



A review on synthetic account of 1,2,4-oxadiazoles as anti-infective agents

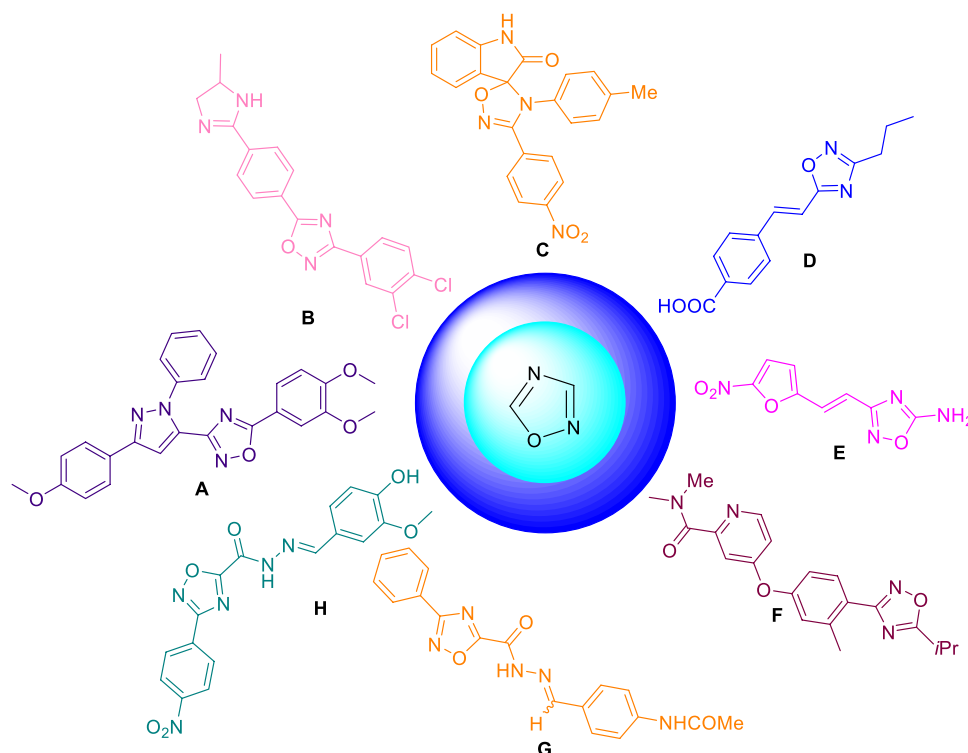
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Abstract

Most of the currently marketed drugs consist of heterocyclic scaffolds containing nitrogen and or oxygen as heteroatoms in their structures. Several research groups have synthesized diversely substituted 1,2,4-oxadiazoles as anti-infective agents having anti-bacterial, anti-viral, anti-leishmanial, etc. activities. For the first time, the present review article will provide the coverage of synthetic account of 1,2,4-oxadiazoles as anti-infective agents along with their potential for SAR, activity potential, promising target for mode of action. The efforts have been made to provide the chemical intuitions to the reader to design new chemical entity with potential of anti-infective activity. This review will mark the impact as the valuable, comprehensive and pioneered work along with the library of synthetic strategies for the organic and medicinal chemists for further refinement of 1,2,4-oxadiazole as anti-infective agents.

Graphical abstract



Keywords 1,2,4-Oxadiazoles · Anti-infective · Anti-bacterial · Anti-malarial · Synthesis

Extended author information available on the last page of the article

Abbreviations

CDI	Carbonyl diimidazole
DIPEA	Di- <i>isopropyl</i> ethyl amine
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDC·HCl	(3-Dimethylaminopropyl)carbodiimide hydrochloride
EtOH	Ethanol
SARS CoV-2	Severe acute respiratory syndrome coronavirus-2
TBAF	Tetra- <i>n</i> -Butyl ammonium fluoride
TBDMS	<i>tert</i> -Butyl dimethylsilyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran

Introduction

Most of the parts of the world have been affected from deadly infectious disease including tuberculosis (*Mycobacterium tuberculosis*, *Mtb*) [1, 2], malaria (*Plasmodium falciparum*) [3], Chagas disease or American trypanosomiasis (*Trypanosoma cruzi*) [4], nosocomial infections (*Staphylococcus aureus* or methicillin-resistant *S. aureus*, MRSA) [5] and also the recent severe acute respiratory syndrome coronavirus-2 (SARS CoV-2, caused by Coronavirus) [6–8]. The scarcity of curative action of antibiotics and anti-infective agents and complex genomic structure of microorganism has led to resistance among them leading to ineffectiveness of the currently used treatment regimen [9]. The resistance to antibiotics has become a threat to the world in the absence of effective anti-infective therapeutics with the demand of new hybrid drugs acting against resistant microorganism [10]. These all facts have necessitated the urge of new chemical entities to act against these microorganisms.

4-Oxadiazoles as important heterocyclic scaffolds

The synthesis of nitrogen- and oxygen-containing scaffolds has gained momentum [11–15] due to their versatility in the arsenal of drug discovery [16–18]. Oxadiazoles, being five-membered heterocyclic scaffold with an oxygen and two nitrogen atoms constitute four regioisomeric structures such as 1,2,3-oxadiazole, 1,2,5-oxadiazole, 1,2,4-oxadiazole and 1,3,4-oxadiazole. Oxadiazoles possess hydrogen bond acceptor properties [19] owing to electronegativities of nitrogen and oxygen, wherein nitrogen has been stronger hydrogen bond acceptor than oxygen [20]. Additionally, oxadiazoles have been recognized as the bioisosteres of (hydroxamic) esters, carboxamides and carbamates leading to metabolic

stability to parent scaffolds [21]. Among these isomeric oxadiazoles, 1,2,4-oxadiazoles have found many applications in pharmaceutical industry for drug discovery, scintillating materials and dyestuff industry [22]. Oxadiazoles are also synthesized from green chemistry approach which microwave-assisted synthesis which is low cost and also they are not producing any toxic material during the preparation of oxadiazoles [23]. Following the search through Scopus using the keywords “1,2,4-oxadiazoles,” research on 1,2,4-oxadiazoles has been expanding exponentially year by year (Fig. 1) [24].

Nowadays, there are a few commercially available drugs containing 1,2,4-oxadiazole nucleus [25] such as pleconaril (anti-infective) [26], oxolamine (anti-inflammatory) [27], prenoxdiazine (cough suppressant), butalamine (vasodilator) [28], ataluren (use in Duchenne muscular dystrophy) [29] and proxazole (used for anti-tussive and anti-plasmodic) [30] (Fig. 2). Additionally, a few marine natural products such as phidianidine A and B possess 1,2,4-oxadiazole as key pharmacophoric features [31]. Apart from this, 1,2,4-oxadiazoles have been recognized as the important scaffold of biological importance [32] along with anti-cancer [33–37], anti-inflammatory [38–40], analgesic [41], anti-Alzheimer [42], monoamine oxidase-B (MAO-B) inhibitor [43] and anti-oxidant activities [44].

The 1,2,4-oxadiazoles (**A–H**) have been recognized as the scaffold of biological importance for anti-parasitic activity (Fig. 3) [45–52]. These 1,2,4-oxadiazoles have been reported as anti-fungal [45], anti-microbial [53], anti-inflammatory, anti-trypanosomal [51, 54], anti-malarial [52], anti-mycobacterial [48], and anti-viral [55]. In 2018, Lima and co-workers have reported the importance of 1,2,4-oxadiazoles as anti-parasitic agents along with other isomeric 1,3,4-oxadiazoles [56]. Recently, de Souza et al. have reported the synthetic applications of nitriles for the synthesis of 1,2,4-oxadiazoles along with 1,2,5-oxadiazoles, 1,3-oxazoles and 2-oxazolines reported during 2014–2021 [57]. To the best of our knowledge, there is no specific synthetic account on synthetic strategies for 1,2,4-oxadiazoles as anti-infective agents till date. In the present work, we made the efforts to summarize the reported synthetic strategies of 1,2,4-oxadiazoles as anti-parasitic agents with the emphasis on identified hits, and their key SARs, etc.

