in aromaticity of the subsequent oxadiazole ring occurs which exhibits the character of conjugated dienes.

Depending on the position of nitrogen atom within the ring structure, oxadiazole contains four possible isomers which may be numbered as presented in Fig. **1** [12].

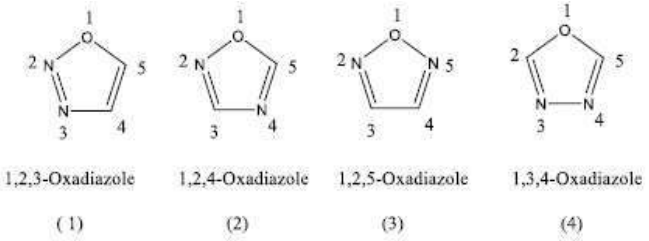


Fig. (1). Four isomers of oxadiazole.

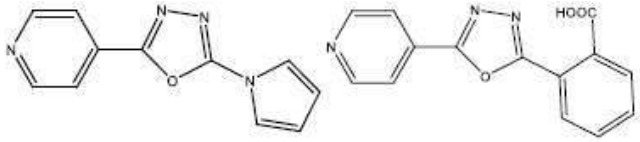
1,3,4-oxadiazoles have been recognized as potential scaffolds since last 80 years due to their structural diversity and varied biological activities [13, 14]. It may be possible to find the oxadiazole moiety in numerous compounds with reported pharmacological activity such as antiviral [15], analgesic and anti-inflammatory [16], antitumor [17], antioxidant [18], insecticidal [19] and antiparasitic [20], etc. Furthermore, ring opening reactions of the 1,3,4-oxadiazole core have also made great attention, as they produce new analogues containing aliphatic nitrogen atom and other ring systems. Usually, the 1,3,4-oxadiazole ring is somewhat more stable to heat but to a certain extent less to the chemical reagents.

3. BIOLOGICAL ASPECTS OF 1,3,4-OXADIAZOLE CONTAINING COMPOUNDS

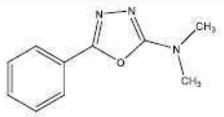
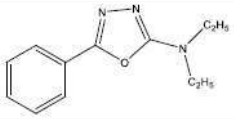
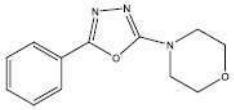
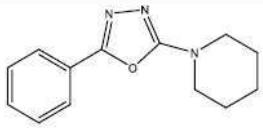
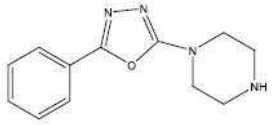
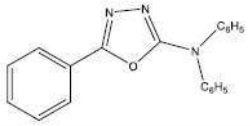
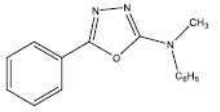
3.1. Analgesic and Anti-inflammatory Activity

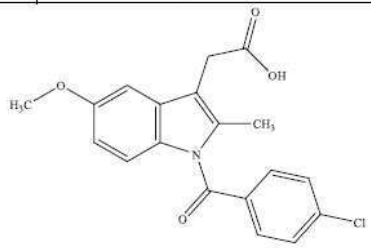
Dewangan D *et al.* (2010) prepared certain compounds containing 1,3,4-oxadiazole core which were synthesized by condensation of pyridine-4-carbohydrazide with phosphoryl chloride as cyclizing agent. All the prepared compounds were investigated for their analgesic and anti-inflammatory activities. Among all, the compounds 2-(pyridin-4-yl)-5-(1H-pyrrol-1-yl)-1,3,4-oxadiazole **(5)** and 2-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl) benzoic acid **(6)** were found to possess better activity [21].

Sahoo B. M. *et al.* (2011) synthesized 5- phenyl- 1, 3, 4-oxadiazole- 2- thiol derivatives which were prepared by the ring closure reactions of carbohydrazides and carbon disulphide in the presence of ethanol & KOH and after that substitution reaction with secondary amine at 2nd position. All the prepared compounds were screened for their anti-inflammatory activity by using carrageenan-induced paw edema method in rats. All the test compounds **(7a-7g)** showed promising anti-inflammatory activity in comparison to indomethacin **(8)** as a standard drug [22].



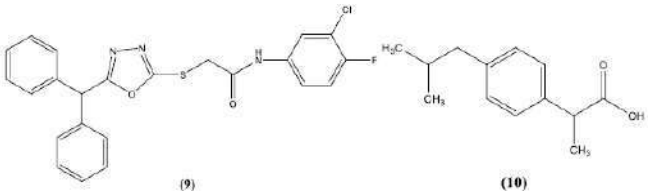
(5) (6)

Compound	Structure
7a	
7b	
7c	
7d	
7e	
7f	
7g	



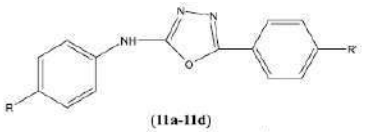
(8)

Amir M. *et al.* (2011) prepared certain derivatives of substituted 1,3,4-oxadiazole which has been obtained from diphenyl acetic acid hydrazide under several reaction conditions. These compounds have been screened for their anti-inflammatory and analgesic activities. The compound 2-((5-benzhydryl-1,3,4-oxadiazol-2-yl)thio)-N-(3-chloro-4-fluorophenyl) acetamide **(9)** has appeared as the most active compound among all and is found to be more potent when compared with standard drug ibuprofen **(10)** [23].



