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A review on synthetic routes for obtaining of 2,5-disubstituted 1,3,4-oxadiazoles *via* cyclodehydration and oxidative cyclization reactions

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ABSTRACT

1,3,4-Oxadiazole core is a known pharmacophore fragment, which possesses a wide opportunities for chemical modification and established versatile pharmacological potential. Moreover, oxadiazole plays a vital role in many drug structures and various biologically active compounds. For the construction of 1,3,4-oxadiazole cycle, different synthetic methods can be employed. In particular, the cyclization of *N,N'*-diacylhydrazines is a very common and convenient way for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. This approach includes dehydration followed by simultaneous cyclization of diacylhydrazines under the action of various dehydrating reagents – thionyl chloride, polyphosphoric acid, phosphorus pentoxide, acetic anhydride, phosphorus oxychloride, sulfuric acid etc. Another direction for the synthesis of non-condensed heterocyclic systems based on 1,3,4-oxadiazole is the oxidative cyclization of hydrazide-hydrazones, which are obtained by condensation of carboxylic acids hydrazides with appropriate aldehydes. The oxidizing reagents that are most commonly used in this reaction are potassium permanganate in acetone medium, bromine in acetic acid, Pb_3O_4 , chloramine-T etc. In this review, we attempt to highlight the detailed approaches for obtaining 1,3,4-oxadiazole derivatives based on cyclodehydration and oxidative cyclization reactions as the most commonly used methods of synthesis for this class compounds.

Keywords: *1,3,4-oxadiazoles; cyclodehydration reaction; one-stage cyclization; oxidative cyclization.*

1. INTRODUCTION

Oxadiazole is a five membered heterocyclic ring system containing oxygen and two nitrogen atoms. They occur in four isomeric forms namely 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,3-oxadiazole and 1,2,5-oxadiazole (Fig. 1). Among the four known isomers of oxadiazole, the first two are most widely studied because of their numerous interesting chemical and biological properties [1].

Figure 1. Isomeric forms of oxadiazole

1,3,4-Oxadiazole heterocycle is a very interesting and important scaffold for modern organic and medicinal chemistry. These compounds have been displayed a diverse range of biological activities including anticancer [2-3], antimicrobial [4-5], antitubercular [6-7], antifungal [8-9], antiviral [10-11], anesthetic [12], antioxidant [13-14], immunosuppressive [15-16], antidiabetic [17], anti-allergic [18], anti-inflammatory, anti-rheumatic and analgesic [19-20] action, CNS activity like antiepileptic [21], anticonvulsant [22], antidepressant [23] etc.

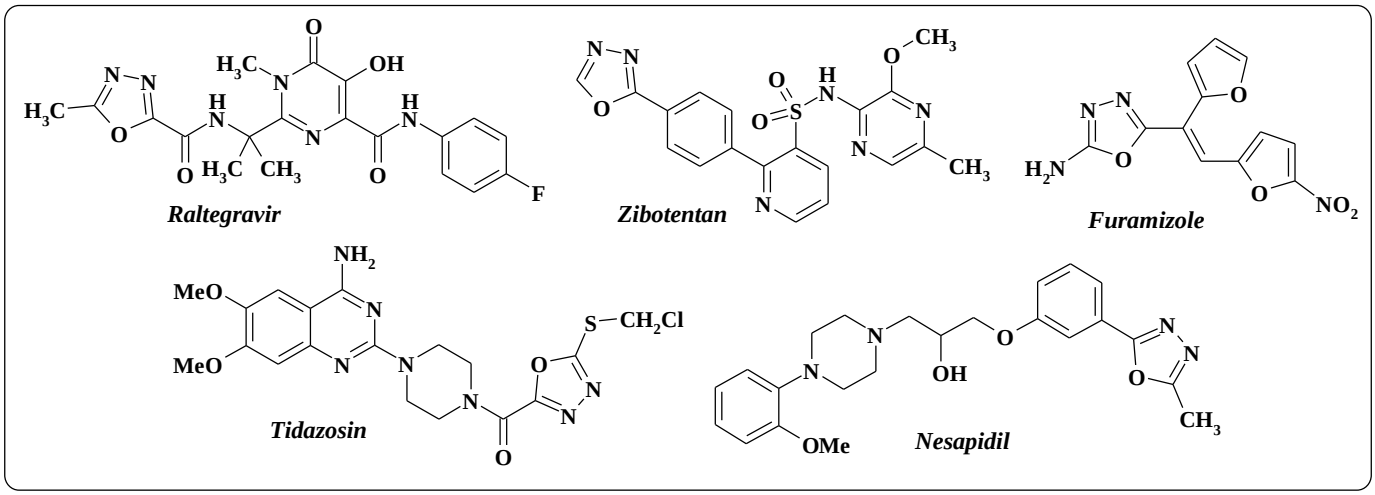


Figure 2. 1,3,4-Oxadiazole containing drugs used in medicinal practice

Oxadiazole derivatives play an important role as antitumor agents because of their good inhibitory activities against histone deacetylase HDAC [24], topoisomerase I [25], telomerase [26], focal adhesion kinase FAK [27] and tubulin polymerization [28] as well mitochondrial mediated apoptosis inducing ability [29].

Also oxadiazoles have been reported as inhibitors of α-glucosidase [30], cathepsin K [31], glycogen synthase kinase-3 (GSK-3) [32], nucleotide pyrophosphatases/phosphodiesterases-1 NPP1 [33], tyrosinase [34], glycogen phosphorylase [35], urease [36], COX-2/5-LOX biosystem [37] etc.

To 1,3,4-oxadiazole containing compounds belongs an approved antiretroviral (*Raltegravir*), anticancer (*Zibotentan*), antimicrobial (*Furamizole*) and antihypertensive (*Tiodazosin* and *Nesapidil*) drugs (Fig. 2).

For the construction of 1,3,4-oxadiazole ring the several methods have been reported in the literature. The most general methods involve the cyclization of diacylhydrazides or hydrazide-hydrazones with a variety of dehydrating or oxidizing reagents, respectively. Also, few reliable and operationally simple examples have been reported for the one-step synthesis of 1,3,4-oxadiazoles, especially from readily available carboxylic acids and it's hydrazides.

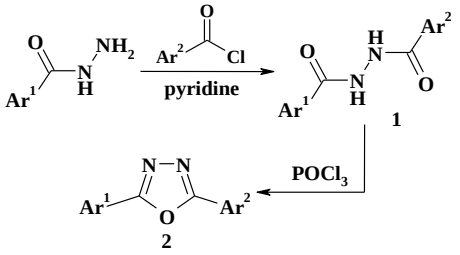
In return, this review aimed to summarize the literature data about some recent strategies on the synthesis of non-condensed heterocyclic systems based on 1,3,4-oxadiazole scaffold including cyclodehydration and oxidative cyclization reactions as the most common and preparative ones.

2. SYNTHETIC APPROACHES FOR CONSTRUCTION OF 1,3,4-OXADIAZOLE RING SYSTEM

2.1. Two-stages methods for obtaining of disubstituted 1,3,4-oxadiazoles based on cyclodehydration of diacylhydrazines.

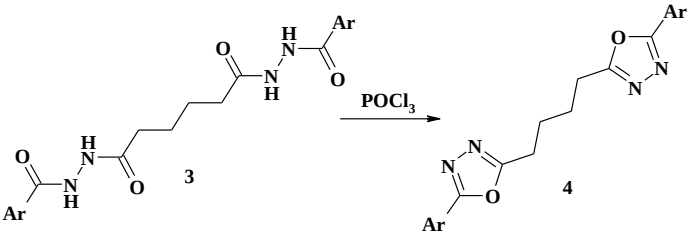
All of the following transformations are conventionally related to two-stage methods of obtaining of disubstituted 1,3,4-oxadiazoles, because they include the phase of formation and separation of *N,N*-diacylhydrazines with subsequent cyclization under the action of dehydrating reagents.

The interaction between hydrazides and chloroanhydrides of aromatic acids in the pyridine medium resulted in an unsymmetrical diaroylhydrazines **1** (Scheme 1). Compounds **1** are cyclized under the action of phosphorus oxychloride into the corresponding 2,5-diaryl-1,3,4-oxadiazoles **2** [38]:



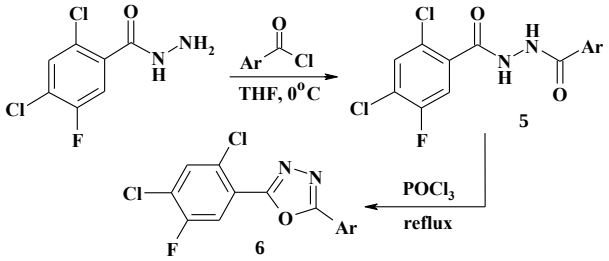
Scheme 1. Synthesis of 2,5-diarylsubstituted 1,3,4-oxadiazoles by cyclization of diaroylhydrazines with phosphorus oxychloride

Based on cyclization of symmetric diaroylhydrazides of adipic acid **3** Al-Talib *et al*. [39] synthesized 1,4-bis-(5-aryl-1,3,4-oxadiazole-2-yl)butane derivatives **4** (Scheme 2) in the above-mentioned conditions:



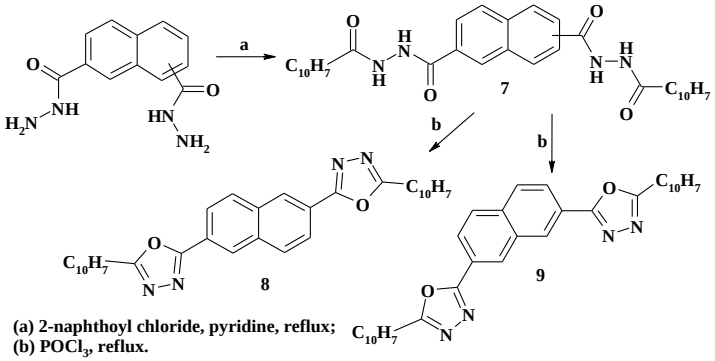
Scheme 2. Synthesis of symmetric 1,4-bis-(5-aryl-1,3,4-oxadiazole-2-yl)butane derivatives by cyclization of adipic acid diaroylhydrazides

The group of 2-(2,4-dichloro-5-fluorophenyl)-5-aryl-1,3,4-oxadiazoles **6** (Scheme 3) as potential insecticidal agents was synthesized by cyclization of corresponding *N′*-aroylhydrazides of 2,4-dichloro-5-fluorobenzoic acid **5** upon boiling for 2-3 hours in phosphorus oxychloride medium [40]:



Scheme 3. Synthesis of 2-(2,4-dichloro-5-fluorophenyl)-5-aryl-1,3,4-oxadiazoles by cyclization of corresponding *N′*-aroylhydrazides

Following the interaction between dihydrazides of naphthalene-2,6(7)-dicarboxylic acids and 2-naphtoyl chloryde the corresponding acylated derivatives **7** were obtained and further cyclized under the action of phosphorus oxochloride with the formation of 1,3,4-oxadiazole ring [41]. This approach allowed us to obtain a series of original polycyclic naphthalene containing systems connected by 1,3,4-oxadiazole linking cycle at positions 2 and 6 (2,6-isomer) **8** or 2 and 7 (2,7-isomer) **9** relatively to the central naphthalene core (Scheme 4). X-ray diffraction analysis of target compounds was carried out, which significantly confirms their structure.