Synthetic account of 1,2,4-oxadiazoles with anti-infective activity

The oxadiazole scaffolds having anti-infective activity were prepared from different synthetic strategies involving the use of amidoxime with carbonyl compounds such as carboxylic acids (Route A, Fig. 4) [45, 48], aldehydes (Route B) [53], 2-chloro-2-oxoacetate (Route C) [51, 55,

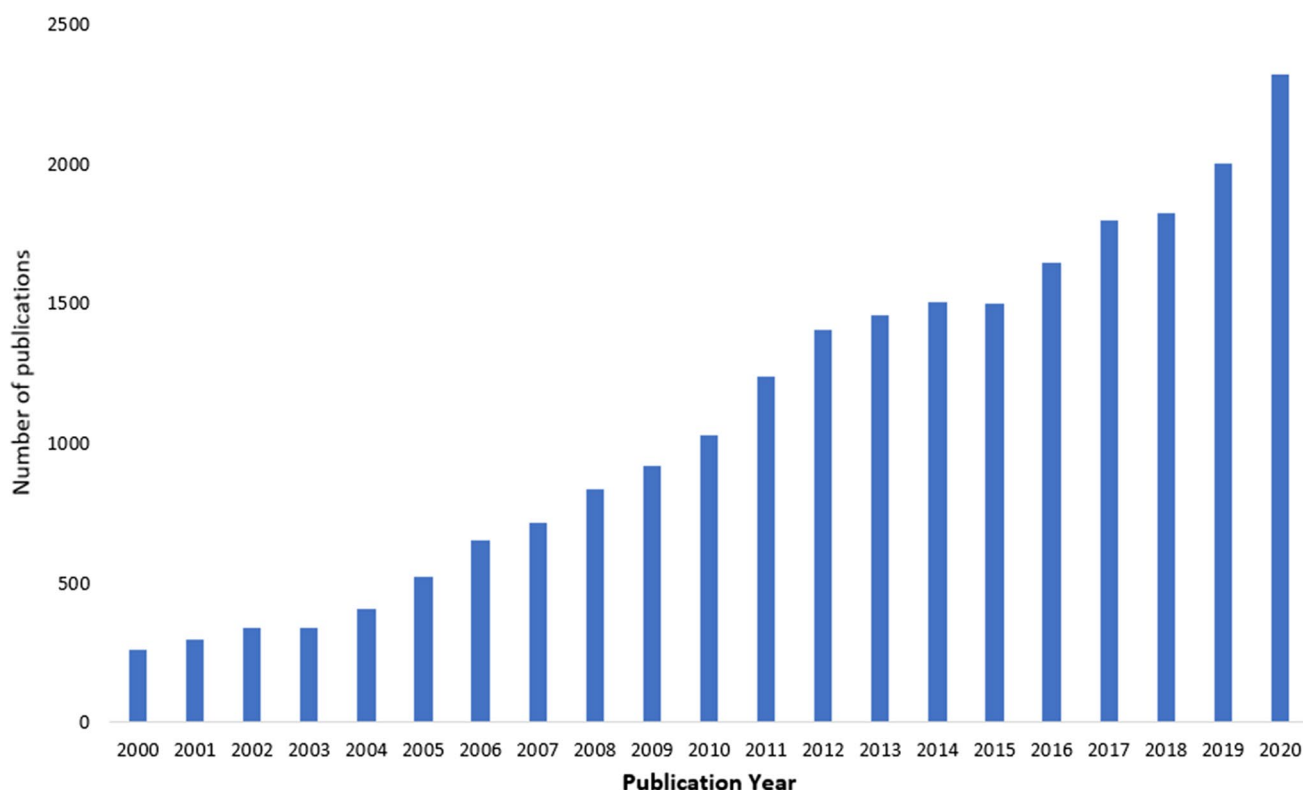
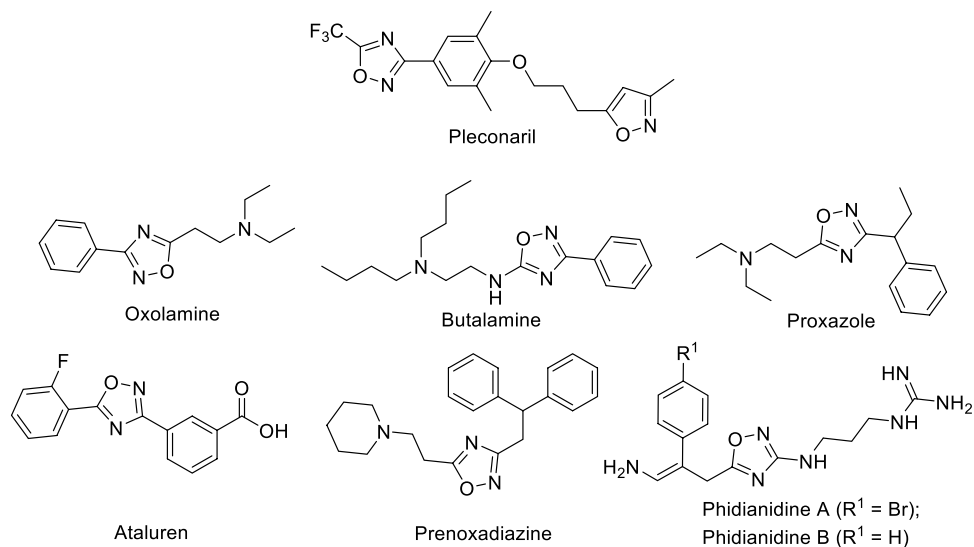


Fig. 1 Exponential growth of on-going research on 1,2,4-oxadiazoles retrieved by Scopus on Sept 27, 2021 using the keywords “1,2,4-oxadiazoles.” [24]

Fig. 2 Chemical structures of commercial drugs and natural products based on a 1,2,4-oxadiazole scaffold



58], and ester (Route D) [46]. Along with these, other routes such as intramolecular cyclization of ester clubbed with amidoxime (Route E) have been reported by Raval et al. [59] with high atom economy. Another excellent approach involving use of aminonitrone, hydroxylamine and isocyanide at rt to yield 1,2,4-oxadiazole (Route F) has been also attempted for the synthesis of anti-infective

1,2,4-oxadiazoles [60]. The present review article has been organized with the focus on the synthetic strategies using all these routes A–F.

Fig. 3 Scaffolds of the 1,2,4-oxadiazoles with different anti-infective activities [45–52]

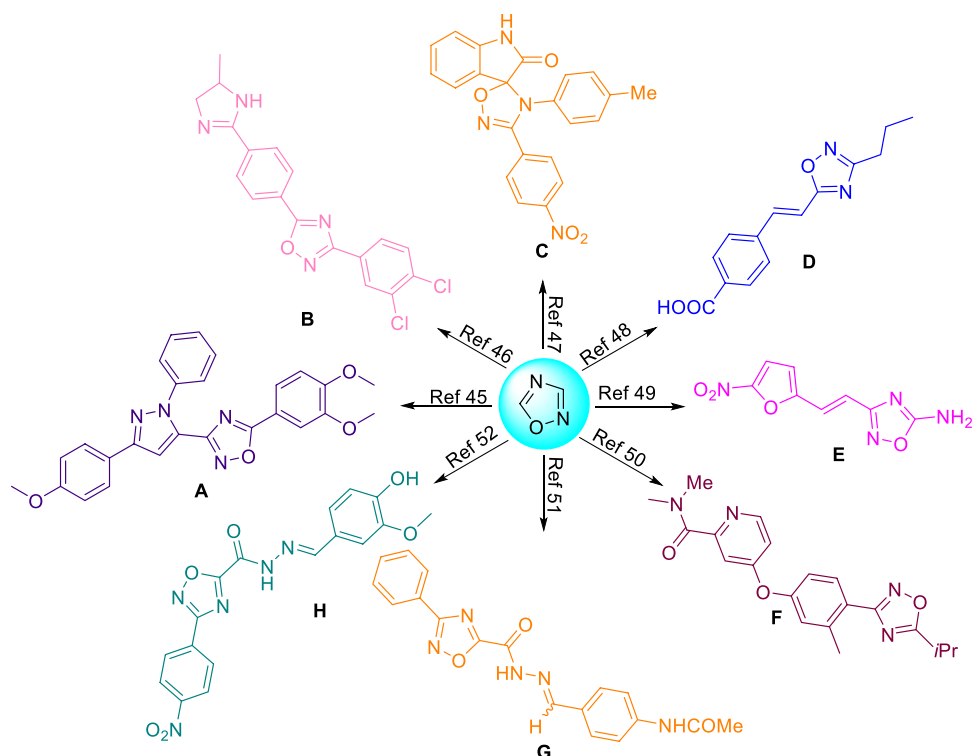
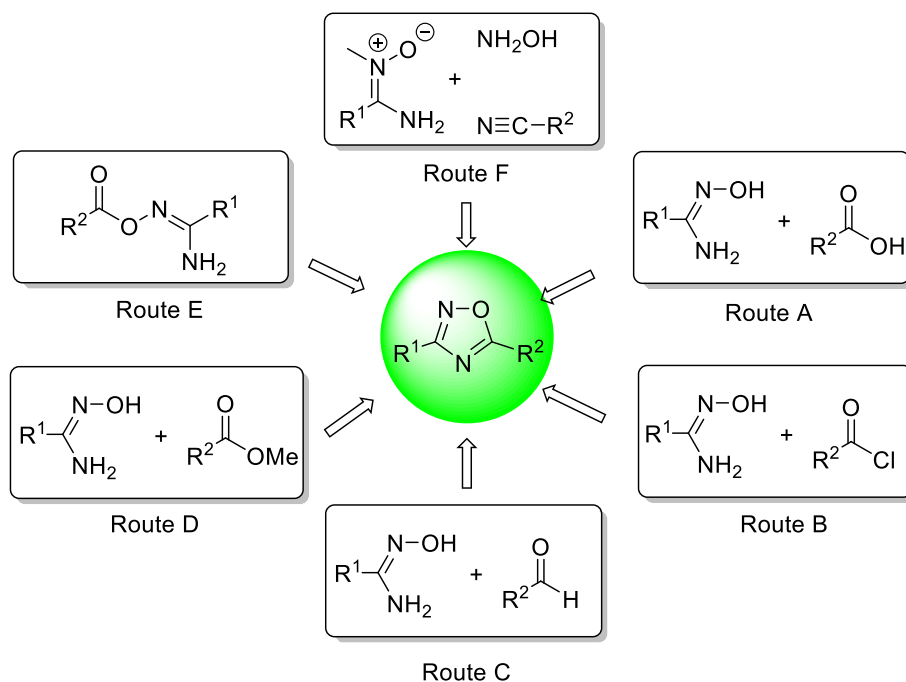