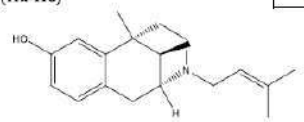
(9) **(10)**

Murti Y *et al.* (2011) synthesized some novel derivatives of 2,5-disubstituted-1,3,4-oxadiazole which were obtained by the reaction of diverse substituted phenyl semicarbazides and substituted benzaldehydes to produce aryl semicarbazones and afterwards in situ cyclisation process by using chloramine-T. The results of pharmacological activities indicated that all the synthesized derivatives have moderate analgesic activity. It can be concluded from SAR study that 2nd and 5th positions are very important in lieu of molecular modifications. Compounds 11a-11d emerged to possess higher analgesic activity when compared to pentazocin **(12)** [24].



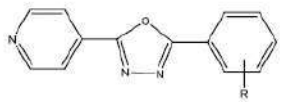
(11a-11d)

Compound	R	R'
11a	Cl	Cl
11b	Br	Cl
11c	Cl	Br
11d	Br	Br

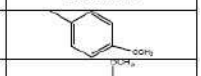
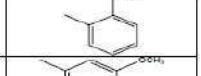
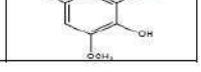


(12)

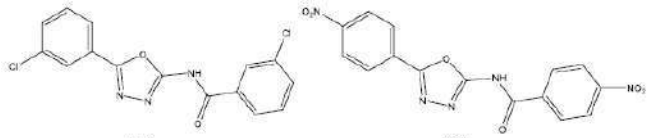
Biju C R *et al* (2012) focused on the integration of the oxadiazole core into isoniazid drug to get 2-aryl-5-(4-pyridyl)-1,3,4-oxadiazole derivatives which were synthesized by microwave process and evaluated for their analgesic and anti-inflammatory activities against a standard drug Indomethacin **(4)**. Among all synthesized 1,3,4-oxadiazole analogues, compounds 13a, 13b and 13c showed good analgesic and anti-inflammatory activity [25].



(13a-13c)

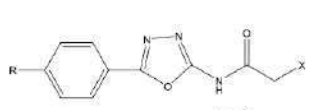
R	Substituent
13a	
13b	
13c	

Singh A. K *et al.* (2011) prepared certain analogues of five-membered heterocyclic rings having oxadiazole core which were obtained by the reaction of benzoyl chloride including various chlolro-nitro-benzoyl chlorides with semi carbazide and were screened for their anti-inflammatory activity by using carrageenan-induced rat-paw-oedema model. The compounds 3-chloro-N-(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)benzamide **(14)** and 4-Nitro-N-[5-(4-Nitro-phenyl)- [1, 3, 4] oxadiazole-2yl] benzamide **(15)** provides better response for the anti-inflammatory activity. For this activity, indomethacin **(8)** was used as a standard drug and compared to newly synthesized derivatives [26].

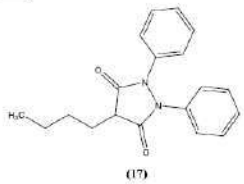


(14) **(15)**

Jain S. K. *et al* (2014) organized a sequence of 2-substituted acetamido-5-aryl-1,3,4-thiadiazoles (sixteen compounds) which were evaluated for their anti-inflammatory and analgesic activity. Compound **16a** showed very good anti-inflammatory activity (51 percent paw oedema inhibition) comparable to phenyl butazone **(17)** as a standard drug. Compounds **16b, 16c** and **16d** showed moderate anti-inflammatory activity (22-37 percent paw oedema inhibition). None of the compounds showed analgesic activity [27].

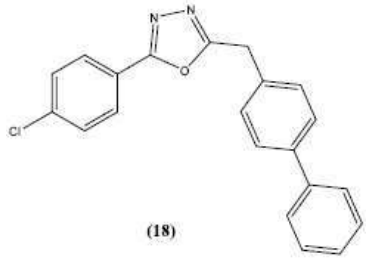


Compounds	R	X
16a	CH_3	N-methyl-N-n-butylamino
16b	CH_3O	N-methyl-N-n-butylamino
16c	H	Dicyclohexylamino
16d	CH_3	Dicyclohexylamino



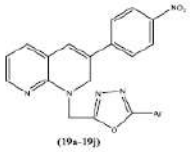
(17)

Khan S. A *et al.* (2017) prepared a series of oxadiazole derivatives and among all the prepared derivatives, 2-(biphenyl-4-ylmethyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole **(18)** appeared as the maximum effective NSAIDS analogue showing the highest anti-inflammatory activity (72.87% inhibition) and analgesic activity (65.24%) [28].



(18)

Mogilaih *et al* (2017) prepared a series of oxadiazole compounds and among all the synthesized compounds, 19b, 19d, 19e and 19f showed promising anti-inflammatory activity. The remaining compounds exhibited moderate anti-inflammatory activity [29].

