Therapeutic potential of oxadiazole or furadiazole containing compounds

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Abstract

As we know that, Oxadiazole or furadiazole ring containing derivatives are an important class of heterocyclic compounds. A heterocyclic five-membered ring that possesses two carbons, one oxygen atom, two nitrogen atoms, and two double bonds is known as oxadiazole. They are derived from furan by the replacement of two methylene groups (==CH) with two nitrogen (-N==) atoms. The aromaticity was reduced with the replacement of these groups in the furan ring to such an extent that it shows conjugated diene character. Four different known isomers of oxadiazole were existed such as 1,2,4-oxadiazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole & 1,3,4-oxadiazole. Among them, 1,3,4-oxadiazoles & 1,2,4-oxadiazoles are better known and more widely studied by the researchers due to their broad range of chemical and biological properties. 1,3,4-oxadiazoles have become important synthons in the development of new drugs. The derivatives of the oxadiazole nucleus (1,3,4-oxadiazoles) show various biological activities such as antibacterial, anti-mycobacterial, antitumor, anti-viral and antioxidant activity, etc. as reported in the literature. There are different examples of commercially available drugs which consist of 1,3,4-oxadiazole ring such as nitrofuran derivative (Furamizole) which has strong antibacterial activity, Raltegravir as an antiviral drug and Nesapidil drug is used in anti-arrhythmic therapy. This present review summarized some pharmacological activities and various kinds of synthetic routes for 2, 5-disubstituted 1,3,4-oxadiazole, and their derived products.

Keywords: 1, 3, 4-oxadiazole, Heterocyclic compounds, Antiviral, Antitumor, Antitubercular

Background

Health problems were increasing day by day and become the most serious clinical problem. Recently, medicinal chemists have been looking for new drugs to be used safely to treat these serious clinical problems. There are a lot of heterocyclic compounds that are in clinical use to treat infectious disease [1].

The most common heterocyclic are those having five or six-member fused rings and possess nitrogen, oxygen, sulfur groups as heteroatoms. Some time boron, silicon, and phosphorus atoms can be used as hetero atoms [2].

Heterocyclic compounds containing nitrogen atom such as oxadiazole moieties are of interest to researchers in the fields of medicinal and pharmaceutical chemistry [3].

A heterocycles five-member ring that possesses one oxygen, two carbons, two nitrogen atoms, and two double bonds is known as oxadiazole [4]. This type of ring system is also known as aza oximes, oxyazao, diozole, diazoxole, furadiazole, and furoxan. Oxadiazole was first synthesized in 1965 by Ainsworth through the thermolysis of hydrazine. Its molecular formula is C2H2ON2 and having a molecular mass of 70.05 g/mol which is soluble in water [2].

Oxadiazoles are thermally stable compounds and their calculated resonance energy is equal to 167.4 kJ/mol. The thermal stability of oxadiazoles is increased with the substitution at the second position [5].

1,3,4-oxadiazole heterocyclic ring is one of the most important heterocyclic moieties due to its versatile biological actions [6]. These are the derivatives of furan in
Fig. 1 Oxadiazole

Fig. 2 Commercially available drugs which contain 1,3,4-oxadiazole nucleus
which two methylene groups were replaced with two nitrogen atoms. Replacement of these two methylene groups by two nitrogen atoms reduces the aromaticity of the ring & the resulting oxadiazole ring exhibits conjugated diene character [7]. Another heteroatom makes a weak base to the oxadiazole due to the inductive effect [6]. Hydrogen atoms were replaced by nucleophiles which are seen in nucleophilic substitution reaction [8].

Nitrogen atoms are present in oxadiazole ring at different positions and based on the position there are four different possible isomers of oxadiazole such as 1,2,3-oxadiazole (a), 1,2,5-oxadiazole (b), 1,3,4-oxadiazole (c) and 1,2,4-Oxadiazole (d) showed in Fig. 1 [6].

Among the different isomers, 1,3,4-oxadiazole isomer shows a lot of therapeutic activities like antibacterial [9, 10], anticonvulsant [11], antitumor [12–22],

![Fig. 3 Mechanism for the formation of 2,5-disubstituted 1,3,4-oxadiazole using phosphorus oxychloride](image)

Electron withdrawing groups enhanced COX-2 inhibition, whereas electron donating groups had a reverse effect

Substitution with $p$-Cl, $p$-NO$_2$ and $p$-$^{13}$Bu render the compounds more COX-2 selective

Replacement of aromatic ring with pyridine diminished COX-2 activity

N-acetylation did not significantly affect the activity

![Fig. 4 Structure–activity relationship of 1,3,4-oxadiazole](image)
hypoglycemic, antipyretic [23], anti-tubercular [10, 24], anti-viral [25], immunosuppressive, spasmytotic, antioxidant [13, 26], anti-inflammatory [23, 27, 28], insecticidal [20], CNS stimulant, ant amoebic, antiemetic, antidepressant, antihelmintic activities, vasodilator activity, antimycotic activity [29], anti-allergic, anti-Alzheimer activity, ulcerogenic and antihypertensive activities etc. as reported in the literature [30]. Keeping the view of this, we have discussed different oxadiazole derivatives carrying urea, amide, and sulphonamide groups to investigate their anticancer, antiviral, antimicrobial, antitubercular, and antioxidant activities [31]. The presence of toxophoric –N=C=O– linkage in 1,3,4-oxadiazole ring might be responsible for their

![Fig. 5 Therapeutic activity of 1,3,4-oxadiazole nucleus](image.png)
potent pharmacological activities. Among these, substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 2,5-disubstituted-1,3,4-oxadiazole derivatives are stable, especially 2,5-diaryl-1,3,4-oxadiazoles are more stable than the corresponding 2,5-dialkyl derivatives. Medicinal chemists have great perseverance in Research and development for the development of newer and safer antitumor agents. Tyrosine kinases (EGFR family) play a very important role in cancer proliferation. So those compounds which inhibit the activity of tyrosine kinases play a substantial role in cancer treatment. Therefore Tyrosine kinases (EGFR family) were selected and explore the binding mode of the novel compounds to EGFR tyrosine kinase active site [32].

There is various kind of synthetic route from which we can synthesize 1,3,4-oxadiazole, and their derived products. In general, 1,3,4-oxadiazole can be synthesized by the reaction of acid hydrazide or hydrazine along with

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**Table 1** Antimicrobial activity of titled compounds (1a-j) [48]

| Compound | Diameter of zone of inhibition (mm) |
|----------|-----------------------------------|
|          | **S. aureus** | **B. subtilis** | **E. coli** | **P. aeruginosa** | **C. albicans** |
| 1a       | 13            | 15             | 14          | 13               | 08              |
| 1b       | 14            | 14             | 13          | 12               | 15              |
| 1c       | 14            | 15             | 14          | 15               | 14              |
| 1d       | 15            | 14             | 13          | 13               | 15              |
| 1e       | 18            | 19             | 18          | 15               | 08              |
| 1f       | 19            | 17             | 18          | 16               | 09              |
| 1g       | 14            | 12             | 15          | 10               | 15              |
| 1h       | 18            | 18             | 19          | 15               | 09              |
| 1i       | 16            | 15             | 14          | 13               | 10              |
| 1j       | 15            | 14             | 15          | 12               | 11              |
| Amoxicillin | 21             | 22             | 21          | 22               | –               |
| Ketoconazole | –              | –              | –           | –                | 23              |
Scheme 2 Synthesis of substituted 1,3,4-oxadiazole derivatives
carboxylic acids/acid chlorides and direct ring closure of diacyl hydrazines employing different kinds of the cyclizing agent such as phosphorus oxychloride, thionyl chloride, phosphorus pentaoxide, triflic anhydride, polyphosphoric acid, acetic anhydride and the direct reaction of an acid with (N-isocyananimino-) triphenylphosphorane [33]. In some reaction, carbon disulfide is also used for ring closure [34].

There are different examples of commercially available drugs containing 1,3,4-oxadiazole ring (Fig. 2) such as a nitrofuran derivative (Furamizole) which has strong antibacterial activity [35]. Raltegravir as an antiviral drug and Nesapil drug is used in anti-arrhythmic therapy. The FDA approved anticancer agent Zibotentan is a 1,3,4-oxadiazole nucleus containing the most privileged derivatives available in the market [36]. Tiodazosin is used as an antihypertensive agent [37]. This present review summarized some pharmacological activities and various kinds of synthetic routes for 2,5-disubstituted 1,3,4-Oxadiazole, and their derived products during the last decade (2005–2020).