Fig. 4 Synthetic strategies for accessing anti-infective 1,2,4-oxadiazole scaffold



Reported synthesis of 1,2,4-oxadiazoles as anti-infective agents

Bhadraiah et al. [45] reported 1,2,4-oxadiazoles as anti-infective agents having anti-bacterial, anti-fungal, anti-inflammatory activity. Chloramine-T mediated synthesis of *N*-phenyl pyrazolines was achieved by cyclocondensation

of *N*-phenyl hydrazine (**1**) with acrylonitrile (**2**) in ethanol at reflux for 3 h. Next, 4,5-dihydro-1,3-diphenyl-1*H*-pyrazole-5-carbonitrile (**3**) was treated with hydroxylamine hydrochloride (**4**) in aqueous ethanol to afford the synthesis of amidoxime (**5**) at reflux for 5–6 h. Next, **5** was treated with carboxylic acids (**6**) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

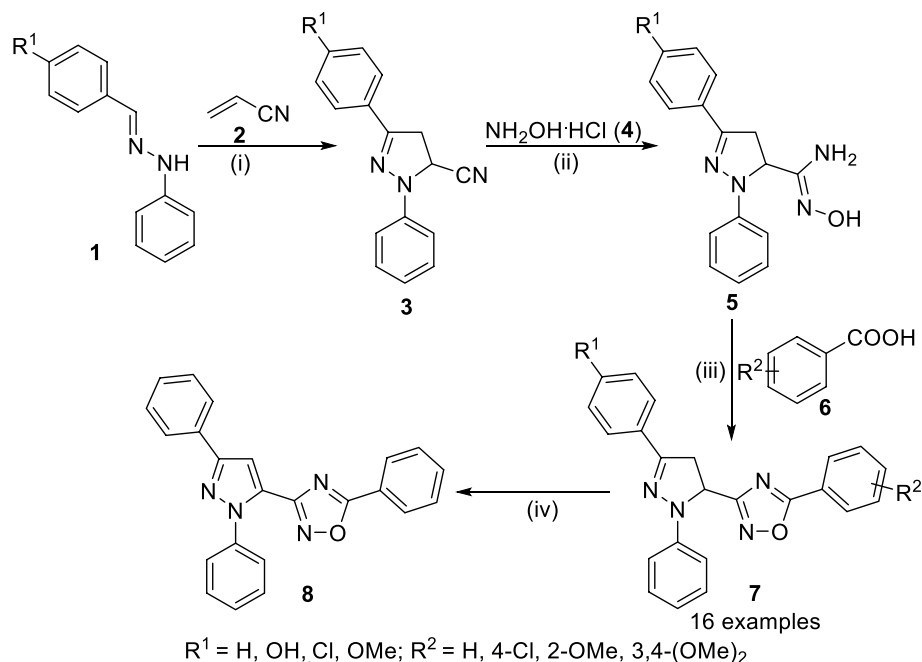
(EDC·HCl) in dichloromethane at 0–30 °C for 6 h followed by stirring at 110 °C to synthesize 1,2,4-oxadiazoles (**7**, Scheme 1). Further, **7** was reacted with bromine to undergo oxidation to form aromatic pyrazoline derivative of 1,2,4-oxadiazole (**8**). Compounds **7** with substitutions ($R^1 = 4\text{-OMe-C}_6\text{H}_4$; $R^2 = 3,4\text{-(OMe)}_2\text{-C}_6\text{H}_3$) were found with the best anti-microbial activity (MIC of 10 $\mu\text{g/mL}$) and **7** having R^1/R^2 as 4-chlorophenyl as potent anti-inflammatory activity.

Srivastava et al. [53] reported the synthesis of 3-aryl-5-propyl-1,2,4-oxadiazole (**12**) by manganese dioxide mediated oxidation of 3-aryl-5-propyl-4,5-dihydro-1,2,4-oxadiazole (**11**), obtained from cyclocondensation of arylamidoxamines (**9**) with *n*-butanal (**10**, Scheme 2). A small quantity of acidic ion-exchange resin (amberlite IRP-64) as catalyst has yielded **11** in 3 days instead of 5–8 days. Secondly, addition of sodium hypochlorite in a mixture of tetrahydrofuran and water yielded **12** ($R^1 = \text{H}$) from **11** ($R^1 = \text{H}$) in 89% yields. Upon the evaluation of compounds **11** against microorganisms, compounds **11** with 3-methyl and 4-methoxy substitutions were found more effective against *S. aureus*, *M. smegmatis* and *C. albicans*. Further, they have performed the evaluation of anti-inflammatory

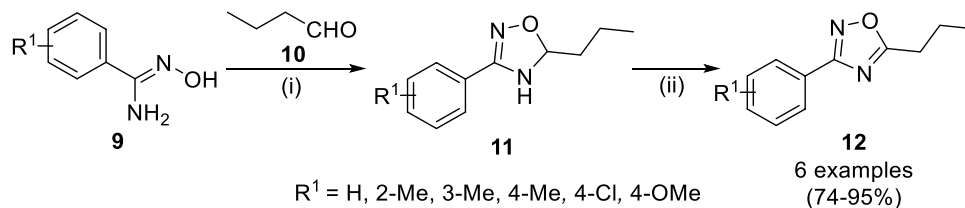
activity of compounds **12**, however, although no compounds were found potent than aspirin during in vivo assay.

Filho et al. [51] reported the synthesis of 3-(4-substituted-aryl)-1,2,4-oxadiazolyl-*N*-acylhydrozone (**18**) as anti-trypanosomal agents (Scheme 3). The cyclocondensation of aryl amidoximes (**9**) and methyl 2-chloro-2-oxoacetate (**13**) under reflux in tetrahydrofuran yielded 1,2,4-oxadiazole (**14**) which was further treated with hydrazine hydrate (**15**) to get the *E* and *Z* mixture of *N*-acylhydrazides (**16**) at 0 °C for 60 min. Finally, its acid-catalyzed addition–elimination reaction with 4-substituted benzaldehydes (**17**) at reflux in ethanol yielded (**18**) in 83–98% yields. Further, they speculated the formation of *E* isomer as major and thermodynamically stable product considering their conformational and configurational energies rather than *Z* isomer. Further, they studied the probable mode of action of the synthesized compounds against *Trypanosoma cruzi* cysteine protease cruzain using molecular docking (PDB ID: 1U9Q) followed by evaluation of cytotoxicity and anti-trypanosomal activity. Compounds (**18**) with $R^1 = \text{H}$ and $R^2 = \text{NHCOMe}$ were found with the satisfactory IC_{50} of 3.6 μM . The evaluation of in vivo toxicity in mice revealed this compound as non-toxic to mice at the concentration of 100 mg/kg.