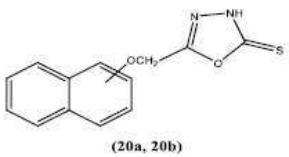


(19a-19j)

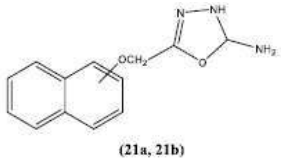
Ar	Ar
19a = C_6H_5	19f = 4-FC_6H_4
19b = 4-$CH_3C_6H_4$	19g = 2-$NO_2C_6H_3$
19c = $CH_3C_6OH_4$	19h = 3-$NO_2C_6H_5$
15d = 2-ClC_6H_4	15i = 4-$NO_2C_6H_4$
15e = 4-ClC_6H_4	15j = 3,4-$(CH_3O)_2C_6H_3$

3.2. Antimicrobial Activity

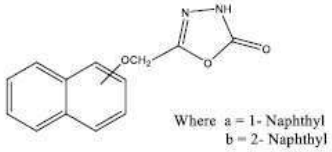
Sahin G *et al.* (2002) prepared a series of compounds in which six new derivatives viz. 5-(1-/ 2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3H)-thione, 2-amino-5-(1-/ 2-naphthyloxymethyl)-1,3,4-oxadiazole, 5-(1-/ 2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3H)-one have been prepared from 1-/ 2-naphthol. The antimicrobial properties of the compounds were examined against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* (bacterial strains) & *Candida albicans*, *Candida krusei* and *Candida parapsilosis* (fungal strains) by using microbroth dilution method. All the compounds were active against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Candida parapsilosis* at the concentration of 64–256 µg/ml [30].



(20a, 20b)



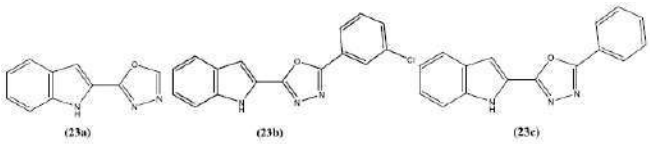
(21a, 21b)



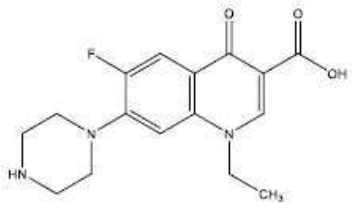
Where a = 1- Naphthyl
b = 2- Naphthyl

(22a,22b)

Bhardwaj N *et al.* (2009) prepared a series of 1,3,4-Oxadiazoles which have been synthesized from different compounds and screened for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Aspergillus niger* by Punched-hole method. The compounds 2-(1H-indol-2-yl)-1,3,4-oxadiazole **(23a)**, 2-(3-chlorophenyl)-5-(1H-indol-2-yl)-1,3,4-oxadiazole **(23b)** and 2-(1H-indol-2-yl)-5-phenyl-1,3,4-oxadiazole **(23c)** showed good antibacterial activity against standard drug norfloxacin **(24)** while none of the compounds exhibited antifungal activity [31].

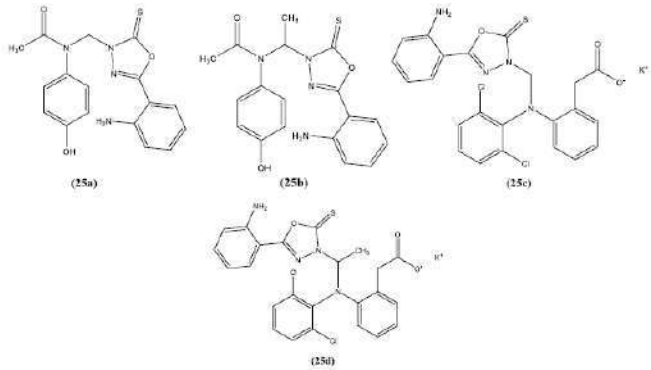


(23a) (23b) (23c)



(24)

Selvakumar Kanthiah *et al.* (2011) prepared few analogues of 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3H)-thione which have been investigated for *in vitro* antibacterial activity by disc diffusion method against *Staphylococcus aureus, Streptococcus pyogenes* as Gram positive organisms and *Escherichia coli, Klebsiella aerogenes* as Gram negative organisms and antifungal activity against *Candida albicans*. Compounds N-((5-(2-aminophenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl)-N-(4-hydroxyphenyl) acetamide **(25a)**, N-(1-(5-(2-aminophenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)ethyl)-N-(4-hydroxyphenyl) acetamide **(25b)**, Potassium-2-(2-(((5-(2-aminophenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) methyl) (2,6-dichloro phenyl) amino)phenyl) acetate **(25c)** and Potassium-2-(2-((1-(5-(2-aminophenyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) ethyl) (2,6-dichloro phenyl) amino)phenyl) acetate **(25d)** showed adequate antibacterial and antifungal activities at a concentration of 100 µg per ml. Amikacin **(26)** for antibacterial action and ketoconazole **(27)** for antifungal action were used as reference standard at the concentration of 10 µg per ml [32].

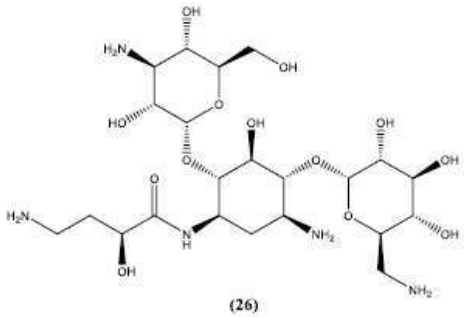


(25a) (25b) (25c)