The mechanism for the formation of 2,5-disubstituted 1,3,4-oxadiazole
The probable mechanism for the formation of the 1,3,4-oxadiazole is given in (Fig. 3). The presence of lone pair of electron on the nitrogen atom of acid hydrazide attacks the carbonyl carbon atom of carboxylic acid eliminates a water molecule to form a hydrazide derivative which further reacts with phosphorus oxychloride, undergoes ring closure with the elimination of hydrogen chloride, and form 1,3,4-oxadiazole ring [38].

| Compound | Diameter of zone of inhibition (mm) |
|----------|--------------------------------------|
|          | Antibacterial activity               | Antifungal activity |
|          | S. aureus  | B. subtilis  | E. coli  | P. aeruginosa  | C. albicans  | A. niger  |
| 2a       | 14        | 21          | 10      | 17             | 09           | 10        |
| 2b       | 18        | 19          | 12      | 15             | 10           | 11        |
| 2c       | 30        | 27          | 14      | 18             | 09           | 11        |
| 2d       | 19        | 22          | 11      | 18             | 10           | 11        |
| 2e       | 28        | 28          | 14      | 14             | 10           | 09        |
| 2f       | 14        | 19          | 10      | 15             | 10           | 10        |
| 2g       | 21        | 23          | 13      | 19             | 11           | 09        |
| 2h       | 14        | 20          | 10      | 16             | 09           | 10        |
| 3a       | 11        | 12          | 10      | 09             | 11           | 11        |
| 3b       | 10        | 12          | 09      | 11             | 12           | 12        |
| 3c       | 20        | 21          | 12      | 13             | 11           | 11        |
| 3d       | 20        | 22          | 16      | 18             | 10           | 11        |
| 3e       | 18        | 19          | 11      | 13             | 11           | 10        |
| 3f       | 11        | 13          | 10      | 11             | 10           | 11        |
| 3g       | 12        | 14          | 09      | 12             | 10           | 10        |
| 3h       | 10        | 13          | 09      | 11             | 10           | 11        |
| Ciprofloxacin | 26    | 26          | 28      | 25             | –            | –         |
| Fluconazole       | –           | –           | –        | –              | 26           | 25        |

Table 2 Antimicrobial activity of titled compounds (2a-h) and (3a-h) [41]
The structure–activity relationship of 1,3,4-oxadiazole is given in (Fig. 4). Substitution of phenyl ring with different substituents like \( p \)-Cl, \( p \)-NO\(_2\) & \( p \)-tBu further increases the activity. The conversion of the methylthio group into the methyl-sulfonyl group also increases the activity. The replacement of the phenyl ring along with the pyridine ring decreases the activity. If the acetyl group is present on the nitrogen atom of the oxadiazole ring did not significantly affect the activity [39]. Thus, based on the aforementioned results, we hypothesized that 2,5-disubstituted 1,3,4-oxadiazole scaffold may lead to novel potent agents with broad biological activity profile and improved pharmacokinetic properties.

### Table 3 In vitro antimicrobial activity of the titled compounds (4a-4h) [43]

| Compound | Diameter of zone of inhibition (mm) | Antibacterial activity |
|----------|-----------------------------------|------------------------|
|          |                                   | S. aureus  | P. aeruginosa | K. pneumonia | E. coli  |
| 4a       |                                   | 19         | 17           | 18           | 19       |
| 4b       |                                   | 17         | 16           | 17           | 15       |
| 4c       |                                   | 14         | 13           | 16           | 17       |
| 4d       |                                   | 21         | 19           | 19           | 20       |
| 4e       |                                   | 12         | 11           | 13           | 12       |
| 4f       |                                   | 13         | 14           | 15           | 12       |
| 4g       |                                   | 12         | 13           | 11           | 11       |
| 4h       |                                   | 17         | 16           | 15           | 17       |
| Ofloxacin|                                   | 41         | 38           | 39           | 37       |

**Structure–activity relationship of 1,3,4-oxadiazole derivatives**

The structure–activity relationship of 1,3,4-oxadiazole is given in (Fig. 4). Substitution of phenyl ring with different substituents like \( p \)-Cl, \( p \)-NO\(_2\) & \( p \)-tBu further increases the activity. The conversion of the methylthio group into the methyl-sulfonyl group also increases the activity. The replacement of the phenyl ring along with the pyridine ring decreases the activity. If the acetyl group is present on the nitrogen atom of the oxadiazole ring did not significantly affect the activity [39]. Thus, based on the aforementioned results, we hypothesized that 2,5-disubstituted 1,3,4-oxadiazole scaffold may lead to novel potent agents with broad biological activity profile and improved pharmacokinetic properties.
Scheme 4 Synthesis of substituted 1,3,4-oxadiazole with 2-aminobenzoic acid as starting material

Table 4 Antimicrobial activity of the titled compounds (5a-5f) [5]

| Compound | R     | R<sub>1</sub>NR<sub>2</sub> |
|----------|-------|-----------------------------|
| 5a       | −H    |                             |
| 5b       | −CH<sub>3</sub> |                             |
| 5c       | −H    |                             |
| 5d       | −CH<sub>3</sub> |                             |
| 5e       | −H    |                             |
| 5f       | −CH<sub>3</sub> |                             |

| Compound | S. aureus | S. pyrogenes | E. coli | P. aeruginosa | C. albicans |
|----------|-----------|--------------|---------|---------------|-------------|
| 5a       | 10        | 13           | 12      | 08            | 14          |
| 5b       | 13        | 11           | 14      | 09            | 12          |
| 5c       | 12        | 13           | 15      | 09            | 14          |
| 5d       | 12        | 11           | 13      | 10            | 13          |
| 5e       | 09        | 09           | 10      | 07            | 11          |
| 5f       | 08        | 09           | 09      | 06            | 10          |
| Amikacin | 16        | 15           | 17      | 18            | –           |
| Ketoconazole | –    | –            | –       | –             | 18          |
Pharmacological profile of some oxadiazole derivatives

Compound N-(4 chlorophenyl) amino-5-(4-pyridyl)-1,3,4-oxadiazole having electron-withdrawing group shows better anticonvulsant activity [40]. Compounds with p-methoxy group increase the antimicrobial potential [41] and 3, 4-dimethoxy containing compound increase anti-inflammatory activity as compared to reference drug [42]. 1,3,4-Oxadiazole nucleus containing compounds along with different substituents shows various kinds of activities (Fig. 5).

Antimicrobial activity

Bhat et al. [48] developed 4-bromo-N-[(5-(substituted phenyl)-1,3,4-oxadiazol-2yl)methyl]aniline (Scheme 1) and these derivatives were screened for antimicrobial activity against S. aureus, E. coli, B. Subtilis, and P. aeruginosa using amoxicillin as a positive control. The antmycotic activity was evaluated for these compounds against A. niger and C. albicans using ketoconazole as a reference standard. Derivatives with different groups like -OH, -NO2 [1b, 1c, 1d, 1g] shows good antimicrobial activity against fungal strains. Derivatives with groups like p-methoxy, p-chloro, p-methyl [1e, 1f, 1h] show better antimicrobial potential as compared to amoxicillin. The results of the antimicrobial activity of synthesized 1,3,4-oxadiazole derivatives were presented in (Table 1, Bhat et al. [48]).

Chawla et al. [41] developed 1-(5-(3-chlorobenzo[b] thiophen-2-yl)-2-(2,3,4-trisubstituted phenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone and 2-(3-chlorobenzo[b]...
thiophen-2-yl)-5-(2,3,4-trisubstituted phenyl)-1,3,4-oxadiazole by using Scheme 2. The antibacterial activity of synthesized derivatives was evaluated against different bacterial strains such as (S. aureus, B. Subtilis, E. coli, and P. aeruginosa) using ciprofloxacin as standard drug. The antimycotic activity of these derivatives was evaluated against A. niger and C. albicans using fluconazole as a reference standard and the results were summarized in (Table 2, Chawla et al. [41]).

Kumar et al. [43] developed 2-((1, 1′-biphenyl)-4-yl)-5-(substituted phenyl)-1,3,4-oxadiazole by using Scheme 3. The antibacterial activity of these derivatives was evaluated against different Gram +ve (S. aureus) and Gram -ve (K. pneumonia, E. coli, and P. aeruginosa) strains using ofloxacin as a reference standard. The cup plate agar diffusion method was used for the determination of the zone of inhibition. The results of antibacterial activity were summarized in (Table 3, Kumar et al. [43]).

Kanthiah et al. [5] developed 5-(2-aminophenyl)-3-(substituted (disubstituted amino) methyl)-1,3,4-oxadiazole-2(3H)-thione by using Scheme 4. The antimicrobial activity of synthesized derivatives was evaluated against different two Gram +ve (S. aureus and S. pyogenes) and Gram -ve (E. coli and K. aerogenes) strains using amikacin.