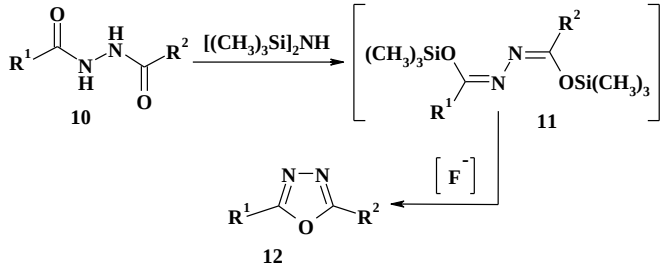
(a) 2-naphthoyl chloride, pyridine, reflux; (b) $POCl_3$, reflux.

Scheme 4. Synthesis of polycyclic naphthalene containing systems connected by 1,3,4-oxadiazole linking cycle at positions 2 and 6 or 7

Rigo *et al*. [42-44] proposed a method of obtaining 2,5-disubstituted 1,3,4-oxadiazoles based on cyclodehydration of *N*-acylhydrazides using various organosilicon compounds, including hexamethyldisilazane (HMDS), trimethylchlorosilane and dichlorodimethylsilane. These transformations are carried out through the formation of intermediate bis-trimethylsilyldiacyl

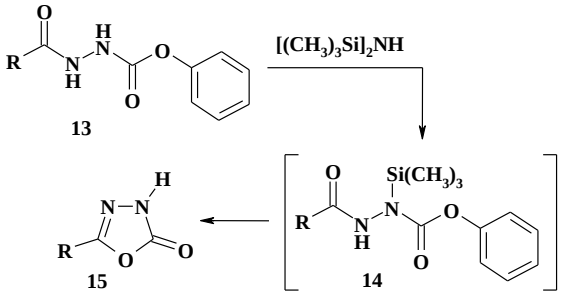
hydrazine, which further cyclized into the oxadiazole ring under the action of specific fluoride ion donor catalysts.

Based on interaction between diacylhydrazines **10** and hexamethyldisilazane by stirring for 9-16 hours the synthesis of intermediates **11** was carried out. The further cyclization of **11** without its separation from the reaction mixture under the action of catalytic amount of tetrabutylammonium fluoride resulted in a series of disubstituted 1,3,4-oxadiazoles **12** (Scheme 5) with a yields of 85-90% [42].



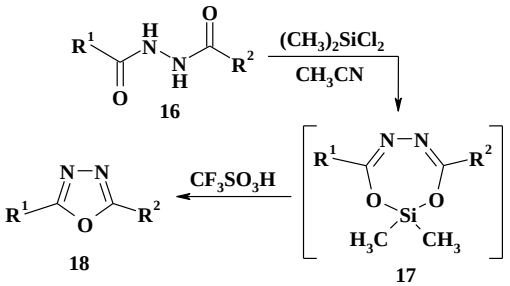
Scheme 5. Synthesis of disubstituted 1,3,4-oxadiazole derivatives by interaction between diacylhydrazines and hexamethyldisilazane under the action of catalytic amounts of tetrabutylammonium fluoride

N^3-Acylated phenylcarbazinate derivatives **13** were transformed into the corresponding 4*H*-1,3,4-oxadiazole-5-ones **15** (Scheme 6) through the stage of the formation of intermediate **14** in similar conditions [42]:



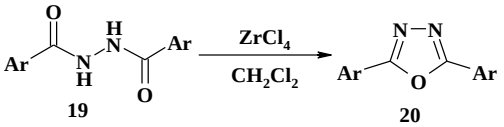
Scheme 6. Synthesis of 4*H*-1,3,4-oxadiazole-5-ones by cyclisation of N^3-acylated phenylcarbazinate derivatives with hexamethyldisilazane

Synthesis of unsymmetrical 1,3,4-oxadiazole derivatives **18** was achieved by cyclization of corresponding diacylhydrazines **16** with trimethylchlorosilane [43] or dimethyldichlorosilane [43-44] using trifluoromethanesulphonic acid as a catalyst as it's depicted on Scheme 7. The reaction proceeds in the same way as with hexamethyldisilazane, but in the case of dimethyldichlorosilane, a cyclic intermediate **17** was formed at the expense of two chlorine atoms in the molecule of the cyclizing reagent. This interaction occurs in the acetonitrile medium by heating for 24 hours.



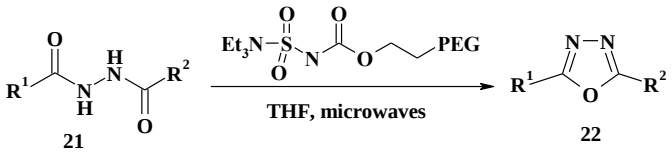
Scheme 7. Synthesis of unsymmetrical 1,3,4-oxadiazoles by cyclization of diacylhydrazines with dimethyldichlorosilane in acetonitrile medium

Synthesis of symmetrical 2,5-diaryl-1,3,4-oxadiazoles **20** (Scheme 8) was carried out by cyclization of the corresponding *N*,*N*-diacylhydrazines **19** under the action of zirconium (IV) chloride as a catalyst in dichloromethane medium at room temperature for 3 hours with a good yields (over 70%) [45]:



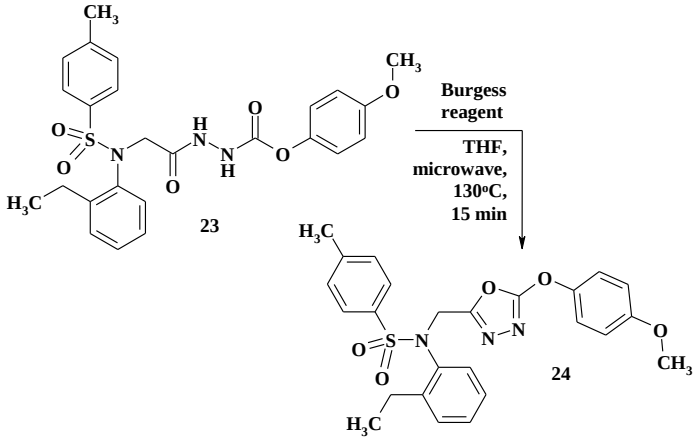
Scheme 8. Synthesis of symmetrical 2,5-diaryl-1,3,4-oxadiazoles by the cyclization of the *N*,*N*-diacylhydrazines using zirconium (IV) chloride

Brain *et al*. [46] established that cyclodehydration of diacylhydrazines **21** into the corresponding disubstituted 1,3,4-oxadiazoles **22** (Scheme 9) occurs under the action of polymer-supported Burgess reagent in the tetrahydrofuran medium using microwave irradiation. The presence of these conditions decreases reaction time to 2 minutes at 96% of yield and 91% of purity.



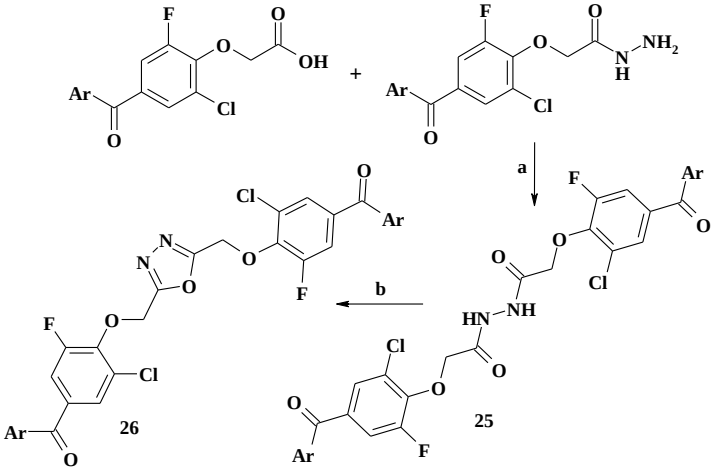
Scheme 9. Synthesis of disubstituted 1,3,4-oxadiazoles by cyclization of diacylhydrazines under the action of polymer-supported Burgess reagent

Based on the cyclization of diacylhydrazine **23** using the Burgess reagent in the above mentioned conditions Hall *et al*. [47] synthesized 2-(4-metoxypheniloxy)-1,3,4-oxadiazole **24** with 4-tolylsulfonamide fragment in position 5 (Scheme 10) as a potential EP_1 receptor antagonists:



Scheme 10. Synthesis of 2-(4-metoxypheniloxy)-1,3,4-oxadiazole with 4-tolylsulfonamide fragment based on the cyclization reaction using the Burgess reagent

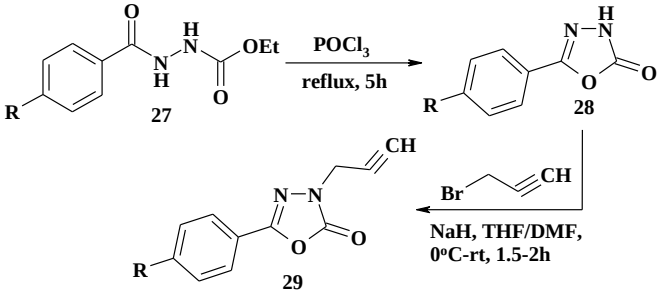
A series of symmetric 2,5-disubstituted 1,3,4-oxadiazoles **26** were obtained by intramolecular cyclization of *N*,*N*-di[2-(4-aroylaryloxy)acetyl]hydrazines **25** with triflic anhydride in the present of pyridine in dichloromethane medium (Scheme 11). Primarily, the synthesis of diacylhydrazines **25** was carried out through the acylation reaction of 4-aryloylaryloxyethanoic acids with similar hydrazides in the presence of 2,6-lutidine and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluronium tetrafluoroborate (*TBTU*) in dichloromethane medium [48].



(a) 2,6-lutidine, TBTU, DCM, r.t., 12h; (b) triflic ahhydride, pyridine, DCM, 0°C, 3h

Scheme 11. Synthesis of symmetric 2,5-disubstituted 1,3,4-oxadiazoles by intramolecular cyclization of corresponding *N*,*N*-diacylhydrazines with triflic anhydride in the present of pyridine in dichloromethane medium

Cyclization of ethyl 2-benzoylhydrazinecarboxylates **27** under reflux conditions using $POCl_3$ afforded a group of 5-aryl-1,3,4-oxadiazol-2(3H)-ones **28** in good yields (Scheme 12). The further interaction between **28** with propargyl bromide in tetrahydrofuran/dimethylformamide (1:1) medium in the presence of NaH resulted in the corresponding *N*-propargylated derivative **29** as a promising synthon for synthesis of nitrogen-containing polyheterocyclic systems [49].

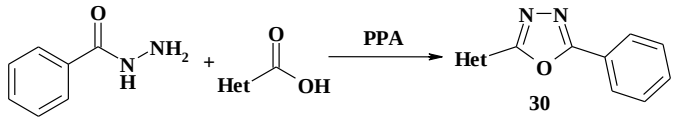


Scheme 12. Synthesis of 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones and their *N*-propargylated derivatives by cyclization of ethyl 2-benzoylhydrazine carboxylates under reflux conditions using phosphorus oxochloride

2.2. Cyclodehydration reaction based one-stage methods for the synthesis of substituted 1,3,4-oxadiazole derivatives.

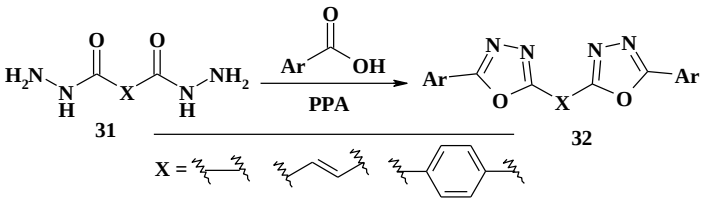
The methods of one-stage synthesis of 1,3,4-oxadiazole derivatives by direct condensation of hydrazides with carboxylic acids or their chloroanhydrides, are often common in the literature, but they all required fairly harsh conditions and long boiling.