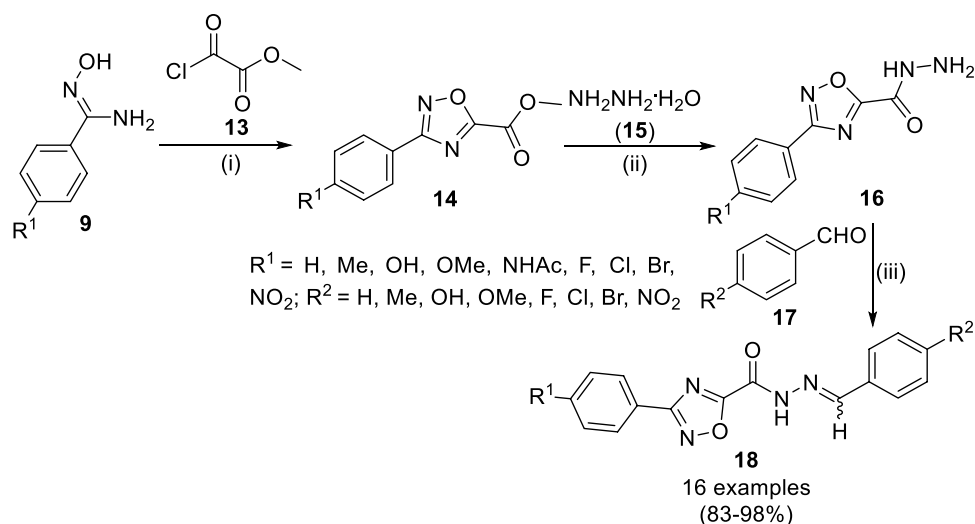
Scheme 1 Synthesis of 1,2,4-oxadiazoles (**7/8**) having anti-bacterial and anti-fungal activity. Conditions: (i) Chloramine-T, EtOH, reflux, 3 h; (ii) Na_2CO_3 , aq. EtOH, reflux, 5–6 h; (iii) EDC·HCl, DCM, 0–30 °C, 1–2 h, then rt for 6 h followed by 110 °C, 6 h; (iv) Br_2 , DCM, reflux, 1 h



Scheme 2 Synthetic strategy for 3-aryl-5-propyl-1,2,4-oxadiazoles (**12**) reported by Srivastava and co-workers. Conditions: (i) EtOH, H_2O , rt, 5–8 days; (ii) MnO_2 , (3.8 equiv), DCM, rt, 2 h



Scheme 3 Synthesis of 3-(4-substituted-aryl)-1,2,4-oxadiazolyl-*N*-acylhydrazone (**18**) acting against *T. cruzi*. Conditions: (i) THF, reflux, 4.5 h; (ii) EtOH, 0 °C, 60 min; (iii) H₂SO₄, EtOH, rt, 10 min

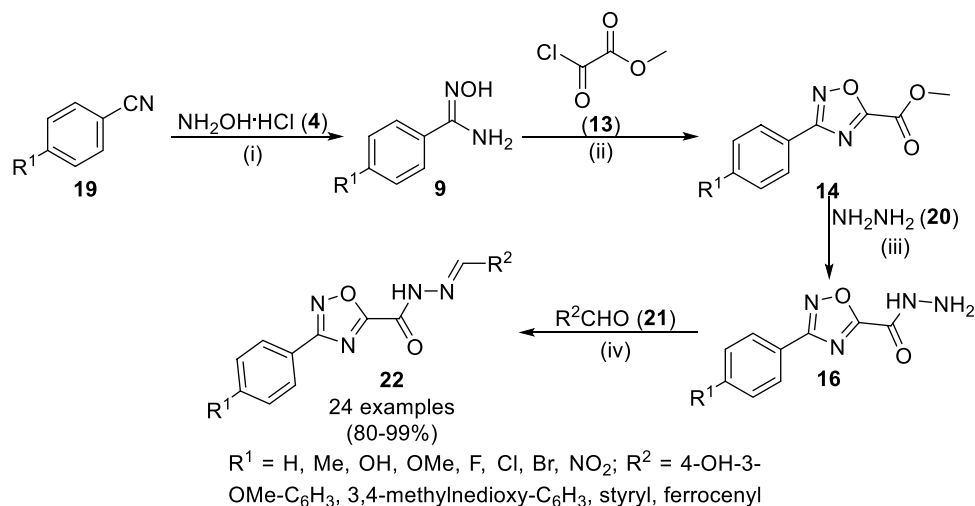


Filho et al. reported the trypanosomicidal [54] and anti-malarial [52] activity of 1,2,4-oxadiazole conjugated with *N*-acylhydrazone (**19** and **22**, Scheme 4). In 2012, they reported the treatment of 4-substituted aryl amidoximes (**9**) with methyl 2-chloro-2-oxoacetate (**13**) at reflux for 4–4.5 h to synthesize 1,2,4-oxadiazoles (**14**) in good yields. This was followed by their sequential reactions with hydrazine (**20**) and aldehydes (**21**) to yield 3,5-disubstituted 1,2,4-oxadiazoles (**22**) in 80–99% yields. Compounds **22** with R² as methylene 3,4-methylenedioxybenzene substitutions having R¹ as chloro and fluoro substitutions were found with potent IC₅₀ of 9.5 ± 2.8 and 3.5 ± 1.8 μM, respectively, against *T. cruzi* [54]. The similar synthetic methodology was adopted in 2016 by them for the synthesis of 1,2,4-oxadiazoles (**22**) as anti-malarial compounds by using styryl and ferrocene carboxaldehydes (**21**) [52]. Herein, the H₂SO₄ catalysts did not afford the product (**22**) with ferrocene carboxaldehyde, so the alternative Lewis acid catalysts, cerium chloride (CeCl₃·7H₂O) was tried to yield thermodynamically stable

E-isomers (**22**). These anti-malarial compounds, synthesized in the laboratory of design and synthesis applied to medicinal chemistry-SintMed,[®] inhibited the formation of β-hematin, which has been recognized as the mechanism of quinoline-based anti-malarial β-hematin inhibitors. Despite of diminished parasitemia, the most active compound **22** (R¹ = NO₂; R² = 4-OH-3-OMe-C₆H₃, with 69% inhibition of chloroquine-resistant *P. falciparum* W2 strain) did not show any improvement in survival of *Plasmodium berghei*-infected mice during the in vivo studies as compared to chloroquine, marketed anti-malarial drug.

Several nitrogen- and oxygen-containing scaffolds have been found of much interest due to their potential as anti-mycobacterial agents [15, 17, 18, 61–63]. In this regard, Upare and coworkers reported the anti-tubercular activity of (*E*)-3-alkyl-5-styryl 1,2,4-oxadiazoles [48]. The treatment of benzaldehyde (**23**) with malonic acid (**24**) in the presence of catalytic amount of piperidine at 110 °C yielded cinnamic acid (**25**), which was reacted with amidoxime (**26**,

Scheme 4 Synthetic strategy of 3,5-disubstituted oxadiazoles (**16** and **22**) as trypanosomicidal and anti-malarial agents. Conditions: (i) Na₂CO₃, H₂O/MeOH, 4 h, reflux; (ii) dry THF, reflux, 4–4.5 h; (iii) EtOH, 0 °C, 2 h; (iv) H₂SO₄ or CeCl₃·7H₂O (10 mol%), EtOH, 40 °C, 10–30 min

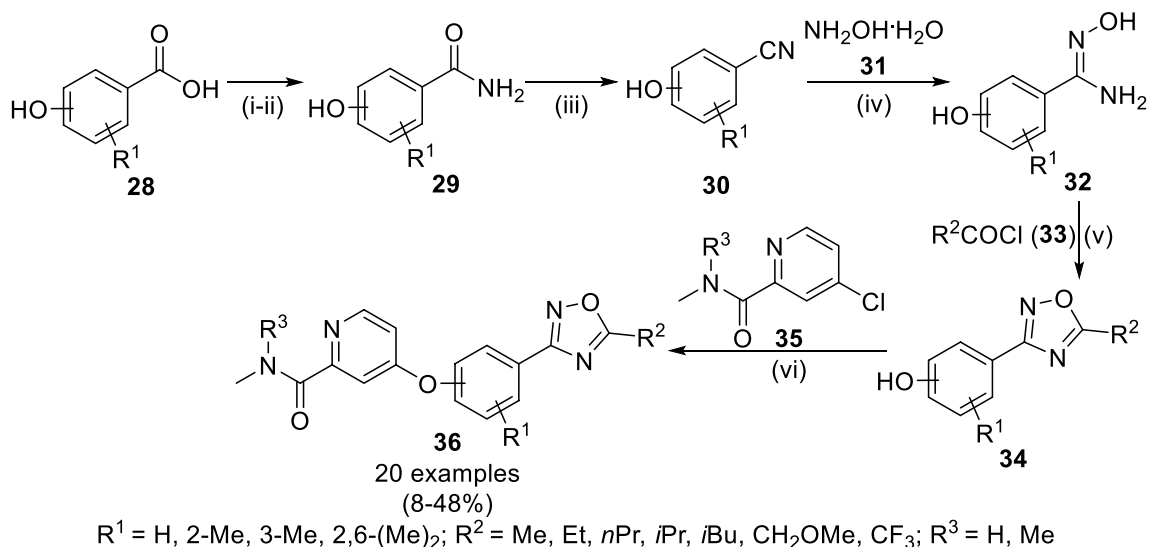
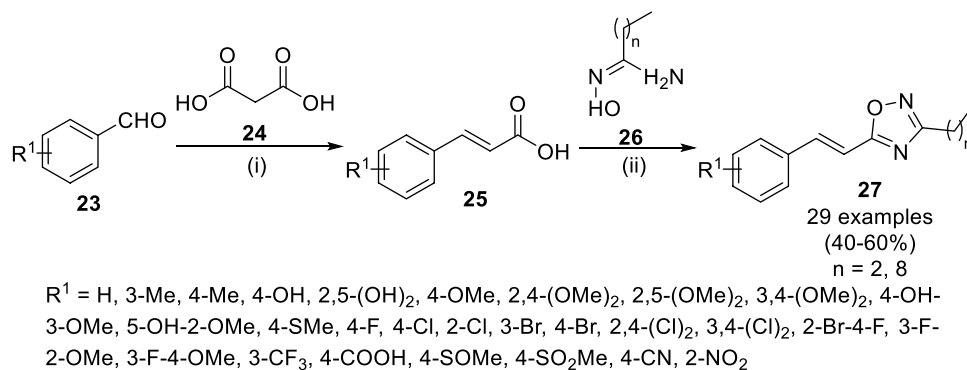