### Table 5 Minimum inhibitory concentration (MIC) of titled compounds [49]

| Compound | R      | X      | S. aureus | B. subtilis | P. aeruginosa | E. coli | C. albicans |
|----------|--------|--------|-----------|-------------|---------------|---------|-------------|
|          | ATCC 25923 | ATCC 6633 | ATCC 27853 | ATCC 27853 | ATCC 10231 |
| 6a       | C6H5    | O      | 0.3       | 0.15        | 0.15          | 1.25    | 2.5         |
| 6b       | 2-CH3   | C6H5   | 0.31      | 0.07        | 1.25          | 0.625   | 5.0         |
| 6c       | 3-CH3   | C6H5   | 0.625     | 0.15        | 5.0           | 2.5     | 10          |
| 6d       | 4-CH3   | C6H5   | 2.5       | 2.5         | 0.03          | 5.0     | 1.25        |
| 6e       | 2-Cl    | C6H5   | 0.15      | 1.25        | 0.019         | 0.019   | 5.0         |
| 6f       | 3-Cl    | C6H5   | 0.15      | 0.625       | 1.25          | 1.25    | 2.5         |
| 6g       | 4-Cl    | C6H5   | 0.15      | 0.3         | 0.019         | 0.07    | 0.15        |
| 6h       | 3-NO2   | C6H5   | -         | 10          | 1.25          | -       | -           |
| 6i       | 4-NO2   | C6H5   | 2.5       | -           | 0.625         | 5.0     | 10          |
| 7a       | 2-CH3   | C6H5   | 1.25      | -           | 2.5           | 10      | -           |
| 7b       | 4-CH3   | C6H5   | 1.25      | 5.0         | 2.5           | 1.25    | 5.0         |
| 7c       | 3-OH    | C6H5   | 2.5       | 1.25        | 0.019         | 2.5     | 10          |
| 7d       | 4-OH    | C6H5   | 0.15      | 0.625       | 2.5           | 0.625   | 1.25        |
| 7e       | 4-Cl    | C6H5   | 0.625     | 0.07        | 5.0           | 0.03    | 0.31        |
| 7f       | 3-NO2   | C6H5   | 2.5       | 2.5         | 10            | 1.25    | 2.5         |
| 7g       | 4-NO2   | C6H5   | 2.5       | 5.0         | 5.0           | 0.1     | 0.15        |
| Ampicillin |        |        | 0.019     | 0.005       | 0.005         | 0.01    | -           |
| Fluconazole |      |        | -         | -           | -             | -       | 0.01        |
Scheme 6 Synthesis of substituted 1,3,4-oxadiazole derivatives

| Compound 8 : R = | Compound 9 : R = |
|-----------------|-----------------|
| 8a H            | 9a H            |
| 8b 3, 4, 5-trimethoxy | 9b 3, 4, 5-trimethoxy |
| 8c 4-methoxy    | 9c 4-methoxy    |
| 8d 4-chloro     | 9d 4-chloro     |
| 8e 4-bromo      | 9e 4-bromo      |
| 8f 4-fluoro     | 9f 4-fluoro     |
| 8g 4-nitro      | 9g 4-nitro      |
| 8h 4-cyano      | 9h 4-cyano      |
| 8i 4-methyl     | 9i 4-methyl     |
| 8j 4-trifluoromethyl | 9j 4-trifluoromethyl |

Reflex, 48h DMF  
EtOH, RT, 4h  
EtOH, NH₂NH₂, H₂O  
Reflex, 6h  
Acetone, K₂CO₃  
Reflex, 5h  
POCl₃  
Reflex, 6h
as a reference standard. The antymycotic activity was also evaluated for these derivatives against *C. albicans* using ketoconazole as positive control and the results were summarized in (Table 4, Kanthiah et al. [5]).

Chikhalia et al. [49] developed 1-substituted-3-(4-morpholino-6-((5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)thio)-1,3,5-triazin-2-yl)substituted urea (Scheme 5) and evaluated for antimicrobial activity against different strains such as (*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*) using ampicillin as a reference standard. The antifungal activity was also evaluated for these derivatives against *C. albicans* using fluconazole as a reference standard. Compound 6e shows better activity against *E. coli* and *P. aeruginosa* as compared to a positive control (ampicillin). Compound 6g also shows better activity towards *P. aeruginosa* but lower than that of ampicillin. Compound 7c and 7g showed good activity against *C. albicans* but slightly lower than that of fluconazole. The results of antimicrobial activity were shown in (Table 5, Chikhalia et al. [49]).

Antitumor activity

Srinivas et al. [30] developed (E)-1-(1-((5-substituted-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-4-(thiazol-2-ylamino)but-2-en-1-one (Scheme 6) and evaluated for antitumor activity by MTT assay against four different cancer cell lines such as HT-29 (colon), A375 (melanoma), MCF-7 (breast) and A549 (lung) using combretastatin-A4 as reference standard. All derivatives of 1,3,4-oxadiazole fused indole ring was showed a variable degree of anticancer activity along with IC$_{50}$ values ranging from 0.010 ± 0.004 and 18.50 ± 0.86 μM. Among the different derivatives 9a, 9b, 9f, 9g, 9h, and 9j were exhibited more potent than the positive control. The results of antitumor activity were presented in (Table 6, Srinivas et al. [30]).

Vinayak et al. [50] developed N-(5-(6-(4-fluorophenyl)pyridine-3-yl)1,3,4-oxadiazol-2-yl)

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**Table 6 In vitro cytotoxicity (IC$_{50}$Μ)$^a$ data of compounds (9a-j) [30]**

| Compound | A549$^{bc}$ | MCF-7$^d$ | A375$^e$ | HT-29$^f$ |
|----------|-------------|------------|--------|--------|
| 9a       | 1.20±0.16   | 0.098±0.004| 2.56±0.36| 0.012±0.001 |
| 9b       | 0.023±0.006 | 0.011±0.001| –      | 1.90±0.71 |
| 9c       | 2.30±0.21   | 2.19±0.28  | –      | 8.30±1.60 |
| 9d       | 3.56±0.19   | 2.11±0.23  | 6.13±1.12| 7.14±0.86 |
| 9e       | 5.02±1.02   | 12.4±0.96  | –      | –      |
| 9f       | 0.27±0.02   | 1.07±0.59  | 2.81±0.25| 1.55±0.65 |
| 9g       | 0.013±0.001 | 0.80±0.15  | 1.05±0.53| 1.24±0.17 |
| 9h       | 1.02±0.50   | 0.010±0.004| 1.99±0.29| 3.78±0.16 |
| 9i       | 13.9±0.54   | 18.50±0.86 | 8.23±1.35| –      |
| 9j       | 0.90±0.09   | 0.12±0.01  | 0.39±0.012| 1.10±0.54 |
| Combretastatin-A4 | 0.11±0.01 | 0.18±0.01 | 0.21±0.02 | 0.93±0.03 |

$^a$ Each data represented as mean ± S.D values. From three different experiments performed in triplicates, $^b$A549: Human lung cancer cell line, $^c$MCF-7: Human breast cancer cell line, $^d$A375: Human melanoma cancer cell line, $^e$HT-29: Human colon cancer cell line. –: Not active.
methyl]-substituted-1-amine by using Scheme 7 and evaluated for antiproliferative activity against different cell lines such as HeLa, HepG2, and Caco by MTT assay using 5-Fluorouracil as a reference standard. The derivative 10a and 10d showed excellent activity against HepG2 cell lines. The compound 10f gives better results against the Caco-2 cancer cell line. The results of the anti-proliferative activity of synthesized derivatives were showed in (Table 7a, b, and c, Vinayak et al. [50]).

Kapoor et al. [51] developed 2-(substituted phenyl)-5-(2-(2-(substituted phenyl)-1H-benzo[d]imidazol-1-yl)
phenyl)-1,3,4-oxadiazole by using Scheme 8 and evaluated for antitumor activity against MCF-7 (breast) cancer cell line by MTT assay. Compound 11e shows better cytotoxic activity as compare to 11a, 11b, and 11c. Compounds 11f, 11g, 11h also show the excellent cytotoxic activity as compared to the rest of the derivatives. Compounds 11e and 11h flourished potent cytotoxic activity with minimum percentage viability. Each compound was tested to calculate the percentage viability of cell line