Following the reaction between benzoic acid hydrazide and heterylcarboxylic acids, a series of 2-heteryl substituted 5-phenyl-1,3,4-oxadiazoles **30** (Scheme 13) was synthesized by Rangnekar and Phadke [50]. This interaction occurs in the presence of polyphosphoric acid (PPA) by heating to 80°C and stirring for 3,5-4 hours followed by cooling of the reaction mixture to 60°C and slowly pouring into crushed ice.



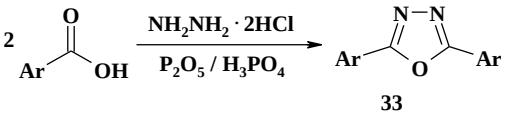
Scheme 13. Synthesis of 2-heteryl-5-phenyl-1,3,4-oxadiazoles following the reaction between benzoic acid hydrazide and heterylcarboxylic acids

A series of bis-5-aryl-1,3,4-oxadiazoles **32** (Scheme 14) as fluorescent whiteners for polyester fibres were synthesized by interaction between dicarboxylic acid dihydrazides **31** and aromatic acids in similar conditions [50]:



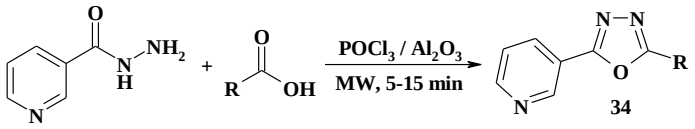
Scheme 14. Synthesis of bis-5-aryl-1,3,4-oxadiazole derivatives by interaction between dicarboxylic acid dihydrazides and aromatic acids

The synthesis of symmetrical 2,5-diaryl-1,3,4-oxadiazoles **33** (Scheme 15) was performed through the condensation of arylcarboxylic acids with hydrazine dihydrochloride with the following cyclization in phosphorus pentaoxide and phosphoric acid without isolation from the reaction mixture of intermediate products [51]:



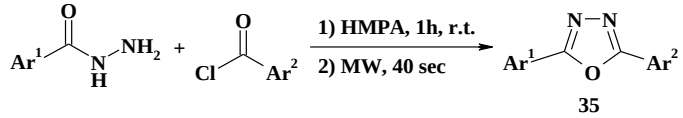
Scheme 15. Synthesis of symmetrical 2,5-diaryl-1,3,4-oxadiazoles by condensation of arylcarboxylic acids with hydrazine dihydrochloride

Khan *et al*. [52] proposed an alternative one-step method for obtaining of 1,3,4-oxadiazole cycle using microwave irradiation. This leads to a reduction of the reaction time from several hours to 5-15 minutes, as well as increases the yield of the target product. Thus, 5-aryl(alkyl) substituted 2-(3-pyridyl)-1,3,4-oxadiazoles **34** (Scheme 16) were prepared by reacting of nicotinic acid hydrazide with aromatic or aliphatic acids in phosphorus oxochloride medium under microwave irradiation:



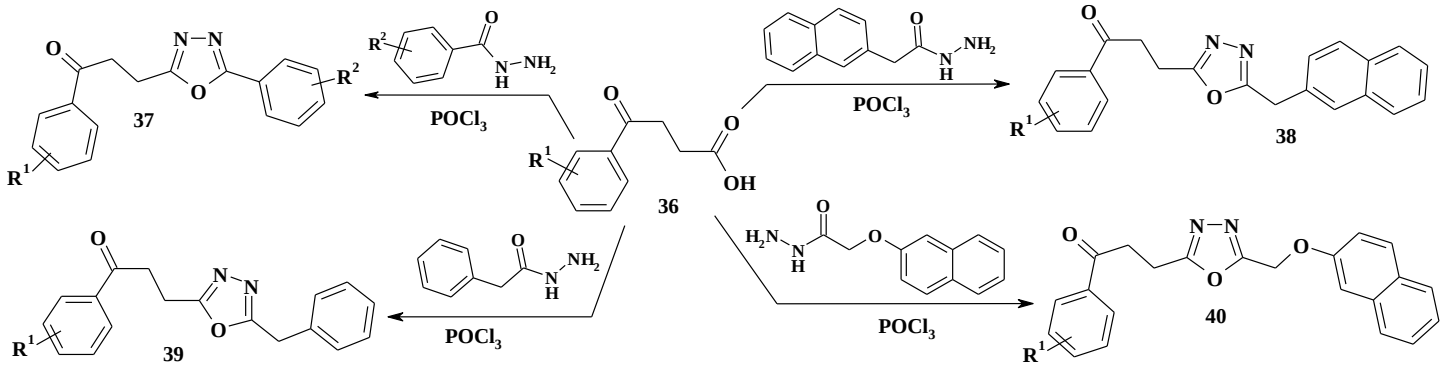
Scheme 16. Synthesis of 5-substituted 2-(3-pyridyl)-1,3,4-oxadiazoles by reacting of nicotinic acid hydrazide with aromatic or aliphatic acids

The interaction of aroylhydrazines with chloroanhydrides of aromatic acids in hexamethylphosphoramide (HMPA) medium resulted in a series of unsymmetrical 2,5-diaryl-1,3,4-oxadiazoles **35** (Scheme 17). The reaction proceeds for 1 hour at room temperature until the exothermic process ceases, then the reaction mixture is subjected to microwave irradiation for cyclization without separation of the intermediate products [53]:



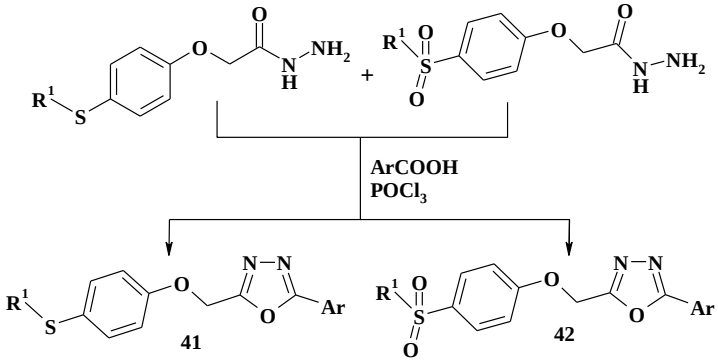
Scheme 17. Synthesis of unsymmetrical 2,5-diaryl-1,3,4-oxadiazoles by interaction of aroylhydrazines with chloroanhydrides of aromatic acids

Synthesis of 2-(β-aroylethyl) substituted 1,3,4-oxadiazoles **37-40** (Scheme 18) was achieved through the cyclization reaction of β-aroylpropionic acid derivatives **36** with hydrazides of phenylacetic, naphthyl-2-(oxy)acetic and aromatic acids [54]:



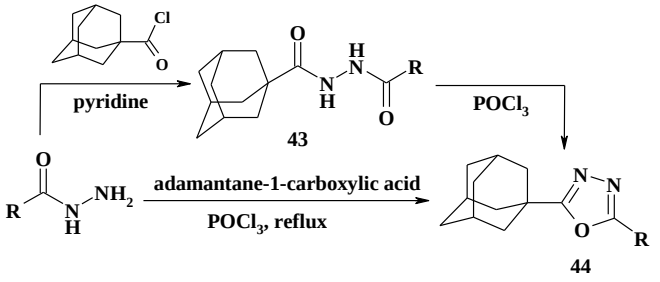
Scheme 18. Synthesis of 2-(β-aroylethyl) substituted 1,3,4-oxadiazoles by cyclization reaction of β-aroylpropionic acid derivatives with hydrazides of phenylacetic, naphthyl-2-(oxy)acetic and aromatic acids

The condensation of alkylthio(sulphonyl)phenoxyacetic acid hydrazides and with arylcarboxylic acids in phosphorus oxochloride medium afforded the corresponding 2,5-disubstituted 1,3,4-oxadiazoles **41** and **42** according to Scheme 19 [55]:



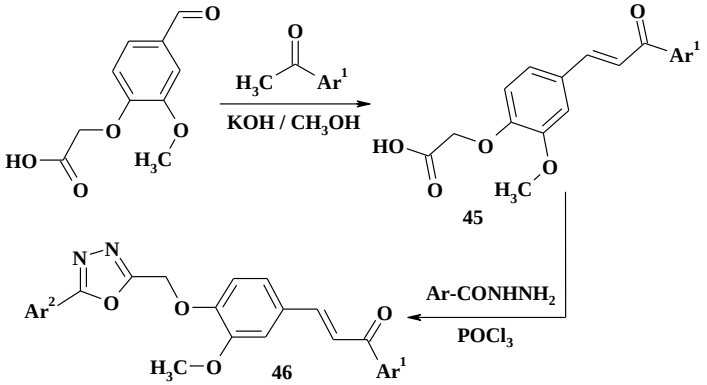
Scheme 19. Synthesis of alkylthio(sulphonyl)phenoxymethyl substituted 1,3,4-oxadiazoles by condensation of appropriate hydrazides with arylcarboxylic acids in phosphorus oxochloride medium

Based on the reaction of carboxylic acids hydrazides with adamantane-1-carbonyl chloride in refluxing pyridine the corresponding *N*-adamantanoylhydrazides **43** were obtained and further cyclized by boiling for 1 hour in phosphorus oxochloride medium into 1,3,4-oxadiazoles with adamantane fragment **44** (Scheme 20). Also, an alternative one-step method for the preparation of compounds **44** was performed by the interaction of the starting hydrazides with adamantane-1-carboxylic acid in the phosphorus oxochloride medium with yield of 85-95% [56]:



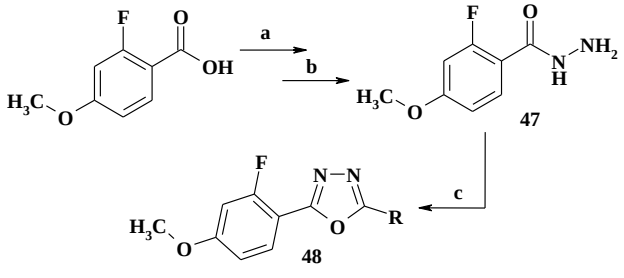
Scheme 20. Synthesis of adamantyl substituted 1,3,4-oxadiazoles by cyclization of corresponding *N*-adamantanoylhydrazides in phosphorus oxochloride medium

The reaction of 2-(4-formyl-2-methoxyphenoxy)acetic acid with acetophenone derivatives by conventional Claisen-Schmidt condensation in the presence of alkaline catalysis gave the appropriate chalcones **45** (Scheme 21). Due to the presence of a free carboxyl group in the molecules of synthesized chalcones **45** their further chemical modification by reacting with aromatic acids hydrazides in phosphorus oxochloride with the formation of 2,5-disubstituted 1,3,4-oxadiazoles **46** was performed [57]:



Scheme 21. Synthesis of 5-substituted 2-aryl-1,3,4-oxadiazole derivatives by reacting of *para*-carboxymethyloxy substituted chalcones with aromatic acids hydrazides in phosphorus oxochloride

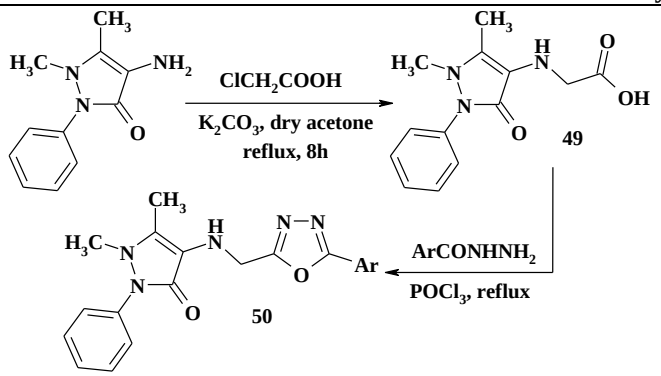
Following the sequential transformation of 2-fluoro-4-methoxybenzoic acid *via* esterification and hydrazinolysis reactions the appropriate hydrazide **47** was synthesized by Chandrakantha et al. [58]. Condensation of compound **47** with various carboxylic acids in refluxing phosphorus oxochloride afforded 2,5-disubstituted 1,3,4-oxadiazoles **48** with 2-fluoro-4-methoxyphenyl moiety in position 2 (Scheme 22):



(a) H⁺, EtOH; (b) $NH_2NH_2·H_2O$, EtOH; (c) R-COOH, $POCl_3$, 110°C.