Scheme 5) using carbonyl diimidazoles (CDI) in toluene to obtain 3,5-disubstituted 1,2,4-oxadiazole derivatives (**27**). Following the SAR studies of 1,2,4-oxadiazoles with different functional groups on the phenyl ring of cinnamic acid, electron-withdrawing groups and halogens were found with good anti-tubercular activity in comparison with electron-donating and bulky substituents. Whereas the chain length and bulkiness at 3rd position of 1,2,4-oxadiazoles increased anti-mycobacterial potential. The compound **27** ($R^1 = \text{COOH}$; $n = 2$) was reported with promising anti-TB activity against *M. tuberculosis* H₃₇Ra having higher anti-TB activity with IC₅₀ of 0.63 and MIC of 8.45 µg/mL after 12 days of incubation. Further, the molecular modeling studies against InhA revealed their binding mode in the active site of enoyl-ACP reductase InhA.

Jung and coworkers have designed the 3-aryl-1,2,4-oxadiazoles (**36**) [55] having activity potential against human rhinovirus from their previously identified

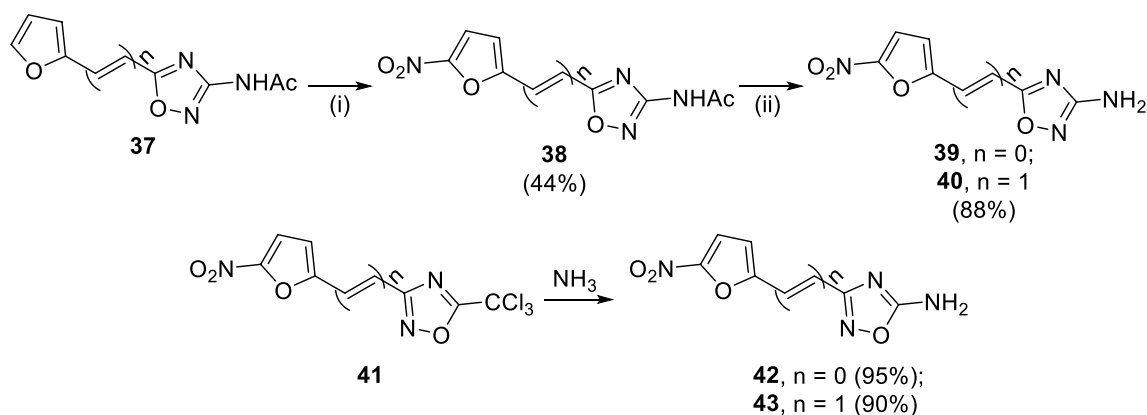
2,6-disubstituted benzo[*d*]thiophene derivative [50]. The conversion of hydroxy benzoic acid **28** into acid chloride and benzamide intermediate (**29**) was followed cyanation of **29** using trifluoroacetic anhydride (TFAA) in pyridine to yield hydroxy benzonitriles (**30**, Scheme 6). The synthetic target picolinamide clubbed 3-phenyl-1,2,4-oxadiazoles (**33**) was obtained by treatment of **30** with hydroxyl amine hydrate (**31**) to get amidoxime (**32**) followed by cyclization using acyl chloride (**33**) and *O*-arylation using 4-chloro-*N*-methylpicolinamide (**35**). The biological investigation of compounds **36** against rat and human liver revealed compound **36** ($R^1 = 3\text{-Me}$, $R^2 = i\text{Pr}$, $R^3 = \text{Me}$) with highest stability under hepatic microsomal conditions (with 60 and 41% of compound being unmetabolized, respectively). Further, it showed the significant efficacy against human rhinovirus (hRV-A71, hRV-B14 and hRV-A21) with better inhibitory concentration (EC₅₀ of 3.7, 66.0 and 22.0 nM, respectively). However, in vivo pharmacokinetic analysis

Scheme 5 Synthesis strategy of (*E*)-3 alkyl-5-styryl-1,2,4-oxadiazoles (**27**) as anti-tubercular agents adopted by Upare et al. Conditions: (i) piperidine, pyridine, 110 °C, 10–12 h; (ii) CDI, PhMe, rt, 3–4 h followed by 100–110 °C, 5–6 h



Scheme 6 Strategy for the multi-step synthesis of phenyl oxadiazole compound (**36**) acting against human rhinovirus. Conditions: (i) SOCl_2 , DMF, 70 °C; (ii) NH_3 , H_2O , THF, 0–25 °C, 5 h; (iii) TFAA,

pyridine, 16 h; (iv) EtOH, 90 °C, 16 h; (v) TFAA, pyridine, 0–120 °C, 16 h; (vi) neat, 150 °C, 90 h



Scheme 7 Synthesis of nitrofuryl substituted 3-amino-1,2,4-oxadiazoles (**39/40**) and 5-amino-1,2,4-oxadiazoles (**42/43**) having potent anti-microbial activity. Conditions: (i) HNO₃, Ac₂O, 15 °C, 30 min; (ii) 10% HCl (ethanolic), 3 h

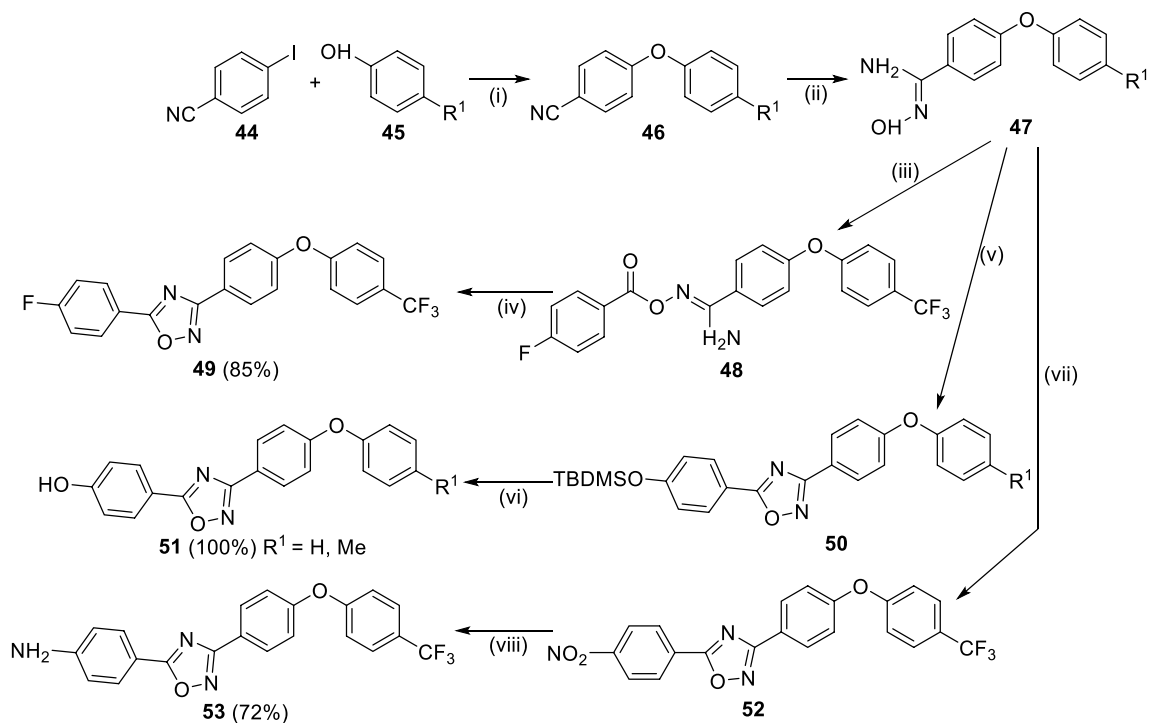
of this compound in rats resulted in low systemic clearance with moderate oral bioavailability.