**Table 7 (a) IC$_{50}$ values of the synthesized novel amine derivatives. (b) CC$_{50}$ values of the synthesized novel amine derivatives. (c) Selectivity index (SI) of the synthesized novel amine derivatives [50]**

| Panel (a) | Compound | IC$_{50}$ values of 10(a-h) in (μM) | HeLa | Caco-2 | HepG2 |
|-----------|----------|-----------------------------------|------|--------|-------|
| 10a       | 212.4±1.2| 203.6±2.3 | 2.6±0.5 |
| 10b       | 85.6±0.8 | 112.5±1.2 | 45.6±1.1 |
| 10c       | 348±1.3  | 123.8±1.4 | 128.9±3.5 |
| 10d       | 112.9±0.4| 145.6±0.4 | 5.8±1.6 |
| 10e       | 1184±0.5 | 212.3±0.4 | 322±0.3 |
| 10f       | 78.3±5.4 | 2.3±0.5  | 235±4.6 |
| 10g       | 564±3.4  | 568±1.2  | 1567±2.3 |
| 10 h      | 88.6±1.2 | 346±0.9  | 1764±1.6 |
| 5-FU      | 7.6±0.3  | 8.8±0.6  | 7.6±0.2 |

| Panel (b) | Compound | CC$_{50}$ of the compound 10(a-h) in (μM) | HeLa | Caco-2 | HepG2 |
|-----------|----------|---------------------------------------|------|--------|-------|
| 10a       | 120±1.2  | 112±1.3                               | 34±0.5 |
| 10b       | 7.6±0.6  | 145±1.1                               | 129±0.3 |
| 10c       | 200      | 178±2.3                               | 102±1.1 |
| 10d       | 450      | 100±2.6                               | 112±1.4 |
| 10e       | 56±2.4   | 62±1.2                                | 76±3.4 |
| 10f       | 127±3.4  | 87±2.6                                | 77±0.4 |
| 10 g      | 200      | 23±1.5                                | 91±4.3 |
| 10 h      | 123±2.3  | 156±0.4                               | 73±1.4 |
| 5-FU      | 57±0.3   | 69±2.3                                | 52±1.8 |

| Panel (c) | Compound | SI of the compound 10(a-h) | HeLa | Caco-2 | HepG2 |
|-----------|----------|--------------------------|------|--------|-------|
| 10a       | 0.566    | 0.551                    | 13.06|
| 10b       | 0.887    | 1.288                    | 2.828|
| 10c       | 5.747    | 1.437                    | 0.791|
| 10d       | 3.985    | 0.686                    | 19.31|
| 10e       | 0.472    | 0.292                    | 0.236|
| 10f       | 1.621    | 37.8                     | 3.276|
| 10g       | 3.546    | 0.404                    | 0.580|
| 10h       | 1.388    | 4.508                    | 0.413|
| 5-FU      | 7.5      | 7.84                     | 6.84 |

*Concentration of compound at 50% of the remaining viable cells
* Inhibitory concentration at 50% of the viable cells
± Average value of the two independent experiments
Scheme 8 Synthesis of substituted 1,3,4-oxadiazole with benzene 1, 2-diamine as starting material.

Table 8 In-vitro cytotoxicity of synthesized compounds against Breast cancer cell line (MCF-7) [51]

| Compound | % Viability |
|----------|-------------|
|          | 6.25 μg/ml | 12.5 μg/ml | 25 μg/ml | 50 μg/ml | 100 μg/ml |
| 11a      | 38.04       | 37.15       | 39.68    | 35.11    | 40.31      |
| 11b      | 38.26       | 42.70       | 37.90    | 38.84    | 43.24      |
| 11c      | 44.35       | 41.6        | 41.81    | 39.64    | 37.24      |
| 11d      | 42.70       | 39.46       | 40.48    | 37.61    | 37.37      |
| 11e      | 30.60       | 32.20       | 34.48    | 33.86    | 37.54      |
| 11f      | 32.57       | 33.09       | 30.88    | 30.75    | 24.87      |
| 11g      | 34.39       | 33.58       | 28.80    | 32.40    | 30.96      |
| 11h      | 32.03       | 35.40       | 31.25    | 33.69    | 34.45      |

Control % viability = 100
against the different concentrations which is presented in (Table 8, Kapoor et al. [51]).

Kavitha et al. [31] developed \(N\)-substituted-(3-(5-cyclohexyl-1,3,4-oxadiazol-2-yl)phenyl)benzamide, urea, and substituted benzenesulfonamide derivatives by using Scheme 9. The anticancer activity of synthesized derivatives was evaluated against different cancer cell lines like HeLa and MCF-7 using cisplatin as a reference standard. Among the different derivatives, compounds 12a, 12b, 12c, 13c, 13d, and 14b showed significant activity after 48 h exposures. Further derivatives 12a, 13c, 13d, and 14b also showed excellent antitumor activity as compared to the positive control. Compound 12b showed excellent antitumor activity as compared to the rest of other compounds. The results of the antitumor activity of these derivatives were presented in (Table 9, Kavitha et al. [31]).

Chakrapani et al. [52] developed 3-(6-chloro-2-methylimidazo[2,1-b][1,3,4]thiazadiazol-5-yl)-5-(substituted phenyl)-1,2,4-oxadiazole by using Scheme 10. The antitumor activity of the synthesized derivatives was evaluated by MTT assay against ACHN (renal), MCF-7 (breast), and
A375 (melanoma) tumor cell line using doxorubicin as a reference standard. The compound 16b shows good cytotoxic activity in comparison to the reference drug. The compound 16j exhibits excellent activity towards melanoma cancer cell line (A375) and potent activities towards MCF-7 and ACHN cancer cell lines. The results of the antitumor activity of synthesized derivatives were presented in (Table 10, Chakrapani et al. [52]).

Gudipati et al. [53] developed (Z)-3-[(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) imino]-5 or 7-substituted indolin-2-one (Scheme 11) and evaluated for antitumor activity by MTT assay against MCF-7, IMR-32, and HeLa tumor cell lines using cisplatin as a reference standard. The compounds 17b-17d showed the most potent antitumor activity than the rest of other

Table 9 Preliminary cytotoxicity screening of synthesized 1,3,4-oxadiazole derivatives [31]

| Compound | IC_{50} μM |
|----------|-----------|
|          | HeLa      | MCF-7    |
| 12a      | 79.7      | 81.6     |
| 12b      | 30.4      | 23.5     |
| 12c      | 45.6      | 28.6     |
| 13a      | ≥100      | ≥100     |
| 13b      | ≥100      | ≥100     |
| 13c      | 80.1      | 78.3     |
| 13d      | 58.8      | 62.4     |
| 13e      | ≥100      | ≥100     |
| 13f      | 100.3     | 100      |
| 13g      | ≥100      | ≥100     |
| 13h      | ≥100      | ≥100     |
| 13i      | ≥100      | ≥100     |
| 14a      | ≥100      | ≥100     |
| 14b      | 62.9      | 60.9     |
| 14c      | ≥100      | ≥100     |
| Standard | 3.5       | 3.5      |

Scheme 10 Synthesis of 1,2,4-oxadiazole derivatives

**Compound 1** R =
15a, 16a: R = H
15b, 16b: R = 3,4,5-trimethoxy
15c, 16c: R = 4-methoxy
15d, 16d: R = 4-chloro
15e, 16e: R = 4-bromo
15f, 16f: R = 4-fluoro
15g, 16g: R = 4-nitro
15h, 16h: R = 3-nitro
15i, 16i: R = 4-methyl
15j, 16j: R = 4-trifluoromethyl
derivatives. The results of antitumor activity were summarized in (Table 11, Gudipati et al. [53]).

Polothi et al. [54] developed 5-(substituted phenyl)-3-(4-(5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl) phenyl)-1,2,4-oxadiazole by using Scheme 12 and evaluated for antitumor activity by MTT assay against MDA MB-231, MCF-7 (breast cell line), A549 (lung cell line) cancer cell lines using doxorubicin as a reference standard. Among the different derivatives, compounds 19b, 19g, 19h, and 19i showed good cytotoxic activity as compared to the reference standard. The compound 19b with 3, 4, 5-trimethoxy group on phenyl ring shows excellent antitumor activity against human cancer cell lines such as A549 and MCF-7. The results of the antitumor activity of

| Compound | IC<sub>50</sub> values, μM |
|----------|-----------------------------|
|          | A375 | MCF-7 | ACHN |
| 16a      | 11.4 | 10.2  | 18.5 |
| 16b      | 1.22 | 0.23  | 0.11 |
| 16c      | 2.98 | 0.70  | 1.89 |
| 16d      | 14.6 | 19.1  | 6.47 |
| 16e      | 8.20 | 11.2  | 7.7  |
| 16f      | 2.70 | 8.41  | 17.6 |
| 16g      | 17.7 | 9.7   | 12.2 |
| 16h      | 2.20 | 5.98  | 10.6 |
| 16i      | 9.56 | 13.7  | 2.44 |
| 16j      | 0.37 | 1.47  | 0.33 |
| Doxorubicin | 5.51 | 2.02  | 0.79 |