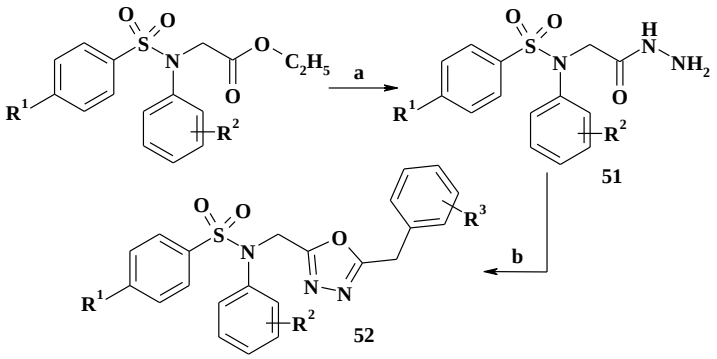
Scheme 22. Synthesis of 2-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazoles by cyclodehydration reaction of appropriate hydrazide with various carboxylic acids in phosphorus oxochloride medium

By condensation of 1,5-dimethyl-2-phenylpyrazol-3-one substituted aminoacetic acid **49** with appropriate hydrazides in refluxing phosphorus oxychloride (Scheme 23) the target 2-aryl-1,3,4-oxadiazoles **50** with aminoantipyrine moiety in position 5 were obtained [50]:



Scheme 23. Synthesis of 2-aryl-1,3,4-oxadiazoles with aminoantipyrine moiety based on condensation of 1,5-dimethyl-2-phenylpyrazol-3-one substituted aminoacetic acid with appropriate hydrazides

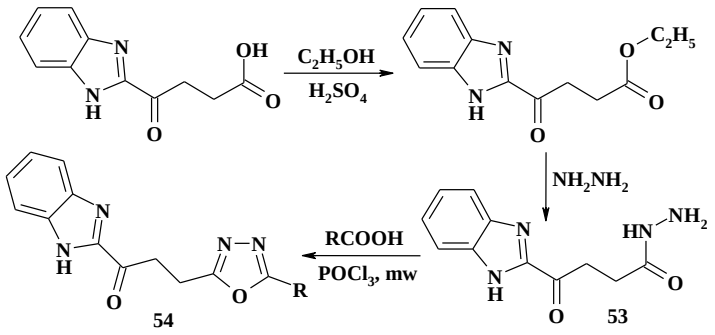
Synthesis of new 1,3,4-oxadiazoles **52** (Scheme 24) as potential EP_1-receptors antagonists was carried out based on cyclodehydration reaction of arylsulfonamide-glycine hydrazides **51** with phenylacetic acid derivatives in microwave-assisted conditions [47]:



(a) hydrazine hydrate, heat or microwave;
(b) phenylacetic acid derivative, $POCl_3$, microwave, 100°C, 30 min.

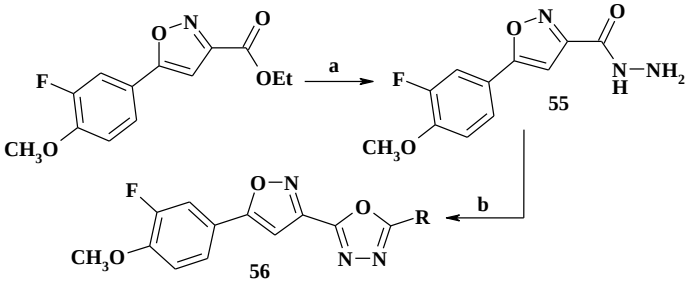
Scheme 24. Synthesis of 5-benzyl-1,3,4-oxadiazoles by cyclodehydration reaction of arylsulfonamide-glycine hydrazides with phenylacetic acids

Based on 4-(1*H*-benzo[*d*]imidazole-2-yl)-4-oxobutanoic acid in a two-stage synthesis the appropriate hydrazide **53** have been obtained and further modified by reacting with carboxylic acids in phosphorus oxochloride medium into 1,3,4-oxadiazole derivatives **54** (Scheme 25) containing benzimidazole moiety [60]:



Scheme 25. Synthesis of benzimidazole substituted 1,3,4-oxadiazoles by a three-stage transformation based on 4-(1*H*-benzo[*d*]imidazole-2-yl)-4-oxobutanoic acid

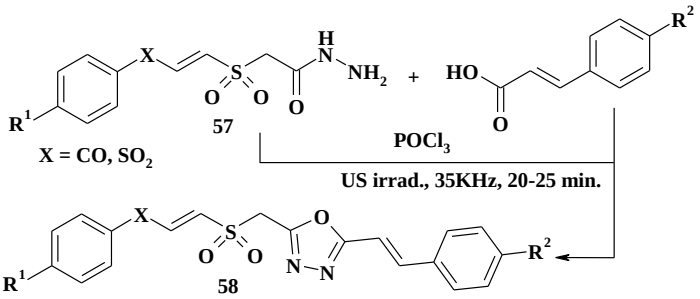
The cyclization of 5-(3-fluoro-4-methoxyphenyl)isoxazole-3-carboxylic acid hydrazide **55** with different substituted benzoic/pyridyl/indolyl acids in phosphorus oxochloride medium at reflux temperature for 8-10h (Scheme 26) gave the target isoxazole substituted 1,3,4-oxadiazoles **56** with 3-fluoro-4-methoxyphenyl moiety [61]:



(a) $NH_2NH_2{\cdot}H_2O$, EtOH; (b) R-COOH, $POCl_3$.

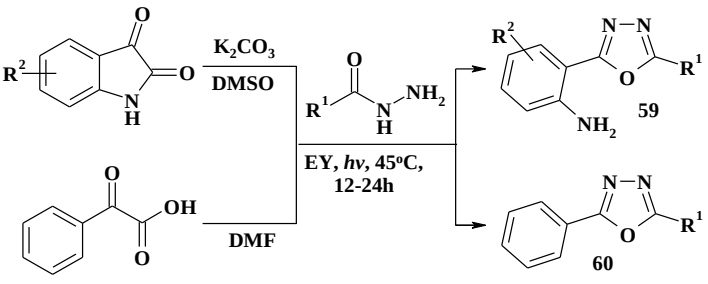
Scheme 26. Synthesis of isoxazole substituted 1,3,4-oxadiazoles by cyclization of 5-(3-fluoro-4-methoxyphenyl)isoxazole-3-carboxylic acid hydrazide with different carboxylic acids

A series of 2-(*E*-aroylethenesulfonylmethyl)-5-styryl-1,3,4-oxadiazoles **58** (Scheme 27) were synthesized by condensation of *E*-aroyl(arylsulfonyl)ethenesulfonylacetic acid hydrazides **57** with cinnamic acid in the phosphorus oxychloride medium using ultrasonication conditions [62]:



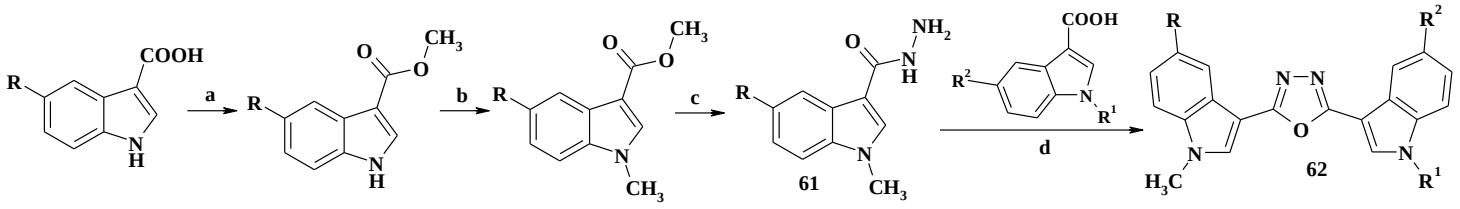
Scheme 27. Synthesis of 5-styryl-1,3,4-oxadiazoles by condensation of *E*-aroyl(arylsulfonyl)ethenesulfonylacetic acid hydrazides with cinnamic acid using ultrasonication conditions

The synthesis of 5-substituted 2-aryl-1,3,4-oxadiazoles **59**-**60** (Scheme 28) based on decarboxylation-cyclization reaction of isatin derivatives or phenylglyoxylic acid with different hydrazides under the visible-light-induced photoredox catalysis was performed by Diao *et al*. [63]. It was established that the availability of eosin Y as a photoredox catalyst, visible light and base is essential for the formation of the target products in moderate to good yields under mild conditions.



Scheme 28. Synthesis of substituted 2-aryl-1,3,4-oxadiazoles by reaction of isatin derivatives or phenylglyoxylic acid with different hydrazides

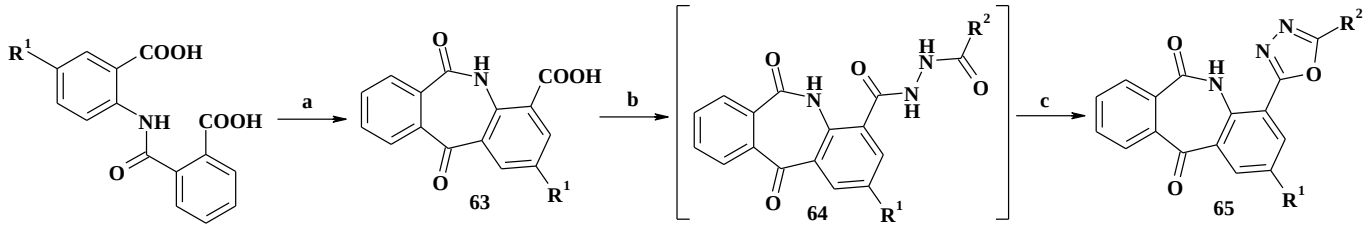
The interaction between 5-substituted *N*-protected indole-3-carbohydrazides **61** and indole-3-carboxylic acids in the presence of solid phase catalyst polyphosphoric acid at 90ºC for over 3-4 h afforded a group of 2,5-bis(indolyl)-1,3,4-oxadiazole derivatives **62** according to the Scheme 29 [64]:



(a) CH_3OH, H_2SO_4 conc, reflux, 5h; (b) DMC, DMF, K_2CO_3, reflux; (c) $NH_2NH_2 \cdot H_2O$, ethanol, reflux, 8h; (d) PPA, 90°C, 3-4h.