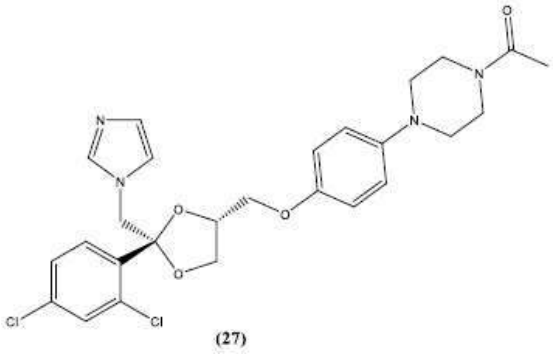
(25d)

Desai *et al.* (2014) prepared a novel series of 2-{5-[4-(1-aza-2-(2-thienyl) vinyl) phenyl](1,3,4-oxadiazole-2-ylthio)}-N-arylacetamides **(28a-28l)** were screened for their antibacterial and antifungal activities against *Staphy-*

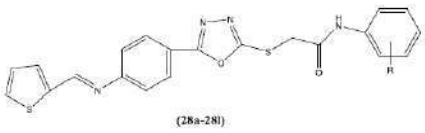
lococcus aureus, Staphylococcus pyogens, Escherischia coli, Pseudomonas aeruginosa, Candida albicans and *Aspergillus clavatus*. It was found that compounds **(28e), (28f), (28g)** possess excellent antibacterial activity whereas compounds **(28g), (28i)** and **(28j)** possess admirable antifungal activity when compared to ampicillin **(29)** and griseofulvin **(30)** as reference standard drugs. SAR study revealed that augmentation of the activity of these compounds may be attributable to the occurrence of methyl, methoxy and halogen groups in the title compounds [33].



(26)



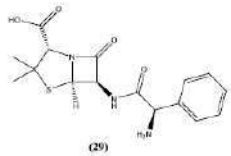
(27)



(28a-28l)

Compound	R
28e	2,4-$(CH_3)_2$
28f	3-OCH_3
28g	3,4-$(Cl)_2$
28i	4-Cl
28j	4-NO_2

Bala S *et al.* (2014) prepared two series of compounds viz. 1-(4-methoxy-phenyl)-3-[5-(substituted phenyl)-1,3,4-oxadiazol-2-yl]propan-1-one and [2-(5-substituted-phenyl-[1, 3, 4]oxadiazol-2-yl)-phenyl]phenyl-methanone and screened against selected microbial strains viz. *Staphylococcus aureus, Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans and Aspergillus niger*. It was found that compounds {2-[5-(4-Chlorophenyl)- [1, 3, 4]oxadiazol-2-yl]-phenyl}-phenyl-methanone **(31a)** having p-chloro group and {2-[5-(3-Methoxy-4-hydroxyphenyl)- [1, 3, 4]oxadiazol-2-yl]-phenyl}-phenyl-methanone **(31b)** containing m-methoxy and p-hydroxyl groups were the utmost effective among all the derivatives when compared to Amoxicillin **(32)**, Cefixime **(33)** and Fluconazole **(34)** as reference standard drugs [34].



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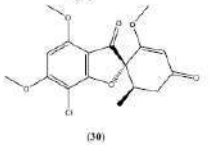

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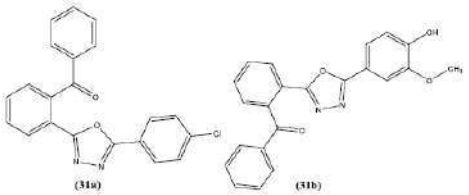
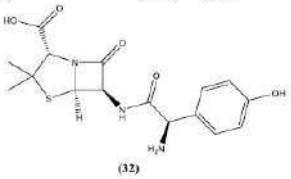


(31a) (31b)

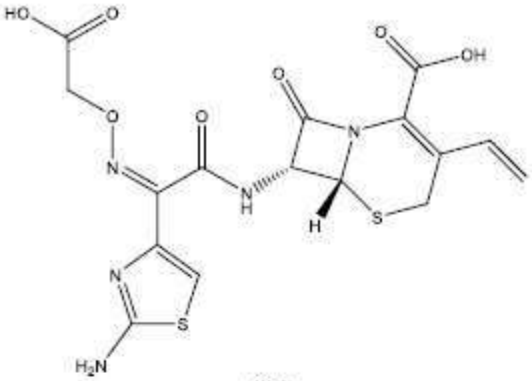


(32)

Raju G. N. *et al.* (2015) synthesized some novel derivatives of 5-substituted-1,3,4-oxadiazole-2-thiol containing piperazinyl benzothiazole by the reaction of piperazinyl benzothiazoles and 5-substituted-1,3,4-oxadiazole-2-thiol. All prepared derivatives were tested against *Staphylococcus aureus, Staphylococcus pyogenus, Escherichia coli* and *Pseudomonas aeruginosa* for their antibacterial activity and screened against *Candida albicans* and *Asperigillus niger* for their antifungal activity. The pharmacological activity of the prepared compounds has been compared with Ampicillin **(29)** and Griseofulvin **(30)** as standard drugs. Among all, the compounds **35a**, **35b**, **35d** and **35e** showed good antibacterial activity while **31c** and **31e** showed good antifungal activity [35].

3.3. Anticancer Activity

Sengupta P. *et al.* (2008) synthesized carboxy-methyl derivatives of several para-substituted and un-substituted oxadiazole-2-thione which were assessed for their possible anticancer activity by using Swiss albino mice (male) as test animal. The anti-cancer activity was assessed by making comparison of the ability of the test compound (25 mg per kg) to inhibit the tumor weight along with tumor cell count with that of the control. The results indicated that all the studied compounds showed a significant reduction in tumor weight as well as tumor cell count with respect to the control. Compound 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetic acid **(36)** is found to be most potent among all when compared to Mitomycin C (1mg per kg) **(37)** as standard [36].