**Table 10 Cytotoxicity data for compound 16a-j [52]**

**Scheme 11** Synthesis of substituted 1,3,4-oxadiazole with p-amino benzoic acid as starting material
Table 11  Anticancer activity of synthesized compounds against HeLa, IMR-32 & MCF-7 cancer cells using MTT assay [53]

| Compound | \(R_1\) | \(R_2\) | IC\(_{50}\) (μM)\(^*\) (HeLa) | IC\(_{50}\) (μM)\(^*\) (IMR-32) | IC\(_{50}\) (μM)\(^*\) (MCF-7) |
|----------|--------|--------|-----------------|-----------------|-----------------|
| Isatin   |        |        | 521.9                        | 352.74          | 410.95          |
| 17       | Intermediate |        | 309.59                      | 176.85          | 206.95          |
| 17a      | H      | H      | 25.47                        | 30.65           | 33.62           |
| 17b      | F      | H      | 11.99                        | 13.48           | 15.57           |
| 17c      | Cl     | H      | 12.84                        | 15.84           | 16.68           |
| 17d      | Br     | H      | 10.64                        | 12.68           | 16.06           |
| 17e      | CH\(_3\) | H      | 22.59                        | 27.25           | 29.38           |
| 17f      | NO\(_2\) | H      | 18.60                        | 22.51           | 24.48           |
| 17g      | COOH   | H      | 17.25                        | 20.85           | 22.95           |
| 17h      | H      | Cl     | 18.69                        | 22.51           | 24.92           |
| 17i      | H      | NO\(_2\) | 16.20                        | 19.35           | 20.38           |
| 17j      | H      | CH\(_3\) | 15.12                        | 18.32           | 20.95           |
| 17l      | H      | COOH   | 20.36                        | 24.28           | 25.98           |
| 17k      | H      | COOCH\(_3\) | 19.32                        | 23.85           | 25.18           |
| Cisplatin |        |        | 14.08                        | 13.64           | 13.54           |

Values are expressed as means (n = 4)

Scheme 12  Synthesis of substituted 1,3,4-oxadiazole linked 1,2,4-oxadiazole

| Compound R = |
|-------------|
| 18a, 19a: R = H |
| 18b, 19b: R = 3,4,5-trimethoxy |
| 18c, 19c: R = 4-methoxy |
| 18d, 19d: R = 4-chloro |
| 18e, 19e: R = 4-bromo |
| 18f, 19f: R = 4-fluoro |
| 18g, 19g: R = 4-nitro |
| 18h, 19h: R = 3-nitro |
| 18i, 19i: R = 4-cyano |
| 18j, 19j: R = 4-trifluoromethyl |
synthesized derivatives were showed in (Table 12, Polothi et al. [54]).

**Antitubercular activity**
Pattan et al. [55] developed 2-(5-(substituted thio)-1,3,4-oxadiazol-2-yl) phenol and 4-(substituted-1-ylmethyl)-1-(2-hydroxy benzoyl)-3-methyl-1H-pyrazol-5(4H)-one by using Scheme 13. The antimycobacterial activity of the synthesized derivatives was evaluated against *Mycobacterium tuberculosis* (H37Rv) by MB 7H9 agar medium. Streptomycin was used as a reference standard. Compounds 20a, 21b, 22a, 22b, 22c, and 22e showed promising antitubercular activity. Compounds 20b, 20c, and 22d showed moderate activity and the results of activity were presented in (Table 13, Pattan et al. [55]).

### Table 12 In vitro cytotoxic activity [IC_{50} (μM)] of compounds (19a-j) [54]

| Compound | Lung cancer A549 | Breast cancer MCF-7 | MDA MB-231 |
|----------|------------------|---------------------|------------|
| 19a      | 9.78 ± 0.27      | 34.55 ± 2.34        |           |
| 19b      | 0.45 ± 0.03      | 1.76 ± 0.34         | 2.11 ± 0.21|
| 19c      | 3.67 ± 0.18      | 2.89 ± 0.67         | 12.76 ± 0.81|
| 19d      | 4.56 ± 0.19      | 2.33 ± 0.56         | 7.34 ± 0.26|
| 19e      | 0.76 ± 1.78      | 12.4 ± 0.79         | 193 ± 2.11 |
| 19f      | 34.9 ± 2.30      | 15.3 ± 1.72         |           |
| 19g      | 0.03 ± 0.17      | 1.25 ± 0.30         | 1.89 ± 0.35|
| 19h      | 2.45 ± 0.23      | 0.34 ± 0.025        | 1.11 ± 0.18|
| 19i      | 1.89 ± 0.38      | 1.90 ± 0.41         | 3.78 ± 0.29|
| 19j      | 7.5 ± 4.67       | 6.30 ± 0.35         | 225 ± 1.28 |
| Doxorubicin | 2.10 ± 0.14    | 3.12 ± 0.17         | 3.41 ± 0.23|

(-) not active. *Each data represents as mean ± S.D values. From three different experiments performed in triplicates. MCF-7: Human breast cancer cell line. A549: Human lung cancer cell line. MDA MB-231: Human breast cancer cell line.

### Scheme 13 Synthesis of 1,3,4-oxadiazole derivatives
Martinez et al. [44] developed N-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl) substituted amide by using Scheme 14. The antimycobacterial activity of synthesized derivatives was evaluated against different *Mycobacterium tuberculosis* strains such as 209, H37Ra, and H37Rv using rifampin as a reference standard. Compound 23a shows more potent activity in comparison to the rest of other compounds. The results of the antimycobacterial activity of the synthesized derivatives were presented in (Table 14, Martinez et al. [44]).

Das et al. [56] synthesized 6-(pyrazin-2-yl)-[1,3,4]oxadiazolo[3,2-d]tetrazole and 6-(pyrazin-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]oxadiazole (Scheme 15) and antimycobacterial activity of these derivatives were evaluated by (LJ) agar method against *Mycobacterium tuberculosis* H37Rv (MTCC200) using isoniazid and rifampicin as a reference standard. The compound 25 shows more potent antitubercular activity but still, it is lesser active.

| Compound | Antitubercular activity |
|----------|-------------------------|
|          | 50 μg/mL | 100 μg/mL |
| 20a      | S        | S         |
| 20b      | R        | R         |
| 20c      | R        | R         |
| 21a      | R        | R         |
| 21b      | S        | S         |
| 21c      | R        | R         |
| 22a      | S        | S         |
| 22b      | S        | S         |
| 22c      | S        | S         |
| 22d      | R        | R         |
| 22e      | S        | S         |
| Streptomycin | S       | S         |

*R* Resistant; *S* Sensitive

Table 13 Antitubercular activity data of the synthesized compounds [55]

Scheme 14 Synthesis of substituted 1,3,4-oxadiazole derivatives
than the reference standard. The results of antimycobacterial activity were showed in (Table 15, Das et al. [56]).

Raval et al. [57] developed S-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)2-((substituted phenyl)amino)ethanethioate using Scheme 16. The antitubercular activity of synthesized derivatives was evaluated against *Mycobacterium tuberculosis* H$_{37}$Rv (ATCC27294). Rifampin was used as a reference standard. Compounds 29e, 29g, and 29k show better activity and exhibited >90% inhibition. The conclusion of antimycobacterial activity was presented in (Table 16, Raval et al. [57]).
Scheme 16 Synthesis of substituted 1,3,4-oxadiazole

![Synthesis Scheme](image)

Table 16  Antitubercular activity of the synthesized compounds (29a-l) against *M. tuberculosis* H₃₇Rv [57]

| Compound | Primary screen (6.25 μg/ml) | % inhibition | Concentration (μM) | Actual MIC (μg/Ml) | Clog P |
|----------|----------------------------|--------------|-------------------|---------------------|--------|
| 29a      | >6.25                      | 64           | 0.0354            | –                   | 0.4996 |
| 29b      | >6.25                      | 12           | 0.1640            | –                   | 1.5150 |
| 29c      | >6.25                      | 32           | 0.1706            | –                   | 1.5150 |
| 29d      | >6.25                      | 28           | 0.1735            | –                   | 1.5150 |
| 29e      | >6.25                      | 92           | 0.0077            | 6.05                | 0.8964 |
| 29f      | >6.25                      | 86           | 0.00132           | 5.92                | 0.8964 |
| 29g      | >6.25                      | 96           | 0.0052            | 6.00                | 0.8964 |
| 29h      | >6.25                      | 63           | 0.1130            | –                   | 0.9986 |
| 29i      | 6.25                       | 62           | 0.1138            | –                   | 0.9986 |
| 29j      | >6.25                      | 64           | 0.1133            | –                   | 0.9986 |
| 29k      | >6.25                      | 96           | 0.0089            | 5.77                | – 0.8943 |
| 29l      | 6.25                       | 69           | 0.1184            | –                   | – 9.1673 |
| Isoniazid| >6.25                      | 98           | 0.025             | 0.05                | – 0.6680 |
Somani et al. [58] developed 3-((substituted amino)methyl)-5-phenyl-1,3,4-oxadiazole-2(3H)-thione by using Scheme 17. The antimycobacterial activity of synthesized derivatives was evaluated against Mycobacterium tuberculosis H37Rv strain in MB 7H-9 agar medium using rifampicin as a reference standard. The conclusion of the antimycobacterial activity of synthesized derivatives was presented in (Table 17, Somani et al. [58]).

Gavarkar et al. [59] developed 3-(5-substituted-1,3,4-oxadiazol-2-yl) naphthalen-2-ol using Scheme 18. These derivatives were evaluated for antimycobacterial activity by tube dilution method against Mycobacterium tuberculosis H37Rv strain using MB 7H-9 agar broth.