Scheme 29. Synthesis of 2,5-bis(indolyl)-1,3,4-oxadiazole derivatives by interaction between 5-substituted *N*-protected indole-3-carbohydrazides and indole-3-carboxylic acids in the presence of solid phase catalyst

A group of novel 5*H*-dibenzo[*b,e*]azepine-6,11-dione derivatives containing 1,3,4-oxadiazole units **65** was synthesized through a multistep synthetic procedure (Scheme 30). It includes the sequential transformation of 5*H*-dibenzo[b,e]azepine-6,11-dione-4-carboxylic acids **63** into the corresponding acyl chlorides and further formation of intermediate diacylhydrazines **64** which cyclized with p-toluenesulfonyl chloride in dichloromethane medium into the target 1,3,4-oxadiazole containing 2-substituted 5*H*-dibenzo[*b,e*]azepine-6,11-diones **65** without separation from the reaction mixture [65]:

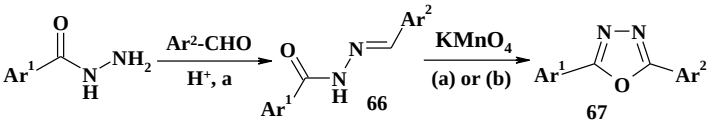


(a) i. $SOCl_2$, $CHCl_3$, 50°C; ii. $AlCl_3$, $CHCl_3$, 50°C; (b) i. $SOCl_2$, DCM; ii. acylhydrazines, Et_3N, DCM, 35°C; (c) TsCl, DCM, 35°C.

Scheme 30. Synthesis of 1,3,4-oxadiazole containing 5*H*-dibenzo[b,e]azepine-6,11-diones based on cyclization of 5*H*-dibenzo[b,e]azepine-6,11-dione-4-carboxylic acid through a multistep synthetic procedure

2.3. Synthesis of disubstituted 1,3,4-oxadiazole derivatives based on oxidative cyclization of hydrazide-hydrazones.

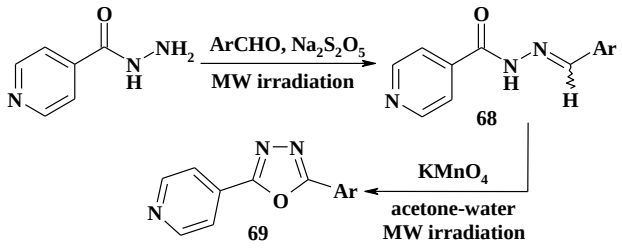
A group of 2,5-diarylsubstituted 1,3,4-oxadiazoles **67** was synthesized by cyclization of 1-aroyl-2-arylidenehydrazines **66** with potassium permanganate on the surface of silica gel in the microwave-assisted synthesis (Scheme 31). It was established that these conditions are significantly more efficient by values of percentage yields of target products compared to conducting this reaction in the acetone-water (4:1) medium [66].



(a) SiO_2, MW; (b) acetone / water (4:1), MW

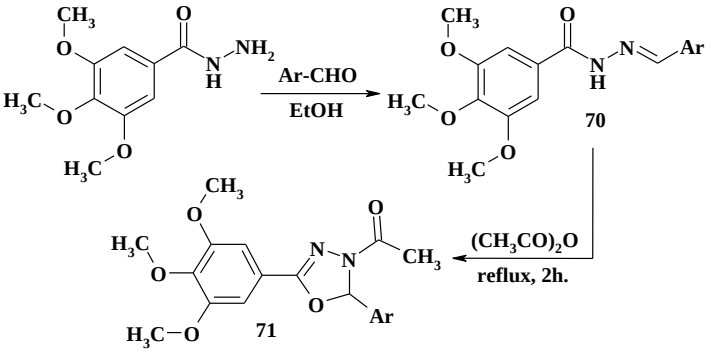
Scheme 31. Synthesis of disubstituted 1,3,4-oxadiazoles by cyclization of 1-aroyl-2-arylidenehydrazines with potassium permanganate

The synthesis of 2-(4-pyridyl) substituted 5-aryl-1,3,4-oxadiazoles **69** (Scheme 32) as potential antimycobacterial agents was carried out by cyclization of appropriate *N*-(arylmethyliden)-isonicotinoylhydrazones **68** with potassium permanganate in acetone-water (5:1) medium under microwave irradiation [67]:



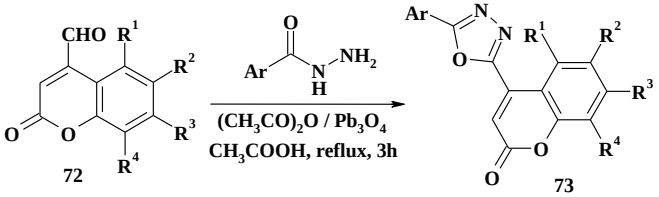
Scheme 32. Synthesis of 2-(4-pyridyl) substituted 5-aryl-1,3,4-oxadiazoles by cyclization of *N*-(arylmethyliden)isonicotinoylhydrazones

The interaction between 3,4,5-trimethoxybenzoic acid hydrazide and aromatic aldehydes yielded *N*-arylidenehydrazides **70** (Scheme 33), which cyclized in acetic anhydride medium into 3-acetyl-2,3-dihydro-1,3,4-oxadiazole derivatives **71** [68]:



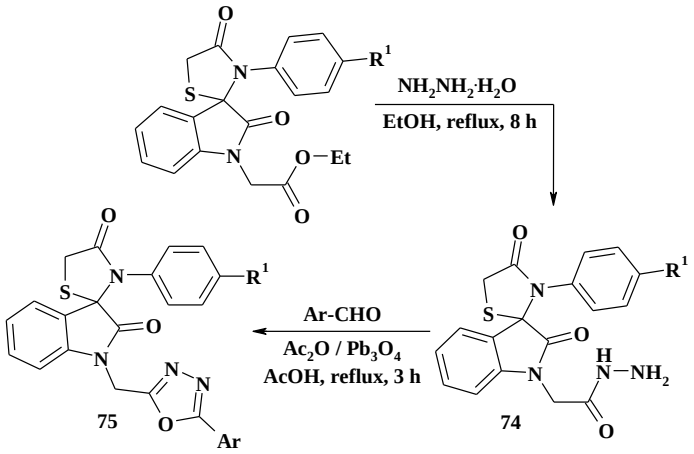
Scheme 33. Synthesis of 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles by cyclization of corresponding *N*-arylidenehydrazides in acetic anhydride

A new 1,3,4-oxadiazoles with coumarin fragment **73** were obtained through the interaction of aldehydes based on 2*H*-1-benzopyran-2-one **72** with aromatic acids hydrazides (Scheme 34). The reaction occurs under the action of Pb_3O_4 and acetic anhydride in the acetic acid medium by boiling for 3 hours [69]:



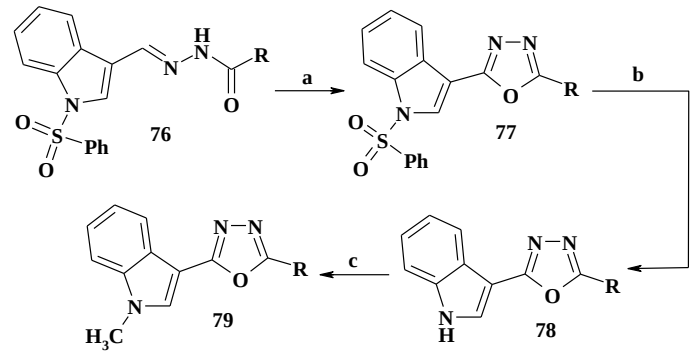
Scheme 34. Synthesis of 1,3,4-oxadiazoles with coumarin fragment by the interaction of aldehydes based on 2*H*-1-benzopyran-2-one with aromatic acids hydrazides under the action of Pb_3O_4 and acetic anhydride

Based on cyclization of hydrazides **74** (Scheme 35) with aromatic aldehydes under the above mentioned conditions Kenny *et al*. [69] synthesized a group of polycyclic spiro[thiazolidinone-indoline] systems **75** with 1,3,4-oxadiazole fragment in molecules:



Scheme 35. Synthesis of spiro[thiazolidinone-indoline] systems with 1,3,4-oxadiazole fragment by cyclization of appropriate hydrazides with aromatic aldehydes under the action of Pb_3O_4 and acetic anhydride

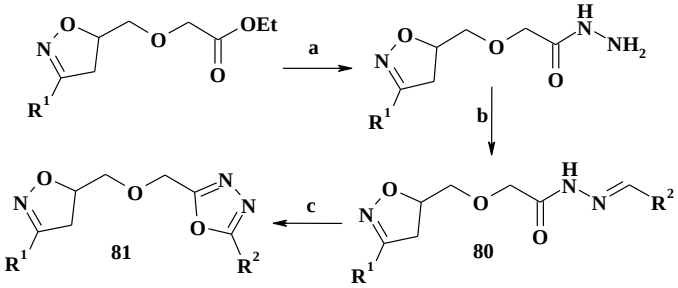
A series of indolyl substituted 1,3,4-oxadiazoles with *N*-phenylsulfonamide fragment **77** (Scheme 36) were obtained following the cyclization of indolyl-3-carboxaldehyde based *N*-acylhydrazones **76** with [bis(trifluoroacetoxy)iodo]benzene (*BTI*). In addition, compounds **77** were modified *via* hydrolysis and alkylation reactions into *N*-methyl derivatives **79** [70]:



(a) $PhI(CF_3COO)_2$, grinding, r.t.; (b) NaOH, EtOH-H_2O, reflux, 3h; (c) CH_3I, KOH, DMSO, stirring, r.t.

Scheme 36. Synthesis of indolyl substituted 1,3,4-oxadiazoles following the cyclization of indolyl-3-carboxaldehyde based *N*-acylhydrazones with [bis(trifluoroacetoxy)iodo]benzene

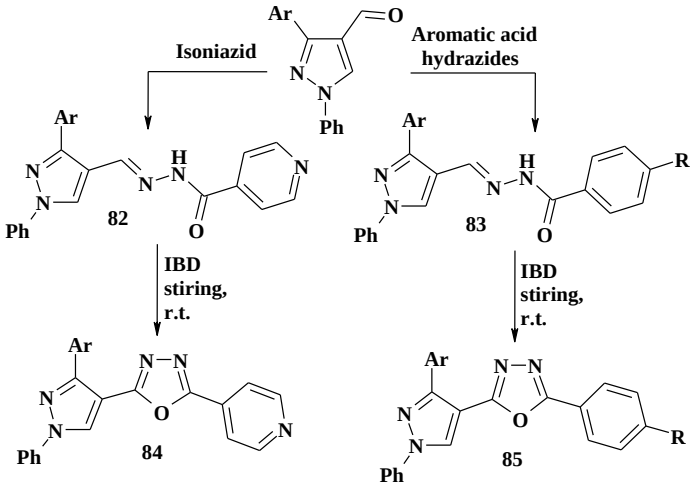
Synthesis of new 1,3,4-oxadiazoles with isoxazole moiety **81** was performed through the cyclization of hydrazones **80** under the action of chloramine T (Scheme 37) by Jayashankar *et al*. [71]:



(a) $NH_2NH_2·H_2O$, EtOH, reflux, 2h; (b) R^2CHO, EtOH, reflux, 3h; (c) chloramine-T trihydrate, EtOH, reflux, 3h.