In 1969, Breuer reported that 5-nitrofuryl substituted 3-amino-1,2,4-oxadiazoles and 5-amino-1,2,4-oxadiazoles with antimicrobial activity [49]. The furyl oxadiazoles (**37**) upon nitration with nitric acid and acetic anhydride provided 5-nitrofuryl derivatives (**38**, Scheme 7), which could be cleaved by warm ethanolic HCl to afford the target compounds (**39/40**), wherein compound **41** was found with broad anti-microbial spectrum. The reaction of trichloromethyl substituted 1,2,4-oxadiazoles (**41**) with NH₃ yielded 3-substituted 5-amino 1,2,4-oxadiazoles (**42/43**). Upon its biological evaluation, the compound **43** was found to be the most potent antimicrobial compound having minimum inhibitory concentration (MIC) against various microorganism *Staphylococcus aureus* (0.15 µg/mL), *Salmonella schottmulleri* (0.05 µg/ml), *Pseudomonas aeruginosa* (7.8 µg/mL), *Proteus vulgaris* (9.4 µg/mL), *Escherichia coli* (0.05 µg/mL), *Candida albicans* (12.5 µg/mL), *Trichophyton mentagrophytes* (6.3 µg/mL) and *Fusarium bulbigenum* (12.5 µg/mL). Against *Mycobacterium tuberculosis*, compound (**43**) was found to be most effective with MIC of 6.3 µg/mL among all other 1,2,4-oxadiazoles.

Mobashery et al. reported the use of 1,2,4-oxadiazole (Scheme 8) class of non-β-lactam antibiotics having activity towards Gram-positive bacteria along with good bioavailability [64]. Through in silico screening of 1.2 million compounds from ZINC database against penicillin-binding protein 2a (PBP2a), compound **49** has shown good MIC against *S. aureus* and *E. faecium* with better reproducibility. From the synthesized 370 structural derivatives of **49**, compounds **52** and **53** were found most effective against the panel of clinical microorganism. Further, they demonstrated bactericidal activity against vancomycin and linezolid resistant MRSA along with other strains of bacterial. The synthesis of compound 49 was achieved by the reaction of

4-iodobenzonitrile (**44**) with 4-substituted phenol (**45**) in the presence of CuI and dicesium carbonate at 90 °C followed by amidoxime formation using di-*isopropyl* ethyl amine (DIPEA) in THF and cyclocondensation to yield 1,2,4-oxadiazole using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF). To synthesize, intermediate **47** was reacted with 4-*tert*-butyl dimethyl silyl benzoyl chloride at 120 °C in toluene to yield **50** followed by desilylation using TBAF to yield **51**. In a similar fashion, **53** was obtained by treatment of **52** with 4-nitrobenzoyl chloride in toluene under reflux followed by catalytic reduction of nitro functional group to its amino counterpart (**53**). Further, they have studied these compounds through in vivo mouse model and revealed 100% oral bioavailability.

In continuation of their efforts for exploration of SAR of 1,2,4-oxadiazoles [65], they reported the use of about 120 synthetic oxadiazole derivatives (**52**) as antibiotics acting against several microorganisms and established their structure–activity relationships (Scheme 9) [66]. The reaction of 4-fluoro or 4-iodobenzonitrile (**54**) with 4-substituted phenol derivatives (**45**) via nucleophilic aromatic substitution or Ullmann coupling resulted in the formation of 4,4'-diphenyl ether (**55**), which upon the treatment with hydroxylamine (**56**) in ethanol at reflux followed by cyclization with acyl chloride (obtained by reacting substituted benzoic acids or heteroaromatic carboxylic acids with oxalyl chloride or thionyl chloride) in pyridine/toluene/1,4-dioxane to obtain 1,2,4-oxadiazoles (**58**). The para position substitution (R¹) improved metabolic stability and diminished the rate of excretion. The synthesized oxadiazoles have been found active against gram-positive bacteria including drug sensitive and methicillin/vancomycin/linezolid-resistant *S. aureus*. Replacement of pyrazole with indole broadened the spectrum against gram-positive organisms. The highest activity (MIC of 4 µg/mL) was observed for antibiotic **58** having indol-5-yl

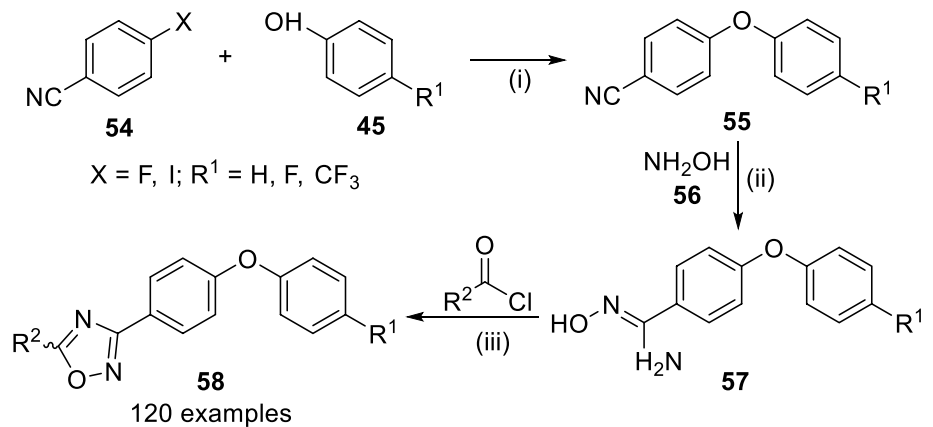


Scheme 8 Synthesis of 1,2,4-oxadiazoles (**49/51/53**) as non-β-lactam antibiotics. Conditions: (i) CuI, Cs₂CO₃, *N,N*-dimethylglycine HCl, 1,4-dioxane, 90 °C; (ii) NH₂OH, EtOH, reflux, 3 h; (iii) DIPEA, DCM, 0 °C → rt; (iv) TBAF, THF, rt, 24 h; (v) 4-TBDMS-BzCl,

PhMe, 120 °C, overnight; (vi) TBAF, (1 equiv), THF, <1 min; (vii) 4-NO₂-BzCl, PhMe, reflux, 5.5 h; (viii) Fe, H₂O, HCl, EtOH, 95 °C, 2 h

Scheme 9 Structure activity relationship of 1,2,4-oxadiazole antibiotics **58**. Conditions:

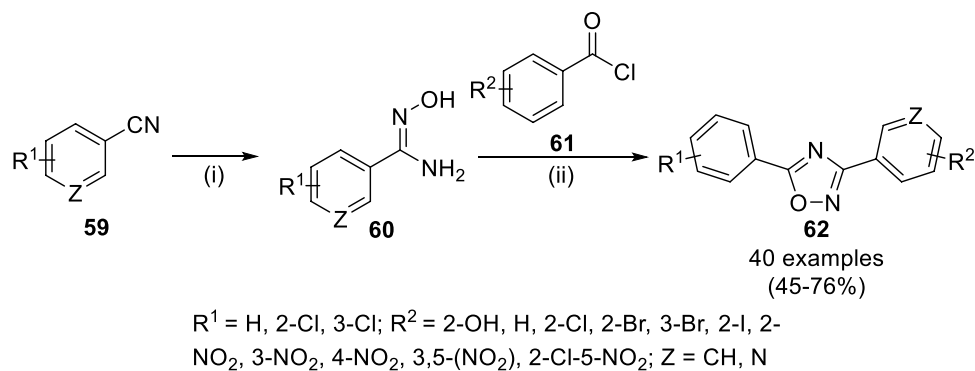
(i) K₂CO₃, DMF, 60–100 °C or CuI, Cs₂CO₃, *N,N*-dimethylglycine HCl, 1,4-dioxane, 90 °C; (ii) NH₂OH, EtOH and (iii) pyridine/toluene/1,4-dioxane



(R²) and 4-trifluoromethyl substitutions against *S. aureus* ATCC. The same compound was also found effective against in vivo mouse peritonitis model of infection with better pharmacokinetic and bioavailability profile. Other 4-trifluoromethyl (R¹) substituted antibiotics with 4-*N*-isopropyl amino-pyrazol-5-yl (R², MIC of 0.5 µg/mL) and 4-ethynyl-pyrazol-5-yl (R², MIC of 0.25 µg/mL) showed good anti-bacterial activity with the highest toxicity towards mammalian cells. However, these potent antibiotics were found ineffective against other microbial strains.