### Table 17 Antitubercular activity of the synthesized compounds (30a-3g) against M. tuberculosis H₃₇Rv [58]

| Compound | Antitubercular activity |
|----------|-------------------------|
|          | 25 (µg/ml) | 50 (µg/ml) | 100 (µg/ml) |
| 30a      | R         | R         | S          |
| 30b      | R         | S         | S          |
| 30c      | S         | S         | S          |
| 30d      | S         | S         | S          |
| 30e      | S         | S         | S          |
| 30f      | R         | R         | S          |
| 30g      | R         | R         | S          |
| Rifampicin | S         | S         | S          |

Somani et al. [58] developed 3-((substituted amino)methyl)-5-phenyl-1,3,4-oxadiazole-2(3H)-thione by using Scheme 17. The antimycobacterial activity of synthesized derivatives was evaluated against Mycobacterium tuberculosis H₃₇Rv strain in MB 7H-9 agar medium using rifampicin as a reference standard. The conclusion of the antimycobacterial activity of synthesized derivatives was presented in (Table 17, Somani et al. [58]).

Gavarkar et al. [59] developed 3-(5-substituted-1,3,4-oxadiazol-2-yl) naphthalen-2-ol using Scheme 18. These derivatives were evaluated for antimycobacterial activity by tube dilution method against Mycobacterium tuberculosis H₃₇Rv strain using MB 7H-9 agar broth.

### Scheme 17 Synthesis of substituted 1,3,4-oxadiazole
Scheme 18 - Synthesis of substituted 1, 3, 4-oxadiazole

**Scheme 18** Synthesis of substituted 1,3,4-oxadiazole
Streptomycin and Pyrazinamide were used as a reference standard. Compounds 31, 33c, and 33d exhibited good antitubercular activity as compared to reference standards and the results were summarized in (Table 18, Gavarkar et al. [59]).

**Antiviral activity**

Somani et al. [47] developed *N*-substituted-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide (Scheme 19) and evaluated for antiviral activity against a different type of strains such as HIV-2 ROD and HIV-1 IIIB using MTT assay in MT-4 cells. Nevirapine was used as a reference standard. These derivatives were also evaluated for cytotoxic activity using MTT assay in

| Compound | Antitubercular activity |
|----------|-------------------------|
|          | 5 (µg/mL) | 10 (µg/mL) | 25 (µg/mL) |
| 31       | R         | S          | S          |
| 32       | R         | R          | R          |
| 33a      | R         | R          | R          |
| 33b      | R         | R          | R          |
| 33c      | R         | S          | S          |
| 33d      | S         | S          | S          |
| 33e      | R         | R          | R          |
| 33f      | R         | R          | R          |
| 34       | R         | S          | R          |
| Streptomycin | R     | S          | S          |
| Pyrazinamide | R      | S          | S          |

Streptomycin and Pyrazinamide were used as a reference standard. Compounds 31, 33c, and 33d exhibited good antitubercular activity as compared to reference standards and the results were summarized in (Table 18, Gavarkar et al. [59]).

**Antiviral activity**

Somani et al. [47] developed *N*-substituted-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide (Scheme 19) and evaluated for antiviral activity against a different type of strains such as HIV-2 ROD and HIV-1 IIIB using MTT assay in MT-4 cells. Nevirapine was used as a reference standard. These derivatives were also evaluated for cytotoxic activity using MTT assay in
Table 19 (a) Anti HIV activity of synthesized compounds. (b) Cytotoxicity and antiviral activity of titled compounds in Vero cell cultures. (c) Cytotoxicity and antiviral activity of titled compounds in HEL cell cultures [47]

Panel (a)

| Compound | HIV I (μg/ml) | SI | HIV II (μg/ml) | SI |
|----------|---------------|----|---------------|----|
|          | IC50          | CC50 | IC50          | CC50 |
| 35a      | > 50          | = 50  | < 1           | = 57  | < 1 |
| 35b      | > 65          | = 65  | < 1           | = 60  | < 1 |
| 35c      | > 125         | > 125 | X1            | > 125 | > 125 | X1 |
| 35f      | > 125         | > 125 | X1            | > 38  | > 125 | > 3 |
| 35g      | > 125         | > 125 | X1            | > 125 | > 125 | X1 |
| 35h      | > 125         | > 125 | X1            | > 125 | > 125 | X1 |
| 35i      | > 125         | > 125 | X1            | > 125 | > 125 | X1 |
| 35j      | > 125         | > 125 | X1            | > 125 | > 125 | X1 |
| Nevirapine(μM) | > 0.25 | > 200 | > 800 | – | – | – |
| DDI (μM) | > 5.37 | > 529  | > 98          | 2.71  | > 529  | > 1.95 |

Panel (b)

| Compound | Minimum cytotocic concentration a (μg/mL) | EC50 b (μg/mL) |
|----------|-------------------------------------------|----------------|
|          | Para‑influenza‑3 virus | Retrovirus | Sindbis virus | Coxacide B4 virus | Punta Toro virus |
| 35a      | 20 | > 20 | > 20 | > 20 | > 20 | > 20 |
| 35b      | 100 | > 20 | > 20 | > 20 | > 20 | > 20 |
| 35c      | 100 | > 20 | > 20 | > 20 | > 20 | > 20 |
| 35f      | > 100 | > 100 | > 100 | > 100 | > 100 | > 100 |
| 35g      | > 100 | > 100 | > 100 | > 100 | > 100 | > 100 |
| 35h      | > 100 | > 100 | > 100 | > 100 | > 100 | > 100 |
| 35i      | > 100 | > 100 | > 100 | > 100 | > 100 | > 100 |
| 35j      | > 100 | > 100 | > 100 | > 100 | > 100 | > 100 |
| Ribavirin (μM) | > 250 | 146 | 250 | > 250 | 146 |

Panel (c)

| Compound | Minimum cytotocic concentration a (μg/mL) | EC50 b (μg/mL) |
|----------|-------------------------------------------|----------------|
|          | Herpes simplex virus-1 | Herpes simplex virus-2 | Vaccinia virus | Vesicular stomatitis virus |
| 35a      | > 100 | 50 | 100 | 45 | > 100 |
| 35b      | 100 | > 20 | > 20 | > 20 | > 20 |
| 35c      | > 100 | > 100 | > 100 | > 100 | > 100 |

[47]
### Table 19 (continued)

#### Panel (c)

| Compound     | Minimum cytotoxic concentration\(^a\) (μg/mL) | \(\text{EC}_{50}\) \(^b\) (μg/mL) | Herpes simplex virus-1 | Herpes simplex virus-2 | Vaccinia virus | Vesicular stomatitis virus |
|--------------|---------------------------------------------|---------------------------------|------------------------|------------------------|---------------|--------------------------|
|              |                                             |                                 |                        |                        |               |                          |
| 35f          | >100                                        | >100                            | >100                   | >100                   | >100          | >100                     |
| 35g          | >100                                        | >100                            | >100                   | >100                   | >100          | >100                     |
| 35h          | >100                                        | >100                            | >100                   | >100                   | >100          | >100                     |
| 35i          | >100                                        | >100                            | >100                   | >100                   | >100          | >100                     |
| 35j          | >100                                        | >100                            | >100                   | >100                   | >100          | >100                     |
| Brivudin (μM)| >250                                        | 0.04                            | 50                     | 2                      | 250           |                          |
| Cidofovir (μM)| >250                                      | 1                               | 1                      | 2                      | >250          |                          |
| Ganciclovir (μM)| >100                                   | 0.02                            | 0.07                   | >100                   | >100          |                          |

\(^a\) Concentration required to cause a microscopically detectable alteration of normal cell morphology.  
\(^b\) Concentration required to reduce virus-induced cytopathogenicity by 50%
uninfected MT-4 cells. The results of synthesized derivatives were expressed as CC50, IC50, and SI values which were summarized in Table 19a. The results of the antiviral activity of synthesized derivatives against other viruses in (HEL) and (Vero) culture were reported in (Table 19b, c, Somani et al. [47]).

Gan et al. [25] developed (1E, 4E)-1-(substituted)-5-(4-(2-((5-substituted)-1,3,4-oxadiazol-2-yl)thio)ethoxy)phenylPenta-1,4-dien-3-one by using Scheme 20. The antiviral activity of synthesized compounds was evaluated against (TMV) using ribavirin as a reference standard. Among the synthesized derivatives, compounds 37a, 37c, 37f, 38a, 38b, 38c, 38d, 38e, 38f, 38g, 38h, 38i, 39e, and 39f exhibited potent curative activities as
compared to a reference standard. Compounds 37a-37h and 38a-38g showed good protective activity against TMV as compared to the reference standard. Moreover, compounds 37a-37g, 38c, 38f, 38g, 38i, and 39a-39j showed better activities as compared to the positive control. Among them, compound 38f shows the best curative, inactivation, and protective activity as compared to the reference standard. The results of the antiviral activity of different derivatives were showed in (Table 20, Gan et al. [25]).