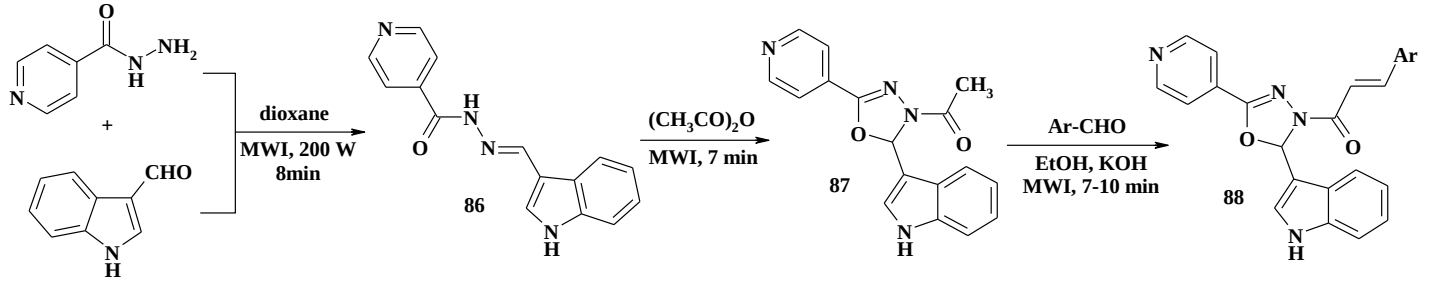
Scheme 37. Synthesis of 1,3,4-oxadiazoles with isoxazole moiety by cyclization of appropriate hydrazones with chloramine T

According to the concept of hybrid-pharmacophore approach Bansal *et al*. [72] synthesized a group of 2-aryl(4-pyridyl)substituted 1,3,4-oxadiazoles **84-85** with diarylpyrazole fragment by oxidative cyclization of pyrazolyl-4-carbaldehydes based *N*-acylhydrazones **82-83** with iodobenzenediacetate (*IBD*) in dichloromethane medium with stirring for 20-25 minutes at room temperature as it's shown on Scheme 38:



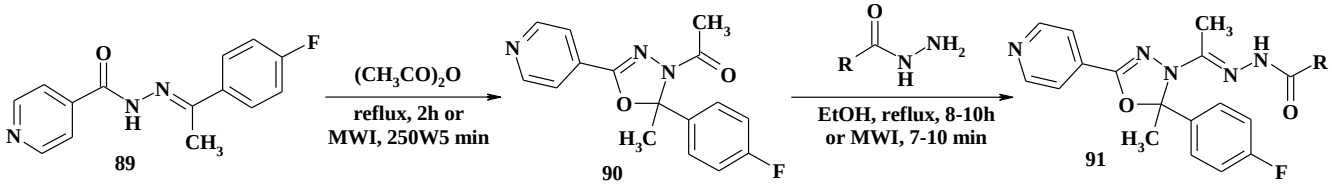
Scheme 38. Synthesis of 2-aryl(4-pyridyl)substituted 1,3,4-oxadiazoles with diarylpyrazole fragment by oxidative cyclization of pyrazolyl-4-carbaldehydes based *N*-acylhydrazones with iodobenzenediacetate

The synthesis of 2,5-disubstituted 3-acetyl-2,3-dihydro-1,3,4-oxadiazole **87** was achieved through the cyclization of *N*'-((1*H*-indol-3-yl)methylene)isonicotinohydrazide **86** with acetic anhydride under the microwave irradiation condition (Scheme 39). Further interaction of obtained compound **87** with appropriate arylcarbaldehydes in ethanol solution of alkali furnished the desired 3-arylpropen-1-one substituted 1,3,4-oxadiazole based indole and pyridine hybrids **88** [73].



Scheme 39. Synthesis and modification of 2,5-disubstituted 3-acetyl-2,3-dihydro-1,3,4-oxadiazole through the cyclization of *N*'-((1*H*-indol-3-yl)methylene)isonicotinohydrazide with acetic anhydride under the microwave irradiation condition

5-Pyridyl substituted 2-methyl-2-(4-fluorophenyl)-3-acetyl-2*H*-1,3,4-oxadiazole **90** was obtained by cyclization of *N*'-(1-(4-fluorophenyl)ethylidene)isonicotinohydrazide **89** (Scheme 40) in similar conditions. The interaction of compound **90** with different substituted benzohydrazide derivatives along with a catalytic amount of anhydrous $ZnCl_2$ in absolute ethanol led to the formation of appropriately 2*H*-1,3,4-oxadiazole based ethylidene hydrazones **91** as potential antituberculars [74]:



Scheme 40. Synthesis and modification of 5-pyridyl substituted 2-methyl-2-(4-fluorophenyl)-3-acetyl-2*H*-1,3,4-oxadiazole by cyclization of *N*'-(1-(4-fluorophenyl)ethylidene)isonicotinohydrazide

3. CONCLUSIONS

1,3,4-Oxadiazole ring system is a very interesting and important scaffold which is associated with a wide range of biological activities including anticancer, antimicrobial, antifungal, antitubercular, antiviral, antioxidant, anti-inflammatory and analgesic action etc. The presence of oxadiazole cycle as a part of drug structures can be determinant for its physicochemical and pharmacokinetic properties. The significant pharmacological potential of oxadiazole derivates promotes the scientists to further investigation of this heterocycle as a building block for medicinal chemistry. For the construction of 1,3,4-oxadiazole cycle different synthetic methods can be employed. In this review, we highlight the synthetic routes for obtaining 1,3,4-oxadiazole derivatives *via* cyclodehydration and oxidative cyclization reactions as the most common and preparative ones. We hope that this work would provide drug designers and medicinal chemists comprehensive information for the development of clinically useful molecules.

4. REFERENCES

1. Rohand, T.; Ramli, Y.; Baruah, M.; Budka, J.; Das, A.M. Synthesis, structure elucidation and antimicrobial properties of new bis-1,3,4-oxadiazole derivatives. *Pharm. Chem. J.* **2019**, *53*, 150-154, https://doi.org/10.1007/s11094-019-01969-2.
2. Sun, J.; Zhu, H.; Yang, Z.M.; Zhu, H.L. Synthesis, molecular modeling anf biological evaluation of 2-aminomethyl-5-(quinolin-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione quinoline derivatives as novel anticancer agents. *Eur. J. Med. Chem*. **2013**, *60*, 23-28, https://doi.org/10.1016/j.ejmech.2012.11.039.
3. Sumalatha, S.; Namrata, V.; Lakshmi, M.; Sridhar, G. Synthesis and anticancer activity of oxadiazole incorporated ellipticine derivatives. *Russ. J. Gen. Chem*. **2019**, *89*, 505-510, https://doi.org/10.1134/S107036321903023X.
4. Naveena, C.S.; Boja, P.; Kumari, N.S. Synthesis, characterization and antimicrobial activity of some disubstituted 1,3,4-oxadiazoles carrying 2-(aryloxymethyl)phenyl moiety. *Eur. J. Med. Chem*. **2010**, *45*, 4708-4719, https://doi.org/10.1016/j.ejmech.2010.06.027.
5. Li, P.; Hu, D.Y.; Xie, D.; Chen, J.; Jin, L.; Baoan, S. Design, synthesis and evaluation of new sulfone derivatives containing a 1,3,4-oxadiazole moiety as active antibacterial agents. *J. Agric. Food Chem*. **2018**, *66*, 3093-3100, https://doi.org/10.1021/acs.jafc.7b06061.
6. Karabanovich, G.; Zemanova, J.; Smutny, T.; Szekely, R.; Sarkan, M.; Centarova, I.; Vocat, A.; Pavkova, I.; Conka, P.; Nemecek, J.; Stolarikova, J.; Vejsova, M.; Vavrova, K.; Klimesova, V.; Hrabalek, A.; Pavek, P.; Cole, S.T.; Mikusova, K.; Roh, J. Development of 3,5-dinitrobenzylsulfanyl-1,3,4-oxadiazoles and thiadiazoles as selective antitubercular agents active against replicating and nonreplicating *Mycobacterium tuberculosis*. *J. Med. Chem*. **2016**, *59*, 2362-2380, https://doi.org/10.1021/acs.jmedchem.5b00608.
7. Dhumal, S.T.; Deshmukh, A.R.; Bhosale, M.R.; Khedkar, V.M.; Nawale, L.U.; Sarkar, D.; Mane, R.A. Synthesis and antitubercular activity of new 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffolds. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 3646-3651, https://doi.org/10.1016/j.bmcl.2016.05.093.
8. Nimbalkar, U.D.; Tupe, S.G.; Seijas Vasquez, J.A.; Kalam Khan, F.A.; Sangshetti, J.N.; Nikalje, A.P.G. Ultrasound- and molecular sieves-assisted synthesis, molecular docking and antifungal evaluation of 5-(4-(benzyloxy)-substituted phenyl)-3-((phenylamino)methyl)-1,3,4-oxadiazole-2(3*H*)-thiones. *Molecules*. **2016**, *21*, 484, https://doi.org/10.3390/molecules21050484.
9. Madhu Sekhar, M.; Nagarjuna, U.; Padmavathi, V.; Padmaja, A.; Vasudeva Reddy, N.; Vijaya, T. Synthesis and antimicrobial activity of pyrimidinyl 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. *Eur. J. Med. Chem*. **2018**, *145*, 1-10, https://doi.org/10.1016/j.ejmech.2017.12.067.
10. Gan, X.; Hu, D.; Chen, Z.; Wang, Y.; Song, B. Synthesis and antiviral evaluation of novel 1,3,4-oxadiazole/thiadiazole-chalcone conjugates. *Bioorg. Med. Chem. Lett*. **2017**, *27*, 4298-4301, https://doi.org/10.1016/j.bmcl.2017.08.038.
11. Albratty, M.; El-Sharkawy, K.A.; Alhazmi, H.A. Synthesis and evaluation of some new 1,3,4-oxadiazoles bearing thiophene, thiazole, coumarin, pyridine and pyridazine derivatives as antiviral agents. *Acta Pharm*. **2019**, *69*, 261-276.
12. Rajak, H.; Kharya, M.D.; Mishra, P. Synthesis and local anesthetic activity of some novel *N*-[5-(4-substituted)phenyl-1,3,4-oxadiazol-2-yl]-2-(substituted)-acetamides. *Arch. Pharm*. **2008**, *341*, 247-261, https://doi.org/10.1002/ardp.200700146.
13. Kotaiah, Y.; Harikrishna, N.; Nagaraju, K.; Rao, C.V. Synthesis and antioxidant activity of 1,3,4-oxadiazole tagged thieno[2,3-*d*]pyrimidine derivatives. *Eur. J. Med. Chem*. **2012**, *58*, 340-345, https://doi.org/10.1016/j.ejmech.2012.10.007.
14. Patrao, P.; Khader, A.M.A.; Kalluraya, B.; Vinayachandra. Synthesis of new 5-naphthyl substituted 1,3,4-oxadiazole derivatives and their antioxidant activity. *Der Pharma Chem*. **2013**, *5*, 24-32.
15. Sun, J.; Cao, N.; Zhang, X.M.; Yang, Y.S.; Zhang, Y.B.; Wang, X.M.; Zhu, H.L. Oxadiazole derivatives containing 1,4-benzodioxan as potential immunosuppressive agents RAW264.7 cells. *Bioorg. Med. Chem*. **2011**, *19*, 4895-4902, https://doi.org/10.1016/j.bmc.2011.06.061.
16. Zhang, Z.M.; Zhang, X.W.; Zhao, Z.Z.; Yan, R.; Xu, R.; Gong, H.B.; Zhu, H.L. Synthesis, biological evaluation and molecular docking studies of 1,3,4-oxadiazole derivatives as potential immunosuppressive agents. *Bioorg. Med. Chem*. **2012**, *20*, 3359-3367, https://doi.org/10.1016/j.bmc.2012.03.064.