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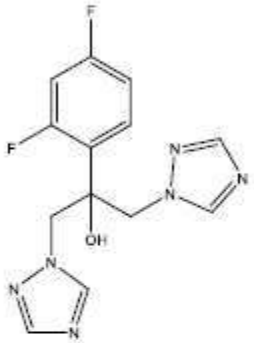

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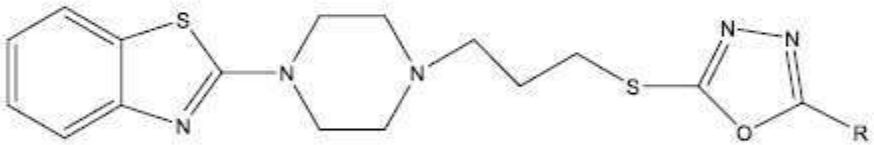
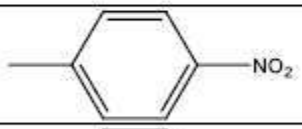
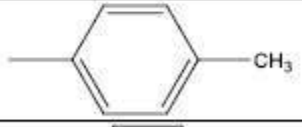
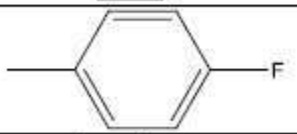
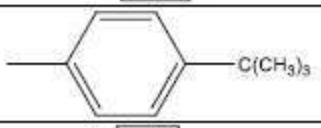
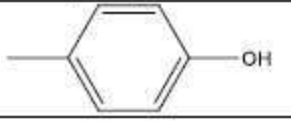
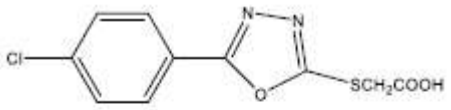


Compound	R
35a	
35b	
35c	
35d	
35e	



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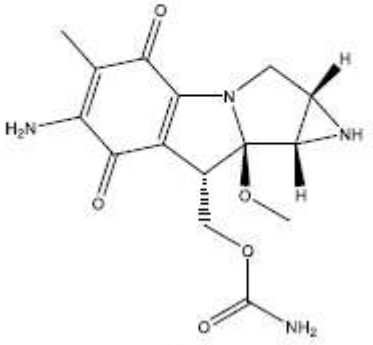
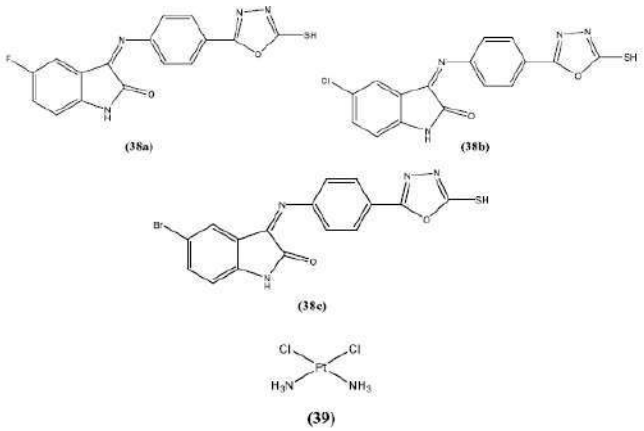


(37)

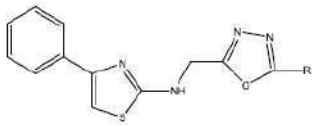
Gudipati R. *et al.* (2011) synthesized certain derivatives of 3-{4-(5-mercapto-1,3,4-oxadiazole-2-yl) phenylimino}indolin-2-one which were screened for their potential anticancer activity against HeLa cancer cell lines by using MTT assay. Among all, the compounds (Z)-5-fluoro-3-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)imino)indolin-2-one **(38a),** (Z)-5-chloro-3-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)imino)indolin-2-one **(38b)** and (Z)-5-bromo-3-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)imino)indolin-2-one **(38c)** found to be the most potent anticancer agents with that of Cisplatin **(39)** as standard drug. It may be attributable to the occurrence of halogen moiety at 5th position of benzene ring which might be useful leads for the development of anticancer drugs in the future [37].



(38a) **(38b)** **(38c)**

(39)

Jisha Mol. V. *et al.* (2013) prepared a series of certain thiazole-1, 3, 4-oxadizole derivatives which were obtained by the interaction of 2-[(4-phenyl-1,3-thiazol-2-yl)amino]acetohydrazide with substituted aliphatic or aromatic acids in the presence of phosphorusoxychloride as a dehydrating agent. The synthesized compounds were then examined for their probable anticancer activity on the human breast cancer cell line MCF-7 and lymphoma cancer cell line DLA. All derivatives displayed significant activity on both the cell lines and Compound N-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl] methyl}-4-phenyl-1,3-thiazol-2-amine **(40c)** exhibited moderate activity against MCF-7 and DLA cell lines [38].