Wang et al. [1] developed N-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-2-nitro benzamide, N-((5-(methylthio)-1,3,4-oxadiazol-2-yl)methyl)-2-nitro benzamide, 2-amino-N-((5-(methylthio)-1,3,4-oxadiazol-2-yl)methyl)benzamide and 2-(substituted)-N-((5-(methylthio)-1,3,4-oxadiazol-2-yl)methyl)benzamide (Scheme 21) and evaluated for antiviral activity. NNM was used as a reference standard. Among the synthesized derivatives, compounds 446, 448, and 4415 showed a more potent activity than the reference standard. The position of the substituent's also affected the antiviral activity and the results of antiviral activity were represented in (Table 21, Wang et al. [1]).

EL-Sayed et al. [60] developed 1,2,3,4,5-Penta-O-acetyl-D-galactopentitolyl and 2,3,4,5-tetra-O-acetyl-D-xylohexitotroyl, hydrazole, and imidrazone of 1,3,4-oxadiazole by using Scheme 22a, b respectively. The antiviral activity of synthesized derivatives was evaluated as reverse transcriptase inhibitors with fresh human peripheral blood mononuclear cells. Compound 47b shows good antiviral

| Compound | R₁ | R₂ | Curative activity(%) | Protective activity(%) | Inactivation activity(%) |
|----------|----|----|----------------------|------------------------|-------------------------|
| 37a      | 4-F | 4-F | 43.2±2.1             | 55.9±1.7               | 84.4±1.2                |
| 37b      | 4-F | 4-Cl | 25.9±1.8             | 52.5±1.5               | 88±4.08                |
| 37c      | 4-F | 4-Br | 45.6±1.9             | 67.9±3.9               | 74.8±1.3                |
| 37d      | 4-F | 2-F | 31.1±2.3             | 68.4±3.2               | 83.4±1.6                |
| 37e      | 4-F | 2-Cl | 23.7±3.1             | 56.8±2.6               | 56.2±1.9                |
| 37f      | 4-F | 2,4-Di-Cl | 52.9±4.5 | 65.1±3.2 | 83.5±2.7               |
| 37g      | 4-F | H | 28.2±1.1             | 52.9±0.7               | 74.5±0.9                |
| 37h      | 4-F | 4-CH₃ | 19.2±0.9             | 60.5±1.1               | 61.3±0.8                |
| 37i      | 4-F | 4-OCH₃ | 27.5±2.1             | 50.0±1.5               | 61.4±1.0                |
| 37j      | 4-F | 2-Cl | 23.7±3.1             | 56.8±2.6               | 56.2±1.9                |
| 38a      | H | 4-F | 45.8±1.8             | 61.5±2.9               | 69.1±1.2                |
| 38b      | H | 4-Cl | 44.1±2.5             | 55.7±1.6               | 59.4±2.5                |
| 38c      | H | 4-Br | 47.2±3.6             | 53.8±3.9               | 83.1±2.4                |
| 38d      | H | 2-F | 38.1±2.6             | 66.3±1.9               | 70.1±2.0                |
| 38e      | H | 2-Cl | 41.1±4.2             | 61.5±3.1               | 75.6±2.1                |
| 38f      | H | 2,4-Di-Cl | 49.8±3.9 | 69.2±2.1 | 90.4±2.8               |
| 38g      | H | H | 20.9±2.1             | 66.7±2.8               | 78.0±2.5                |
| 38h      | H | 4-CH₃ | 48.1±3.6             | 57.5±2.7               | 72.7±3.3                |
| 38i      | H | 4-OCH₃ | 40.6±3.2             | 58.4±3.8               | 79.3±4.1                |
| 38j      | H | 2-CF₃ | 35.5±1.7             | 50.5±1.9               | 56.8±2.1                |
| 39a      | 4-OCH₃ | 4-F | 20.8±1.2             | 44.0±0.9               | 83.0±1.1                |
| 39b      | 4-OCH₃ | 4-Cl | 18.4±0.9             | 34.4±1.1               | 87.1±1.8                |
| 39c      | 4-OCH₃ | 4-Br | 34.8±2.1             | 41.1±3.6               | 82.3±5.1                |
| 39d      | 4-OCH₃ | 2-F | 25.4±1.7             | 35.8±1.4               | 81.3±2.1                |
| 39e      | 4-OCH₃ | 2-Cl | 43.5±2.2             | 46.1±2.6               | 77.7±2.0                |
| 39f      | 4-OCH₃ | 2,4-Di-Cl | 43.9±2.4 | 49.6±1.8 | 85.6±1.9               |
| 39g      | 4-OCH₃ | H | 37.8±1.6             | 42.5±2.0               | 78.8±2.1                |
| 39h      | 4-OCH₃ | 4-CH₃ | 26.5±1.2             | 42.1±2.1               | 86.3±5.4                |
| 39i      | 4-OCH₃ | 4-OCH₃ | 35.1±1.5             | 41.5±1.8               | 81.5±2.6                |
| 39j      | 4-OCH₃ | 2-CF₃ | 30.5±2.1             | 49.3±2.3               | 77.9±4.5                |
| 38k      | H | 2,4-Di-F | 55.4±2.8             | 71.3±1.9               | 85.2±4.0                |
| Ribavirin | | | 37.9±1.9             | 51.8±2.3               | 72.9±2.4                |
Scheme 21 Synthesis of 1,3,4-oxadiazole derivatives with 2-nitrobenzoic acid as starting material

Table 21 Anti-TMV activities of titled compounds at 500 μg/mL in vivo [1]

| Compounds | Rate (%) | Rate (%) |
|-----------|----------|----------|
|           | Curative activity | Protective activity | Compounds | Curative activity | Protective activity |
|-----------|-------------------|-------------------|-----------|-------------------|-------------------|
| 40        | 38.5 ± 1.2        | 35.2 ± 3.1        | 448       | 60.0 ± 5.6        | 36.4 ± 1.0        |
| 41        | 36.9 ± 5.1        | 14.4 ± 2.9        | 449       | 26.9 ± 2.9        | 43.3 ± 3.0        |
| 42        | 268 ± 5.2         | 54.5 ± 2.9        | 4410      | 48.7 ± 5.1        | 25.2 ± 2.9        |
| 43a       | 22.3 ± 6.4        | 54.6 ± 5.2        | 4415      | 51.9 ± 3.0        | 45.6 ± 4.2        |
| 43b       | 47.2 ± 2.8        | 38.8 ± 4.5        | 40'       | 41.8 ± 1.0        | 41.7 ± 1.7        |
| 43c       | 44.8 ± 9.5        | 36.8 ± 0.8        | 41'       | 17.5 ± 1.2        | 32.2 ± 1.6        |
| 44\_4     | 7.1 ± 1.7         | 51.2 ± 7.6        | 42'       | 17.7 ± 1.2        | 42.6 ± 2.2        |
| 44\_5     | 37.4 ± 3.5        | 27.8 ± 5.5        | 43\_2'    | 49.3 ± 2.0        | 19.6 ± 2.4        |
| 44\_6     | 50.6 ± 4.7        | 42.9 ± 2.5        | 44\_10'   | 33.9 ± 1.3        | 20.2 ± 1.0        |
| 44\_7     | 37.1 ± 3.3        | 23.5 ± 1.1        | 44\_15'   | 35.3 ± 2.3        | 19.3 ± 0.8        |
| NNM       | 54.2 ± 2.9        | 65.7 ± 2.2        |           |                   |                   |
activity followed by compounds 45 and 49a. Compounds 48b and 52 showed moderate activity while 47a and 48a showed the weakest activity among the series of tested compounds. The results of the antiviral activity of synthesized derivatives were presented in (Table 22, El-Sayed et al. [60]).
Table 22 HIV inhibition activities (reverse transcriptase inhibitor) with therapeutic index [60]

| Compound | EC50 (μM) | IC50 (μM) | Therapeutic index |
|----------|-----------|-----------|-------------------|
| 45       | 3.24 \times 10^{-3} | 1.88       | 2.88 \times 10^{-7} |
| 47a      | 1.1 \times 10^{-5}  | 12.89      | 66.24 \times 10^{-8} |
| 47b      | 5.26 \times 10^{-4} | 1.44       | 3.15 \times 10^{-7}  |
| 48a      | 5.23 \times 10^{-4} | 12.44      | 5.78 \times 10^{-6}  |
| 48b      | 1.56 \times 10^{-3} | 3.11       | 3.45 \times 10^{-6}  |
| 49a      | 3.81 \times 10^{-1} | 2.12       | 8.14 \times 10^{-6}  |
| 52       | 2.72 \times 10^{-3} | 2.9        | 5.12 \times 10^{-6}  |