17. Taha, M.; Ismail, N.H.; Jamil, W.; Imran, S.; Rahim, F.; Kashif, S.M.; Zulkefeli, M. Synthesis of 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives abd evaluation of their antiglycation potential. *Med. Chem. Res*. **2016**, *25*, 225-234, https://doi.org/10.1007/s00044-015-1476-8.
18. Guda, D.R.; Park, S.J.; Lee, M.W.; Kim, T.J.; Lee, M.E. Syntheses and anti-allergic activity of 2-((bis(trimethylsilyl)methylthio/methylsulfonyl)methyl)-5-aryl-1,3,4-oxadiazoles. *Eur. J. Med. Chem*. **2013**, *62*, 84-88, https://doi.org/10.1016/j.ejmech.2012.12.035.
19. Palkar, M.B.; Singhai, A.S.; Ronad, P.M.; Vishwanathswamy, A.H.M.; Boreddy, T.S.; Veerapur, V.P.; Shaikh, M.S.; Rane, R.A.; Karpoomath, R. Synthesis, pharmacological screening and *in silico* studies of new class of Diclofenac analogues as a promising anti-anflammatory agents. *Bioorg. Med. Chem*. **2014**, *22*, 2855-2866, https://doi.org/10.1016/j.bmc.2014.03.043.
20. Rasheed, H.; Afridi, R.; Khan, A.U.; Zia Ullah, M.; Khalid, S.; Atiq, A.; Kashif, H.; Ahmed, M.N.; Kim, Y.S.; Khan, S. Anti-inflammatory, anti-rheumatic and analgesic activities of 2-(5-mercapto-1,3,4-oxadiazol-2-yl)-*N*-propylbenzenesulphonami-de (MOPBS) in rodent. *Inflammopharmacology*. **2018**, *26*, 1037-1049, https://doi.org/10.1007/s10787-018-0461-5.
21. Rajak, H.; Thakur, B.S.; Singh, A.; Raghuvanshi, K.; Sah, A.K.; Veerasamy, R.; Sharma, P.C.; Pawar, R.S.; Kharya, M.D. Novel limonene and citral based 2,5-disubstituted-1,3,4-oxadiazoles: A natural product coupled approach to semicarbazones for antiepileptic activity. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 864-868, https://doi.org/10.1016/j.bmcl.2012.11.051.
22. Zarghi, A.; Tabatabai, S.A.; Faizi, M.; Ahadian, A.; Navabi, P.; Zanganeh, V.; Shafiee, A. Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1863-1865, https://doi.org/10.1016/j.bmcl.2005.02.014.
23. Tantray, M.A.; Khan, I.; Hamid, H.; Alam, M.S.; Dhulap, A.; Kalam, A. Synthesis of benzimidazole-linked-1,3,4-oxadiazole carboxamides as GSK-3β inhibitors with *in vivo* antidepressant activity. *Bioorg. Chem*. **2018**, *77*, 393-401, https://doi.org/10.1016/j.bioorg.2018.01.040.
24. Rajak, H.; Agarawal, A.; Parmar, P.; Thakur, B.S.; Veerasamy, R.; Sharma, P.C.; Kharya, M.D. 2,5-Disubstituted-1,3,4-oxadiazoles/thiadiazoles as surface recognition moiety: Design and synthesis of novel hydroxamic acid based histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 5735-5738, https://doi.org/10.1016/j.bmcl.2011.08.022.
25. Çevik, U.A.; Osmaniye, D.; Çavuşoğlu, B.K.; Sağlik, B.N.; Levent, S.; Ilgin, S.; Can, N.Ö.; Özkay, Y.; Kaplancikli, Z.A. Synthesis of novel benzimidazole-oxadiazole derivatives as potent anticancer activity. *Med. Chem. Res*. **2019**, *28*, 2252-2261, https://doi.org/10.1007/s00044-019-02451-0.
26. Zhang, Y.-B.; Wang, X.L.; Liu, W.; Yang, Y.S.; Tang, J.F.; Zhu, H.L. Design, synthesis and biological evaluation of heterocyclic azoles derivatives containing pyrazine moiety as potential telomerase inhibitors. *Bioorg. Med. Chem*. **2012**, *20*, 6356-6365, https://doi.org/10.1016/j.bmc.2012.08.059.
27. Zhang, S.; Luo, Y.; He, L.Q.; Liu, Z.J.; Jiang, A.Q.; Yang, Y.H.; Zhu, H.L. Synthesis, biological evaluation, and molecular docking studies of novel 1,3,4-oxadiazole derivatives possesing benzotriazole moiety as FAK inhibitors with anticancer activity. *Bioorg. Med. Chem*. **2013**, *21*, 3723-3729, https://doi.org/10.1016/j.bmc.2013.04.043.
28. Ahsan, J.A.; Choupra, A.; Sharma, R.K.; Jadav, S.S.; Padmaja, P.; Hassan, M.Z.; Al-Tamimi, A.B.S.; Geesi, M.H.; Bakht, M.A. Rationale design, synthesis, cytotoxicity evaluation, and molecular docking studies of 1,3,4-oxadiazole analogues. *Anti-Cancer Agents Med. Chem*. **2018**, *18*, 121-138, https://doi.org/10.2174/1871520617666170419124702.
29. Kamal, A.; Dastagiri, D.; Ramaiah, M.J.; Bharathi, E.V.; Reddy, J.S.; Balakishan, G.; Sarma, P.; Pushpavalli, S.N.C.V.L.; Pal-Bhadra, M.; Juvekar, A.; Sen, S.; Zingde, S. Synthesis, anticancer activity and mitochondrial mediated apoptosis inducing ability of 2,5-diaryloxadiazole-pyrrolobenzodiazepine conjugates. *Bioorg. Med. Chem*. **2010**, *18*, 6666-6677, https://doi.org/10.1016/j.bmc.2010.07.067.
30. Kashtoh, H.; Hussain, S.; Khan, A.; Saad, S.M.; Khan, J.A.J.; Khan, K.M.; Perveen, S.; Choudhary, M.I. Oxadiazoles and thiadiazoles: Novel α-glucosidase inhibitors. *Bioorg. Med. Chem*. **2014**, *22*, 5454-5465, https://doi.org/10.1016/j.bmc.2014.07.032.
31. Palmer, J.T.; Hirschbein, B.L.; Cheung, H.; McCarter, J.; Janc, J.W.; Yu, Z.W.; Wesolowski, G. Keto-1,3,4-oxadiazoles as cathepsin K inhibitors. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2909-2914, https://doi.org/10.1016/j.bmcl.2006.03.001.
32. Monte, F.L.; Kramer, T.; Gu, J.; Brodrecht, M.; Pilakowski, J.; Fuertes, A.; Domingues, J.M.; Plotkin, B.; Eldar-Finkelman, H.; Schmidt, B. Structure-based optimization of oxadiazole-based GSK-3 inhibitors. *Eur. J. Med. Chem*. **2013**, *61*, 26-40, https://doi.org/10.1016/j.ejmech.2012.06.006.
33. Khan, K.M.; Fatima, N.; Rasheed, M.; Jalil, S.; Ambreen, N.; Perveen, S.; Choudhary, M.I. 1,3,4-Oxadiazole-2(3*H*)-thione and its analogues: A new class of non-competitive nucleotide pyrophosphatases/ phosphodiesterases 1 inhibitors. *Bioorg. Med. Chem*. **2009**, *17*, 7816-7822, https://doi.org/10.1016/j.bmc.2009.09.011.
34. Khan, M.T.H.; Choudhary, M.I.; Khan, K.M.; Rani, M.; Atta-ur-Rahman. Structure-activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues. *Bioorg. Med. Chem*. **2005**, *13*, 3385-3395, https://doi.org/10.1016/j.bmc.2005.03.012.
35. Hadady, Z.; Tóth, M.; Somsák, L. *C*-(β-D-Glucopyranosyl) heterocycles as potential glycogen phosphorylase inhibitors. *ARKIVOC*. **2004**, *2004*, 140-149, http://dx.doi.org/10.3998/ark.5550190.0005.711.
36. Abbasi, M.A.; Hassan, M.; Aziz-ur-Rehman; Siddiqui, S.Z.; Raza, H.; Shah, S.A.A.; Seo, S.Y. Synthesis, *in vitro* and *in silico* studies of novel potent urease inhibitors: *N*-[4-({5-[(3-Un/substituted-anilino-3-oxopropyl)-sulfanyl]-1,3,4-oxadiazol-2-yl}methyl)-1,3-thiazol-2-yl]benzamides. *Bioorg. Med. Chem*. **2018**, *26*, 3791-3804, https://doi.org/10.1016/j.bmc.2018.06.005.
37. Boschelli, D.H.; Connor, D.T.; Bornemeier, D.A.; Dyer, R.D.; Kennedy, J.A.; Kuipers, P.J.; Okonkwo, G.C.; Schrier, D.J.; Wright, C.D. 1,3,4-Oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole analogs of the fenamates: *In vitro* inhibition of cyclooxygenase and 5-lipoxygenase activities. *J. Med. Chem*. **1993**, *36*, 1802-1810, https://doi.org/10.1021/jm00065a002.
38. Hayes, F.N.; Rogers, B.S.; Ott, D.G. 2,5-Diaryloxazoles and 2,5-diaryl-1,3,4-oxadiazoles. *J. Am. Chem. Soc*. **1955**, *77*, 1850-1852, https://doi.org/10.1021/ja01612a041.
39. Al-Talib, M.; Tashtoush, H.; Odeh, N. A convenient synthesis of alkyl and aryl substituted bis-1,3,4-oxadiazoles. *Synth. Commun*. **1990**, *20*, 1811-1817, https://doi.org/10.1080/00397919008053105.
40. Zheng, X.; Li, Z.; Wang, Y.; Chen, W.; Huang, Q.; Liu, C.; Song, G. Synthesis and insecticidal activities of novel 2,5-disubstituted 1,3,4-oxadiazoles. *J. Fluorine Chem*. **2003**, *123*, 163-169, https://doi.org/10.1016/S0022-1139(03)00168-4.
41. Ono, K.; Ito, H.; Nakashima, A.; Uemoto, M.; Tomura, M.; Saito, K. Synthesis and properties of naphthalene trimers linked by 1,3,4-oxadiazole spacers. *Tetrahedron Lett*. **2008**, *49*, 5816-5819, https://doi.org/10.1016/j.tetlet.2008.07.122.