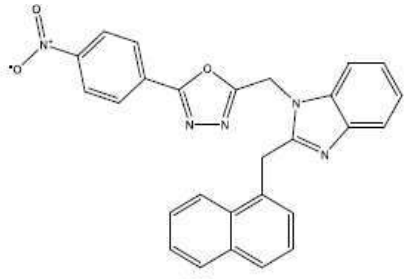


(40a-40f)

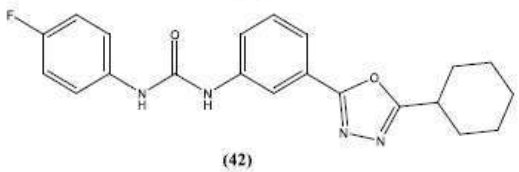
Compound	R
40a	CH_2Cl
40b	C_6H_5
40c	C_6H_5Cl
40d	$C_6H_5NH_2$
40e	$C_6H_5NH_2$
40f	C_6H_5OH

Salahuddin *et al.* (2014) organized two series of compounds containing 1,3,4-oxadiazole ring by using chloramines-T from Schiff base and phosphorus oxychloride from hydrazides. All the compounds of both series were assessed for their *in vitro* anticancer activity. Among all, the compound 2-Naphthalen-1-ylmethyl-1-[5-(4-nitro-phenyl)- [1, 3, 4]oxadiazol-2-ylmethyl]-1H-benzimidazole **(41)** showed a promising activity against MDA-MB-468 cell line (Breast Cancer) and SK-MEL-28 cell line (Melanoma)(GP=36.23 & 47.56, respectively) while the compounds ethyl {2-[(naphthalen-2-yloxy)methyl]-1H-benzimidazol-1-yl}acetate **(42)** and 1-[5-(4-Methoxy-phenyl)- [1, 3, 4]oxadiazol-2-ylmethyl]-2-naphthalen-1-ylmethyl-1H-benzimidazole **(43)** exhibited moderate activity [39].

Mochona B. *et al* (2015) prepared a series of benzimidazole analogues containing 1,3,4-oxadiazole ring which was evaluated for cytotoxic activity. All derivatives exhibited moderate cytotoxic activity against breast tumor cell lines. The activity might be attributed to synergism effect between benzimidazole and 1,3,4-oxadiazole molecule. Compound **(44c)** exhibited moderate inhibition potency (< 50 μM) [40].



(41)



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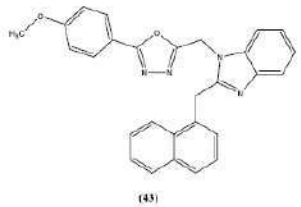

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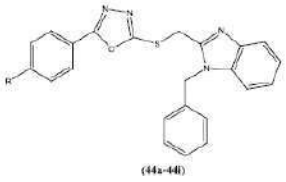
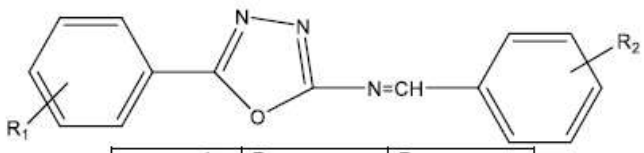


(44a-44l)

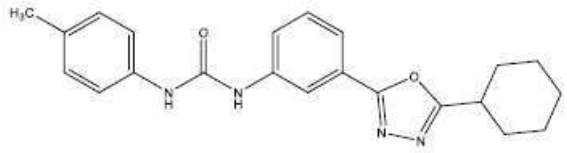
Compound	R	Compound	R
44a	H	44f	Cl
44b	OCH_3	44g	$C(CH_3)_3$
44c	F	44h	NH_2
44d	NO_2	44i	Br
44e	CH_3		

Roy *et al.* (2016) prepared a series of 2, 5-disubstituted 1, 3, 4-Oxadiazole derivatives **(45a-45g)** which were prepared with the help of different aromatic benzaldehyde. All synthesized compounds **(45a-45g)** showed significant anticancer activity which may result marked increase in an average life span of experimental animals [41].

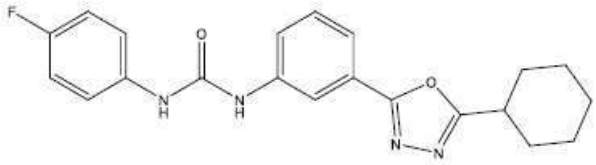


compound	R_1	R_2
45a	4-OH	4'-$N(CH_3)_2$
45b	2-Cl	2'-NO_2
45c	3-Br	4'-Cl
45d	4-$N(CH_3)_2$	4'-$N(CH_3)_2$
45e	2-Cl	4'-$N(CH_3)_2$
45f	3-Br	4'-OH
45g	4-OCH_3	4'-$N(CH_3)_2$

Selvaraj K. *et al* (2017) prepared a series of 3-(5-cyclohexyl-1,3,4-oxadiazole-2-yl)-N-substituted aniline which was obtained from benzohydrazide by using multi-step reaction scheme. All the synthesized derivatives of 1,3,4-Oxadiazole were assessed for their possible anticancer activity towards two different cell lines using 3-(4,5-di methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cisplatin **(39)** was used as a reference standard drug and among all, compound 1-[3-(5-Cyclohexyl- [1, 3, 4]oxadiazol-2-yl)-phenyl]-3-p-tolyl-urea **(46)** displayed potent anticancer activity while compounds 1-[3-(5-Cyclohexyl- [1, 3, 4] oxadiazol-2-yl)-phenyl]-3-(4-fluoro-phenyl)-urea **(47),** 1-[3-(5-Cyclohexyl- [1, 3, 4] oxadiazol-2-yl)-phenyl]-3-(3-methoxy-phenyl)-urea **(48)**, N-[3-(5--Cyclohexyl- [1, 3, 4]oxadiazol-2-yl)-phenyl]-2-(2-fluoro-phenyl)acetamide **(49)**, N-[3-(5-Cyclohexyl- [1, 3, 4]oxadiazol-2-yl)-phenyl]-3,5-difluoro-benzamide **(50),** and 4-tert-Butyl-N-[3-(5-cyclohexyl- [1, 3, 4]oxadiazol-2-yl)-phenyl]-benzenesulphonamide **(51)** exhibited cytotoxicity on both cell lines after 48 hours of exposures [42].