**Antioxidant activity**

Malhotra et al. [46] developed (Z)-2-((1, 1-biphenyl)-4-yl)-3-(1-((substituted)imino) ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (Scheme 23) and evaluated for antioxidant activity in terms of hydrogen peroxide scavenging activity. The results of the antioxidant activity of the synthesized derivatives were presented in (Table 23, Malhotra et al. [46]).
Rahul R. et al. [8] synthesized 5-(4-(4-chlorophenyl)thiazol-2-yl)-3-(substituted benzyl)-1,3,4-oxadiazole-2(3H)-thione by using Scheme 24 and evaluated for antioxidant activity by different methods such as Hydrogen peroxide scavenging, Nitric oxide scavenging, and DPPH assay. In DPPH assay compound 54c shows more significant activity in comparison to ascorbic acid. In other methods such as hydrogen peroxide and nitric oxide scavenging assay, compound 54c gives more potent activity than the rest of
Table 23 Hydrogen peroxide scavenging activity of synthesized compounds [46]

| Compound | Scavenging of hydrogen peroxide at different concentration (%) |
|----------|---------------------------------------------------------------|
|          | 100 (µg/ml) | 300 (µg/ml) | 500 (µg/ml) |
| 53a      | 41.55       | 39.84       | 41.22       |
| 53b      | 46.34       | 44.55       | 45.77       |
| 53c      | 51.11       | 48.12       | 44.59       |
| 53d      | 41.92       | 42.33       | 41.72       |
| 53e      | 45.65       | 46.19       | 45.91       |
| 53f      | 51.21       | 43.12       | 39.57       |
| 53g      | 39.58       | 42.61       | 43.18       |
| 53h      | 43.45       | 41.37       | 45.27       |
| 53i      | 41.88       | 45.19       | 48.11       |
| 53j      | 47.52       | 54.15       | 53.18       |
| 53k      | 45.35       | 50.27       | 52.15       |
| 53l      | 51.15       | 52.27       | 58.18       |
| 53m      | 45.87       | 41.37       | 41.93       |
| 53n      | 42.98       | 39.72       | 39.57       |
| 53o      | 41.03       | 43.06       | 44.14       |
| 53p      | 51.62       | 52.18       | 52.91       |
| 53q      | 54.18       | 53.76       | 57.36       |
| 53r      | 49.87       | 51.35       | 48.74       |
| BHA      | 63.27       | 66.19       | 68.25       |
| Ascorbic acid | 51.47       | 53.45       | 55.38       |

The other compounds but was not significant as compare to the results obtained in the DPPH assay. This shows that compound 54c gives more potent antioxidant activity as compared to the rest of the synthesized compounds. The results of the antioxidant activity of synthesized derivatives were presented in (Table 24, Rahul R. et al. [8]).

Dureja [61] developed 3-(4-acetyl-5-(substituted phenyl)-4, 5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (Scheme 25) and evaluated for antioxidant activity by using DPPH assay. Ascorbic acid was used as a reference standard and the results were summarized in (Table 25, Dureja [61]).

Conclusion
In this present review article, we have summarized different pharmacological activities of 1,3,4-oxadiazole containing compounds. From this study, we have found that 1,3,4-oxadiazole containing compounds can be used as...
Table 24 (a) DPPH assay of synthesized compounds. (b) Nitric oxide scavenging of synthesized compounds. (c) Hydrogen peroxide scavenging of synthesized compounds

| Compound | % Scavenging activity at different concentrations | IC<sub>50</sub> |
|----------|--------------------------------------------------|-------------|
|          | 20 (µg/ml) 40 (µg/ml) 60 (µg/ml) 80 (µg/ml) 100 (µg/ml) |             |
| Panel (a) |                                                  |             |
| 54a       | 39.94 ± 0.521 59.14 ± 0.652 61.38 ± 0.631 63.59 ± 0.245 65.34 ± 0.534 | 29.7        |
| 54b       | 46.63 ± 0.342 49.7 ± 0.352 57.51 ± 0.421 60.51 ± 0.634 62.65 ± 0.453 | 43.3        |
| 54c       | 44.86 ± 0.245 62.22 ± 0.214 64.66 ± 0.341 65.82 ± 0.372 67.76 ± 0.215 | 26.7        |
| 54d       | 44.64 ± 0.234 53.89 ± 0.123 62.73 ± 0.223 64.02 ± 0.321 66.92 ± 0.431 | 27.1        |
| 54e       | 47.34 ± 0.235 48.16 ± 0.516 49.54 ± 0.461 52.98 ± 0.371 55.75 ± 0.297 | 61.3        |
| Ascorbic acid | 49.38 ± 0.515 67.03 ± 0.541 75.78 ± 0.223 91.92 ± 0.561 95.34 ± 0.111 | 21.3        |
| Panel (b) |                                                  |             |
| 54a       | 34.83 ± 0.527 40.63 ± 0.654 43.87 ± 0.691 52.15 ± 0.215 53.11 ± 0.514 | 72.1        |
| 54b       | 27.34 ± 0.372 29.81 ± 0.352 38.25 ± 0.421 42.55 ± 0.0639 50.54 ± 0.450 | 98.3        |
| 54c       | 33.57 ± 0.243 44.97 ± 0.211 48.69 ± 0.348 52.35 ± 0.0442 53.15 ± 0.218 | 66.2        |
| 54d       | 33.28 ± 0.232 44.40 ± 0.128 45.70 ± 0.224 52.01 ± 0.0311 54.29 ± 0.481 | 69.8        |
| 54e       | 26.67 ± 0.295 29.30 ± 0.506 44.95 ± 0.411 51.98 ± 0.381 52.07 ± 0.297 | 70.6        |
| Ascorbic acid | 49.38 ± 0.515 67.03 ± 0.541 75.78 ± 0.223 91.92 ± 0.561 95.34 ± 0.111 | 21.3        |
| Panel (c) |                                                  |             |
| 54a       | 35.75 ± 0.612 44.97 ± 0.237 55.19 ± 0.226 65.93 ± 0.0662 67.14 ± 0.0563 | 47.1        |
| 54b       | 34.01 ± 0.563 43.51 ± 0.464 58.83 ± 0.152 60.48 ± 0.0353 62.50 ± 0.0452 | 49.1        |
| 54c       | 34.24 ± 0.263 46.06 ± 0.533 58.82 ± 0.623 62.12 ± 0.621 63.63 ± 0.236 | 43.3        |
| 54d       | 33.93 ± 0.235 46.81 ± 0.516 56.52 ± 0.532 59.89 ± 0.623 61.39 ± 0.425 | 45.6        |
| 54e       | 34.48 ± 0.342 44.88 ± 0.345 55.57 ± 0.173 56.61 ± 0.535 58.63 ± 0.064 | 50.6        |
| Ascorbic acid | 44.53 ± 0.526 64.65 ± 0.653 71.74 ± 0.036 89.22 ± 0.621 96.19 ± 0.456 | 269        |

IC<sub>50</sub> values in µg/ml for samples were determined using ED50 plus V 1.0 software. Data are the mean of three or more experiments and reported as mean ± standard error of the mean (SEM)
synthesized by various kinds of synthetic routes, and these derivatives having a wide range of biological activities such as antitumor, antitubercular, antimicrobial, antiviral and antioxidant, etc. This review article established the fact that 1,3,4-oxadiazole as useful templates for further modification or derivatization to design more potent biologically active compounds.

**Table 25** Antioxidant activity of synthesized compounds by DPPH method [61]

| Compound | % Scavenging activity | IC_{50}     |
|----------|-----------------------|-------------|
| 55a      | 19.97–85.95           | 47.47 ± 2.473 |
| 55b      | 3.07–64.92            | 197.96 ± 2.454 |
| 55c      | 7.4–48.75             | > 500       |
| 55d      | 13.87–77.45           | 60.93 ± 1.560 |
| 55e      | 12.60–85.95           | > 500       |
| 55f      | 14.70–69.70           | 130.8 ± 3.602 |
| 55g      | 4.9–74.77             | 90.26 ± 2.442 |
| 55h      | 6.85–69.42            | 91.70 ± 2.778 |
| Ascorbic acid | 44.95–95.5  | 12.7 ± 0.68  |

Abbreviations

CNS: Central Nervous System; FDA: Food and Drug Administration; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; IC_{50}: Half maximal inhibitory concentration; L.J: Lowenstein-Jensen; M.B: Middlebrook; H.E.L.a: Henrietta Lacks; M.I.C: Minimum inhibitory concentration; H.I.V: Human immuno deficiency virus; C.C_{50}: Half maximal cytotoxic concentration; S.I: Selectivity index; H.E.L: Human embryonic lung fibroblast; V.E.R.O: Verda reno (means green kidney); T.M.V: Tobacco mosaic virus; D.P.P.H: 2,2-Diphenyl-1-picrylhydrazyl; M.T.C.C: Microbial type cell cultures.
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Authors’ contributions
PKV- endeavored and accomplished the scheme; AS-completed review work and wrote the manuscript. Both authors read and approved the final manuscript.

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