42. Rigo, B.; Cauliez, P.; Fasseur, D.; Couturier, D. Reaction of hexamethyldisilazane with diacylhydrazines an easy 1,3,4-oxadiazole synthesis. *Synth. Commun*. **1986**, *16*, 1665-1669, https://doi.org/10.1080/00397918608056425.
43. Rigo, B.; Cauliez, P.; Fasseur, D.; Couturier, D. Acid catalyzed cyclization of bis silyl diacylhydrazines: A new 1,3,4-oxadiazole synthesis. *Synth. Commun*. **1988**, *18*, 1247-1251, https://doi.org/10.1080/00397918808060917.
44. Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. Disilylated compounds as precursors of heterocycles: A new and easy oxadiazole synthesis. *Synth. Commun*. **1989**, *19*, 2321-2335, https://doi.org/10.1080/00397918908052631.
45. Sharma, G.V.M.; Begum, A.; Rakesh; Krishna, P.R. Zirconium (IV) chloride mediated cyclodehydration of 1,2-diacylhydrazines: A convenient synthesis of 2,5-diaryl 1,3,4-oxadiazoles. *Synth. Commun*. **2004**, *34*, 2387-2391, https://doi.org/10.1081/SCC-120039492.
46. Brain, C.T.; Paul, J.M.; Loong, Y.; Oakley, P.J. Novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using polymer-supported Burgess reagent under microwave conditions. *Tetrahedron Lett*. **1999**, *40*, 3275-3278, https://doi.org/10.1016/S0040-4039(99)00382-2.
47. Hall, A.; Brown, S.H.; Chowdhury, A.; Giblin, G.M.P.; Gibson, M.; Healy, M.P.; Livermore, D.G.; McArthur Wilson, R.J.; Naylor, A.; Rawlings, D.A.; Roman, S.; Ward, E.; Willay, C. Identification and optimization of novel 1,3,4-oxadiazole EP_1 receptor antagonist. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4450-4455, https://doi.org/10.1016/j.bmcl.2007.06.014.
48. Gurupadaswamy, H.D.; Girish, V.; Kavitha, C.V.; Raghavan, S.C.; Kharum, S.A. Synthesis and evaluation of 2,5-di(4-aryloylaryloxymethyl)-1,3,4-oxadiazole as anticancer agents. *Eur. J. Med. Chem*. **2013**, *63*, 536-543, https://doi.org/10.1016/j.ejmech.2013.02.040.
49. Madhavilatha, B.; Bhattacharjee, D.; Sabitha, G.; Subba Reddy, B.V.; Yadav, J.S.; Jain, N.; Mohan Reddy, B.J. Synthesis and *in vitro* anticancer activity of novel 1,3,4-oxadiazole-linked 1,2,3-triazole/isoxazole hybrids. *J. Heterocycl. Chem*. **2018**, *55*, 863-870. https://doi.org/10.1002/jhet.3110.
50. Rangnekar, D.W.; Phadke, R.C. Synthesis of 2-hetaryl-5-phenyl-1,3,4-oxadiazole and bis-1,3,4-oxadiazole derivatives and their use as fluorescent whiteners for polyester fibres. *Dyes Pigm*. **1985**, *6*, 293-302, https://doi.org/10.1016/0143-7208(85)87005-4.
51. Bentiss, F.; Lagrenee, M.; Barbry, D. Rapid synthesis of 2,5-disubstituted 1,3,4-oxadiazoles under microwave irradiation. *Synth. Commun*. **2001**, *31*, 935-938, https://doi.org/10.1081/SCC-100103330.
52. Khan, K.M.; Zia-Ullah; Rani, M.; Perveen, S.; Haider, S.M.; Choudhary, M.I.; Atta-ur-Rahman; Loelter, W. Microwawe-assisted synthesis of 2,5-disubstituted-1,3,4-oxadiazoles. *Lett. Org. Chem*. **2004**, *1*, 50-52, https://doi.org/10.2174/1570178043488608.
53. Masharaqui, S.H.; Ghadigaonkar, S.G.; Kenny, R.S. An expeditious and convenient one pot synthesis of 2,5-disubstituted-1,3,4-oxadiazoles. *Synth. Commun*. **2003**, *33*, 2541-2545, https://doi.org/10.1081/SCC-120021845.
54. Akhter, M.; Husain, A.; Azad, B.; Ajmal, M. Aroylpropionic acid based 2,5-disubstituted-1,3,4-oxadiazoles: Synthesis and their anti-inflammatory and analgesic activities. *Eur. J. Med. Chem*. **2009**, *44*, 2372-2378, https://doi.org/10.1016/j.ejmech.2008.09.005.
55. Karabasanagouda, T.; Adhikari, A.V.; Shetty, N.S. Synthesis and antimicrobial activities of some novel 1,3,4-oxadiazoles carrying alkylthio and alkylsulphonyl phenoxy moieties. *Phosphorus, Sulfur Silicon Relat. Elem*. **2007**, *182*, 2925-2941, https://doi.org/10.1080/10426500701542981.
56. Kadi, A.A.; El-Brollosy, N.R.; Al-Deeb, O.A.; Habib, E.E.; Ibrahim, T.M.; El-Emam, A.A. Synthesis, antimicrobial and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantyl)-5-substituted-1,3,4-thiadiazoles. *Eur. J. Med. Chem*. **2007**, *42*, 235-242, https://doi.org/10.1016/j.ejmech.2006.10.003.
57. Bakht, M.A.; Yar, M.S.; Abdel-Hamid, S.G.; Al Qasoumi, S.I.; Samad, A. Molecular properties prediction, synthesis and antimicrobial activity of some newer oxadiazole derivative. *Eur. J. Med. Chem*. **2010**, *45*, 5862-5869, https://doi.org/10.1016/j.ejmech.2010.07.069.
58. Chandrakantha, B.; Shetty, P.; Nambiyar, V.; Isloor, N.; Isloor, A.M. Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-fluoro-4-methoxy phenyl moiety. *Eur. J. Med. Chem*. **2010**, *45*, 1206-1210, https://doi.org/10.1016/j.ejmech.2009.11.046.
59. Ahsan, M.J.; Samy, J.G.; Khalilullah, H.; Nomani, M.S.; Saraswat, P.; Gaur, R.; Singh, A. Molecular properties prediction and synthesis of novel 1,3,4-oxadiazole analogues as potent antimicrobial and antitubercular agents. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 7246-7250, https://doi.org/10.1016/j.bmcl.2011.10.057.
60. Rashid, M.; Husain, A.; Mishra, R. Synthesis of benzimidazole bearing oxadiazole nucleus as anticancer agents. *Eur. J. Med. Chem*. **2012**, *54*, 855-866, https://doi.org/10.1016/j.ejmech.2012.04.027.
61. Shingare, R.M.; Patil, Y.S.; Sangshetty, J.N.; Patil, R.B.; Rajani, D.P.; Madje, B.R. Synthesis, biological evaluation and docking study of some novel isoxazole clubbed 1,3,4-oxadiazoles derivatives. *Med. Chem. Res*. **2018**, *27*, 1283-1291, https://doi.org/10.1007/s00044-018-2148-2.
62. Madhu Sekhar, M.; Yamini, G.; Divya, K.R.G.; Padmavathi, V.; Padmaja, A. Synthesis and bioassay of a new class of disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. *Med. Chem. Res*. **2019**, *28*, 1049-1062, https://doi.org/10.1007/s00044-019-02360-2.
63. Diao, P.; Ge, Y.; Zhang, W.; Xu, C.; Zhang, N.; Guo, C. Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by visible-light-mediated decarboxylation-cyclization of hydrazides and diketones. *Tetrahedron Lett*. **2018**, *59*, 767-770, https://doi.org/10.1016/j.tetlet.2018.01.037.
64. Sreenivasulu, R.; Tej, M.B.; Jadav, S.S.; Sujitha, P.; Kumar, C.G.; Raju, R.R. Synthesis, anticancer evaluation and molecular docking studies of 2,5-bis(indolyl)-1,3,4-oxadiazoles, Nortopsentin analogues. *J. Mol. Struct*. **2020**, *1208*, https://doi.org/10.1016/j.molstruc.2020.127875.
65. He, X.; Li, X.-Y.; Liang, J.-W.; Cao, C.; Li, S.; Zhang, T.J.; Meng, F.H. Design, synthesis and anticancer activity evaluation of novel 5*H*-dibenzo[*b*,*e*]azepine-6,11-dione derivatives containing 1,3,4-oxadiazole units. *Bioorg. Med. Chem. Lett*. **2018**, *28*, 847-852, https://doi.org/10.1016/j.bmcl.2018.02.008.
66. Rostamizadeh, S.; Housaini, S.A.G. Microwave assisted syntheses of 2,5-disubstituted 1,3,4-oxadiazoles. *Tetrahedron Lett*. **2004**, *45*, 8753-8756, https://doi.org/10.1016/j.tetlet.2004.09.095.
67. Navarrete-Vazquez, G.; Molina-Salinas, G.M.; Duarte-Fajardo, Z.V.; Vargas-Villarreal, J.; Estrada-Soto, S.; Gonzales-Salazar, F.; Hernández-Núñez, E.; Said-Fernandez, S. Synthesis and antimycobacterial activity of 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines. *Bioorg. Med. Chem*. **2007**, *15*, 5502-5508, https://doi.org/10.1016/j.bmc.2007.05.053.
68. Jin, L.; Chen, J.; Song, B.; Chen, Z.; Yang, S.; Li, Q.; Hu, D.; Xu, R. Synthesis, structure, and bioactivity of *N*'-substituted benzylidene-3,4,5-trimethoxybenzohydrazide and 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethixyphenyl)-2,3-dihydro-1,3,4-

oxadiazole derivatives. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 5036-5040, https://doi.org/10.1016/j.bmcl.2006.07.048.
69. Kenny, R.S.; Mashelkar, U.C.; Rane, D.M. Synthesis of 2-coumarinyl and spiroindolil-5-phenil-1,3,4-oxadiazoles. *J. Chin. Chem. Soc*. **2006**, *53*, 367-373, https://doi.org/10.1002/jccs.200600046.
70. Kumar, D.; Sundaree, S.; Johnson, E.O.; Shah, K. An efficient synthesis and biological study of novel indolyl-1,3,4-oxadiazoles as potent anticancer agents. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4492-4494, https://doi.org/10.1016/j.bmcl.2009.03.172.
71. Jayashankar, B.; Lokanath Rai, K.M.; Baskaran, N.; Sathish, H.S. Synthesis and pharmacological evaluation of 1,3,4-oxadiazole bearing bis(heterocycle) derivatives as anti-inflammatory and analgesic agents. *Eur. J. Med. Chem*. **2009**, *44*, 3898-3902, https://doi.org/10.1016/j.ejmech.2009.04.006.
72. Bansal, S.; Bala, M.; Suthar, S.K.; Choudhary, S.; Bhattacharya, S.; Bhardway, V.; Singla, S.; Joseph, A. Design and synthesis of novel 2-phenyl-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1,3,4-oxadiazoles as selective COX-2 inhibitors with potent anti-inflammatory activity. *Eur. J. Med. Chem*. **2014**, *80*, 167-174, https://doi.org/10.1016/j.ejmech.2014.04.045.
73. Desai, N.C.; Somani, H.; Trivedi, A.; Bhatt, K.; Nawale, L.; Khedkar, V.M.; Jha, P.C.; Sarkar, D. Synthesis, biological evaluation and molecular docking study of some novel indole and pyridine based 1,3,4-oxadiazole derivatives as potential antitubercular agents. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 1776-1783, https://doi.org/10.1016/j.bmcl.2016.02.043.
74. Desai, N.C.; Trivedi, A.; Somani, H.; Jadeja, K.A.; Vaja, D.; Nawale, L.; Khedkar, V.M.; Sarkar, D. Synthesis, biological evaluation, and molecular docking study of pyridine clubbed 1,3,4-oxadiazole as potential antituberculars. *Synth. Commun*. **2018**, *48*, 524-540, https://doi.org/10.1080/00397911.2017.1410892.