(46)



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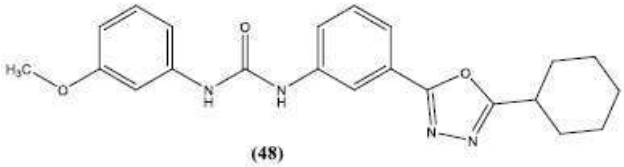

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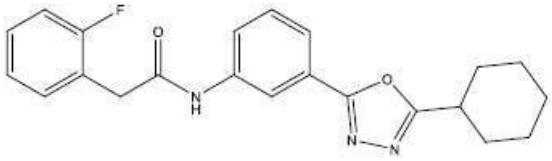

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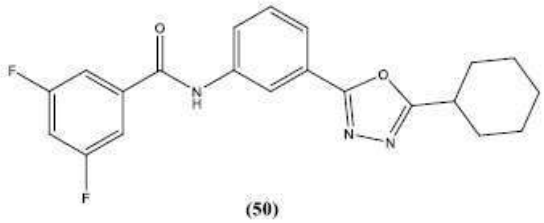

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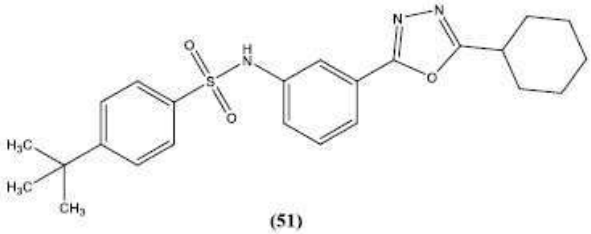
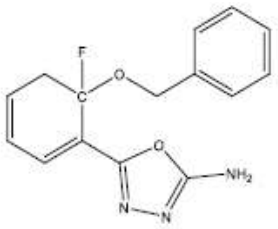


(51)

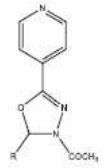
3.4. Anti-Convulsant Activity

Zarghi A. *et al.* (2008) prepared a series of compounds containing 1,3,4-oxadiazole moiety which were investigated for their probable anticonvulsant activity by using maximal electroshock) and pentylenetetrazole models. Compound 2-Amino-5-(2-fluoro-2-benzyloxyphenyl)-1,3,4-oxadiazoles **(52)** has shown superior anticonvulsant activity. SAR study revealed that when amino group occurs at 5th position of 1,3,4-oxadiazole ring it displays good anticonvulsant activity [43, 44].



(52)

Gilani SJ *et al.* (2009) prepared a series of 1-(2-(2-substitutedphenyl)-5-(pyridine-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone derivatives 20a-h which were screened for their anticonvulsant activity by using maximal electroshock and pentylenetetrazole (subcutaneous mode) test by using adult male albino mice in 25-30 g body weight. Compounds 1-(2-(2-chlorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl) ethanone **(53a),** 1-(2-(2-hydroxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl) ethanone **(53c)** and 1-(2-(4-nitrophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl) ethanone (**53g)** showed significant activity in case of both type of models [45].

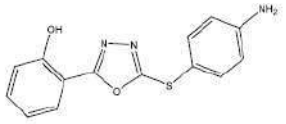


(53)

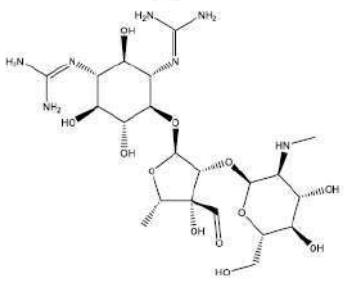
Compound	R
53a	o-C_6H_5Cl
53b	p-C_6H_5Cl
53c	o-C_6H_5OH
53d	m-C_6H_5OH
53e	p-$C_6H_5OCH_3$
53f	p-C_6H_5F
53g	p- $C_6H_5NO_2$
53h	*p* - $C_6H_5N(CH_3)_2$

3.5. Anti-tubercular Activity

Pattan SR *et al.* (2009) prepared a series of 1,3,4 oxadiazole derivatives which were assessed for their anti-tubercular activity. All the compounds have shown significant anti--tubercular activity and compound 2-(5-((4-aminophenyl)thio)-1,3,4-oxadiazol-2-yl) phenol **(54)** displayed prominent activity as compared to the standard drug streptomycin **(55)** [46].



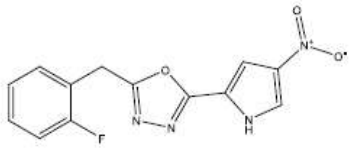
(54)



(55)

Rane *et al*. (2013) prepared a series of 2-(4-nitro-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole analogues. It was found that compound 2-(2-fluorobenzyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-

Oxadiazole **(56)** revealed uppermost anti-tubercular activity (0.46 µg per ml) among all which is very close to standard drug Isoniazid **(57)** (0.40 µg per ml) [47].