Aguar and colleagues evaluated the antimicrobial properties of 3,5-diphenyl or 3-pyridino-5-phenyl 1,2,4-oxadiazoles (**62**) [58]. These derivatives were synthesized (Scheme 10) by cyclization of amidoxime derivatives (**60**), synthesized from hydroxylamine hydrochloride and anhydrous sodium carbonate with acyl chloride (**61**, obtained from corresponding substituted carboxylic acid and thionyl chloride). Upon the biological evaluation of all the synthesized compounds against *E. coli*, *P. aeruginosa*, *S. aureus*, *P. mirabilis*, *E. faecalis*, the compounds **62a** (R¹ = 4-Cl,

Scheme 10 Synthesis of 1,2,4-oxadiazole derivatives (**62**) having anti-microbial property. Conditions: (i) EtOH, H₂O, reflux, 5 h and (ii) PhMe, reflux, 5 h



$R^2 = 2\text{-NO}_2, Z = \text{C}$), **62b** ($R^1 = 4\text{-Cl}, R^2 = 4\text{-NO}_2, Z = \text{C}$) and **62c** ($R^1 = 4\text{-Cl}, R^2 = 2\text{-Cl-5-NO}_2, Z = \text{C}$) have been found with the best anti-bacterial activity. The compounds with nitro as electron-donating group have shown potent anti-bacterial activity. Further, they anticipated the mode of action of these active hits through inhibition of promising enzyme of citric acid cycle through free radical formation involving reduction of nitro to amino counterparts via enzymatic bio-reduction approach.

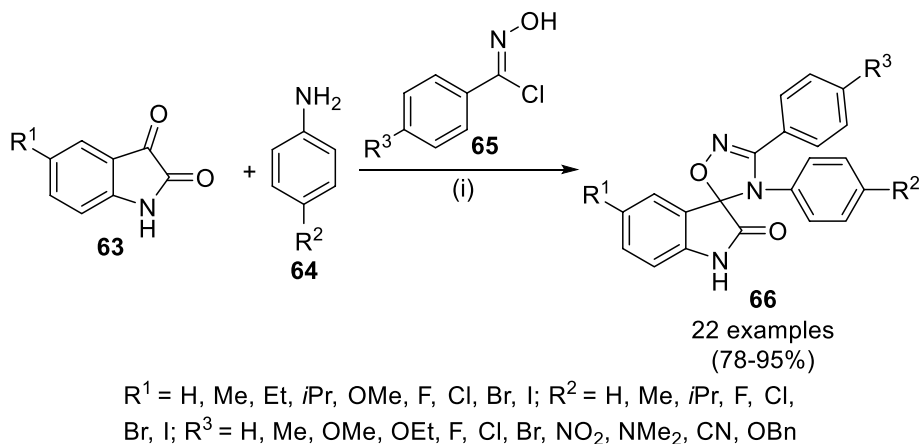
Du et al. [47] synthesized 3',4'-diaryl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-ones (**66**) having antibacterial activity (Scheme 11) by the reaction of isatin (**63**) and aniline (**64**) in ethanol at rt followed by 1,3-dipolar cycloaddition of the intermediates with *N*-hydroxybenzimidoyl chloride (**65**) in the presence of catalytic amount of DMAP (10 mol%) at rt for 3 h. Compound **66** ($R^1 = \text{H}; R^2 = \text{Me}; R^3 = \text{NO}_2$) was found to be most effective against *S. epidermidis*, wherein the anti-bacterial activity could be attributed to the electron-withdrawing group on phenyl ring. However, none of the compounds were found more effective than the anti-bacterial drug, levofloxacin against *Staphylococcus epidermidis*, *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumoniae*.

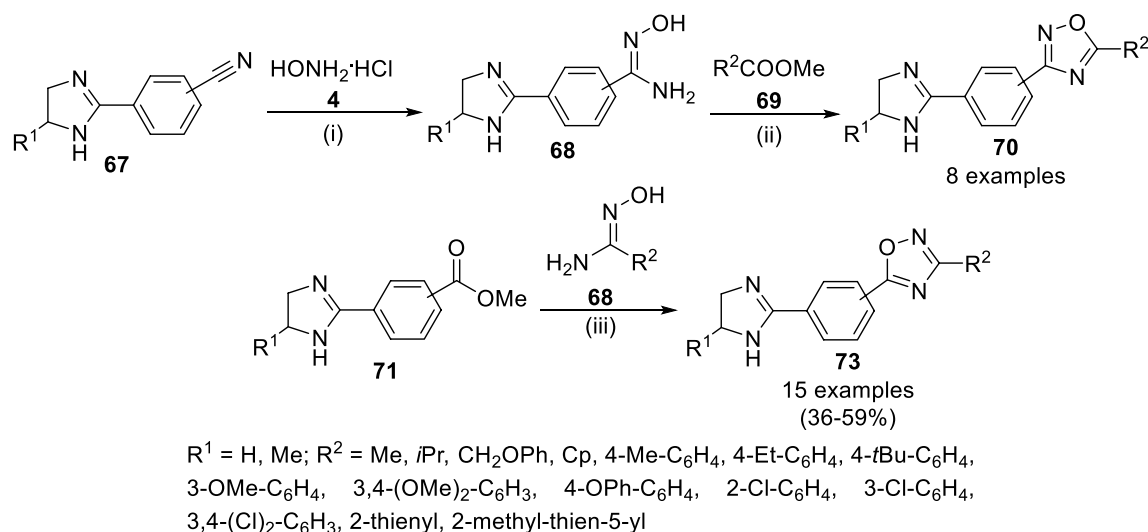
The synthetic strategy of 1,2,4-oxadiazole hybrids as anti-bacterial agents acting against both gram-positive and

gram-negative bacteria has been presented in Scheme 12 reported by Baykov et al. [46] The substituted 2-imidazoline (**67**) on reaction with hydroxylamine hydrochloride (**4**) in alkaline ethanolic medium at 80 °C formed *N*-aryl amidoxime (**68**), which was reacted with methyl carboxylate (**69**) in DMSO added with powdered caustic soda to yield **70**. In the reverse way, treatment of *N*-aryl methyl ester (**71**) and *N*-alkyl amidoxime (**68**) yielded 1,2,4-oxadiazoles. Compound **70** being *p*-phenylene derivative with $R^1 = \text{Me}, R^2 = 3,4\text{-(Cl)}_2\text{-C}_6\text{H}_3$ resulted in most potent compound having MIC in 8–16 µg/mL where bacteriostatic property has been also observed with *p*-phenylene derivative **73** in 8–32 µg/mL ($R^1 = \text{H}, R^2 = 3\text{-Cl-C}_6\text{H}_4$ and $R^1 = \text{Me}, R^2 = 4\text{-Me-C}_6\text{H}_4$).

In 2017, Raval and co-workers have synthesized novel 2-morpholinoquinoline nucleus appended 1,2,4-oxadiazoles having antimicrobial and antifungal activity (Scheme 13) [59]. The treatment of 2-chloroquinoline-3-carbaldehydes (**74**) in THF (30%) with aqueous ammonia (**75**) and sublimed iodine at rt for 30 min yielded 2-chloro-6-substituted quinoline-3-carbonitrile (**76**). The next reaction of **76** with morpholine (**77**) in presence of K₂CO₃ in DMF followed by reaction with hydroxylamine hydrochloride in alkaline mixture of ethanol:water (7:3) to synthesize amidoximes (**79**). Finally, the condensation

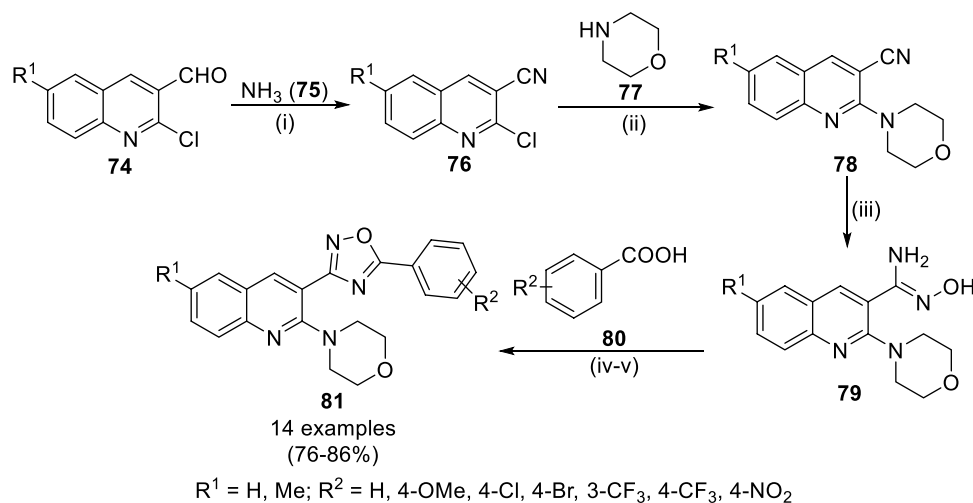
Scheme 11 Synthesis of 3',4'-diaryl-4'*H*-spiro[indoline-3,5'-[1',2',4']oxadiazol]-2-ones (**66**) via DMAP-catalyzed domino reaction. Conditions: (i) EtOH, rt, 3 h, DMAP (10 mol%), rt, 3 h





Scheme 12 Synthesis of 1,2,4-oxadiazoles (**73**) from *N*-aryl amidoxime (**72**) and alkyl ester (**71**). Conditions: (i) NaHCO₃, EtOH, 80 °C, 6 h, (ii) NaOH, DMSO, rt; (iii) NaOH, DMSO, rt, 4 h

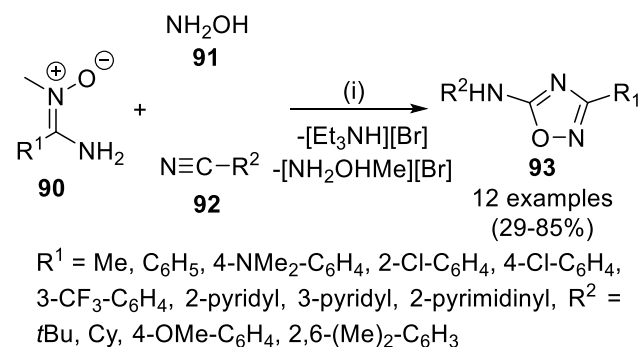
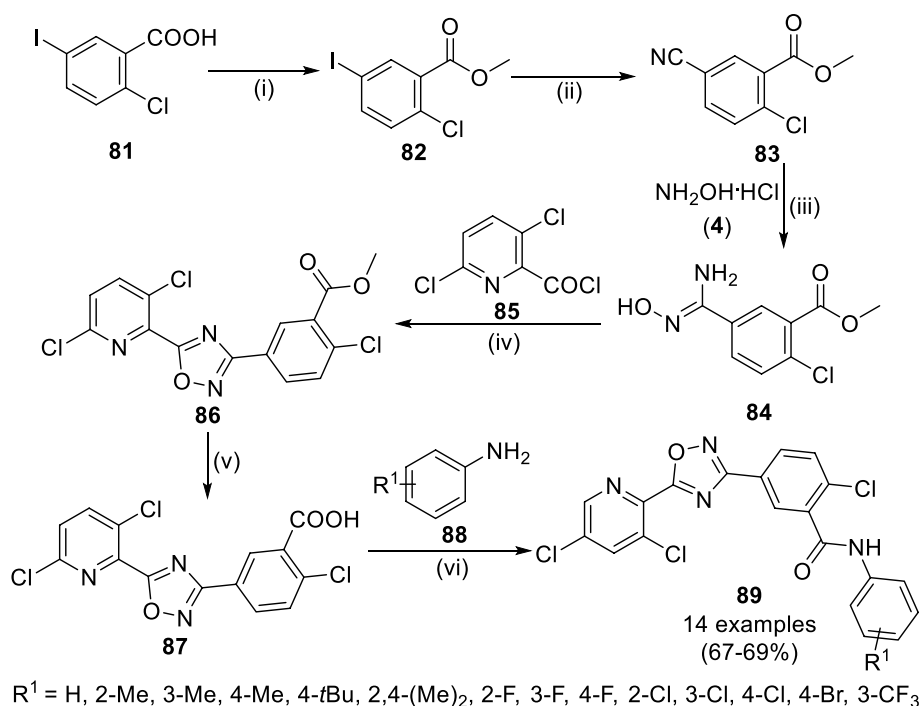
Scheme 13 Synthesis of 2-morpholinoquinoline integrated 1,2,4-oxadiazole scaffolds (**81**). Conditions: (i) I₂, THF, rt, 30 min; (ii) DMF, K₂CO₃, reflux, 2 h; (iii) NH₂OH·HCl, Na₂CO₃, EtOH, reflux, 5 h and (iv) EDC·HCl, DCM, rt, 30 min then reflux, 2 h; (v) NaOAc, EtOH, reflux, 3 h



of aromatic acids (**80**) in dichloromethane using coupling reagent ethyl-*(N,N'*-dimethylamino)propylcarbodiimide hydrochloride (EDC·HCl) under nitrogen atmosphere to obtain the target compounds, 1,2,4-oxadiazoles (**81**). All the target compounds were evaluated for assessment of drug likeness using Lipinski's rule of five indicating their druggability. The evaluation of anti-microbial potential of final compounds revealed compounds **81a-d** (R^1 = Me and R^2 = 4-NO₂, 4-Cl, 4-CF₃, 3-CF₃, respectively) as most potent compounds against gram-positive and gram-negative microbial and compounds fungal strains having better potency than ampicillin and griseofulvin. The presence of electron-withdrawing groups such nitro and trifluoromethyl on 5-phenyl ring have increased the anti-infective potential of the 1,2,4-oxadiazoles.

Recently, Tan et al. reported the synthesis of benzamide coupled pyridine anchored 1,2,4-oxadiazoles (**89**) as anti-fungal agents (Scheme 14) [67]. The esterification of 2-chloro-5-iodobenzoic acid (**81**) was achieved in methanol at reflux followed by cyanation using copper cyanide in the presence of L-proline and treatment with hydroxylamine hydrochloride (**4**) yielded benzamidoxime (**84**). Compound **84** was further reacted with 3,6-dichloropicolinoyl chloride (**85**) to 2-chloro-5-(5-(3,6-dichloropyridin-2-yl)-1,2,4-oxadiazol-3-yl)benzoate (**86**) via cyclization followed by alkali catalyzed hydrolysis to yield carboxylic acid (**87**). The amidation reaction of **86** with substituted aniline (**88**) at 0 °C for 7 h yielded (**89**). All the synthetic targets were evaluated through in vitro mycelia growth inhibition method against fungal strains including *Alternaria solani*, *FusaHum*

Scheme 14 Synthetic scheme for 3,5-disubstituted 1,2,4-oxadiazoles (**89**) as anti-fungal agents. Conditions: (i) MeOH, reflux, 8 h; (ii) CuCN, L-proline, DMF, 11 h; (iii) EtOH, rt; (iv) PhMe; (v) NaOH, THF, 2 h; (vi) 0 °C, 8 h



Scheme 15 Synthesis of 1,2,4-oxadiazoles (**93**) active as anti-bacterial agents. Conditions: (i) Br₂, Et₃N, CHCl₃, MeOH, rt, 10 min

graminearum, *Cercospora arachidicola*, *Phytophthora capsica*, *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Thanatephorus cucumeris* and *Fusarium oxysporum* and these results were compared with fluxapyroxad, a broad-spectrum fungicide. Compounds **87** ($R^1 = 2\text{-F}$) showed the good inhibitory activity (90.5%) against *Botrytis cinerea*, respectively.

Kukushkin and coworkers reported 5-amino-1,2,4-oxadiazoles (**93**) with higher anti-bacterial activity against multidrug-resistant strains such as *Staphylococcus aureus* and *Klebsiella pneumonia* (Scheme 15) [60]. These were prepared from different synthetic strategies involving the use of amidonitrone (**90**), hydroxylamine (**91**) and isocyanide (**92**) at rt in 29–86% yields. However, none of the compounds were found superior in activity as compared to ciprofloxacin, the currently marketed anti-bacterial drug.

Summary and future directions

In a nutshell, the synthesis of 1,2,4-oxadiazoles has been recognized as the key pharmacophore for broad-spectrum anti-infective or anti-microbial activities including anti-fungal, anti-bacterial, anti-trypanosomal, anti-malarial, anti-tubercular and anti-viral activities. In general, these scaffolds can be synthesized from amidoxime (obtained from reaction of nitrile and hydroxylamine) with carbonyl derivatives such as acyl chloride, ester, carboxylic acid or isatin. Mechanistically, the reaction of amidoxime with aldehyde yields the 1,2,4-oxadiazoline, which can be oxidized to 1,2,4-oxadiazole with the stoichiometric assistance of oxidizing agents. The objective behind the present work has been set to create the spotlight around 1,2,4-oxadiazole considering their synthetic strategies and usefulness as anti-parasitic activity for the benefit of medicinal chemists to design new scaffolds with potential activity of interest.

Authors Contribution SJC Literature review, Writing-Original draft and revised manuscript preparation, Reviewing and Editing; TMP Writing-Original draft preparation; BPD Writing-Original draft preparation; TMD Conceptualization, Supervision, Writing-Original draft and revised manuscript preparation, Reviewing and Editing.

Declarations

Conflict of interest The authors declare no competing financial interest.

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