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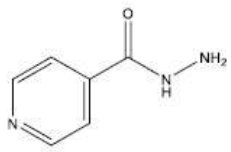
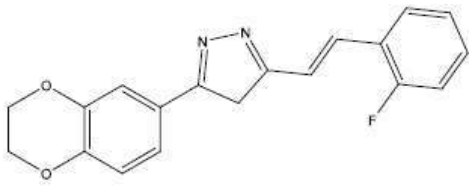


(57)

3.6. Anti-tumor Activity

Sun J *et al.* (2013) synthesized certain derivatives of 1,3,4-oxadiazole containing 1,4-benzodioxan moiety and assessed for their probable antitumor activity. Among all, many compounds were found to have significant antitumor activity and low toxicity. Compound (E)-3-(2,3-dihydrobenzo[b] [1, 4]dioxin-6-yl)-5-(2-fluorostyryl)-4H-pyrazole **(58)** displayed the maximum effective pharmacological activity against human umbilical vein endothelial cells (HUVEC) [48].



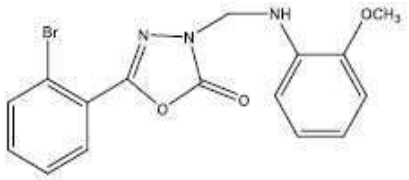
(58)

Shahzad *et al* (2014) synthesized several new derivatives of 3-(2-Methoxyphenylaminomethyl)-5-(2-bromophenyl)-1,3,4-oxadiazoline-2-thione which have been proven to have significant anti-tumor property and compound 5-(2-bromophenyl)-3-(((2-methoxyphenyl) amino)methyl)-1,3,4-oxadiazol-2(3H)-one **(59)** exhibited prominent activity [49].

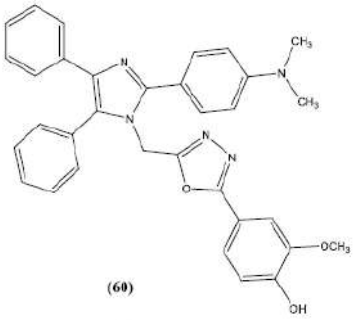
3.7. Cardiovascular Activity

Malhotra V *et al.* (2011) organized a series of some newer derivatives containing imidazole which have been examined for their *in vivo* hypotensive and acute toxicity activities. Out of total seventeen analogues, eight analogues have presented considerable hypotensive and bradycardiac re-

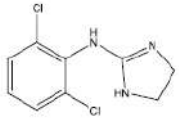
sponses and compound 4-(5-((2-(4-(dimethylamino) phenyl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)-2-methoxyphenol **(60)** has shown better activity than reference drug clonidine **(61)** [50].



(59)



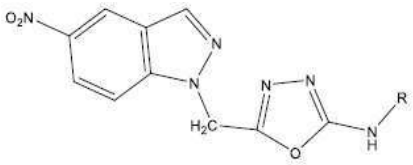
(60)



(61)

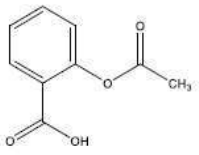
3.8. Antipyretic Activity

Cheptea C *et al.* (2012) prepared a series of 2-[(5'-nitroindazole-1'-methyl)]-5 (p-bromophenylamino)-1,3,4-oxadiazole analogues. Among all, the compounds N-(4-bromophenyl)-5-((5-nitro-1H-indazol-1-yl)methyl)-1,3,4-oxadiazol-2-amine **(62a)** and N-(4-chlorophenyl)-5-((5-nitro-1H-indazol-1-yl)methyl)-1,3,4-oxadiazol-2-amine **(62b)** exhibited outstanding antipyretic activity which is very close to acetylsalicylic acid **(63)** [51].



R = C_6H_4Br, C_6H_4Cl

(62)



(63)

CONCLUDING REMARK AND PERSPECTIVES

In relation to the occurrence of oxadiazoles in biologically active molecules, four types, namely 1,2,3-Oxadiazole, 1,2,4-Oxadiazole, 1,2,5-Oxadiazole and 1,3,4-Oxadiazole stand out. Out of these, 1,3,4-oxadiazole core emerges as a structural subunit of countless significance and usefulness for the development of new drug aspirants applicable to the treatment of many diseases. The 1,3,4-oxadiazoles undergo a number of chemical reactions, including nucleophilic substitution, electrophilic substitution, thermal and photochemical reactions. 1,3,4-oxadiazole containing compounds are resourceful substrates, wherever they can be utilised for the preparation of a huge range of heterocyclic molecules and as starting material for the synthesis of many drugs.

The review of the literature shown that 1,3,4-oxadiazole core is a resourceful lead for the design of prospective bioactive compounds, and their derivatives which were described to retain broad-spectrum of biological activities. This analysis indicates the importance of 1,3,4-oxadiazole core and proven to be prominent since it is relevant to wide range of biological activities.

It has been concluded that 1,3,4-oxadiazole core containing derivatives had promising analgesic and anti-inflammatory, anticonvulsant, antitubercular, antimicrobial, antitumor and anticancer properties. This nucleus is the new insight to ascertain a new lead target. Due to the high efficacy and lower adverse effects of 1,3,4-oxadiazole, this core may be useful tool in current drug discovery relevant to modern anticancer therapy.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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