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Approaches for synthesis and chemical modification of non-condensed heterocyclic systems based on 1,3,4-oxadiazole ring and their biological activity: A review

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ABSTRACT

1,3,4-Oxadiazole scaffold is one of the most important heterocyclic fragments, which is considered as a perspective building block for drug discovery. Substituted 1,3,4-oxadiazoles had been reported to display a diverse range of pharmacological activities including anticancer, anti-inflammatory, antitubercular, antibacterial, antiviral, antifungal, insecticidal, antioxidant, and analgesic activities. Moreover, the 1,3,4-oxadiazole core is a structural component of approved antiretroviral (*Raltegravir*), anticancer (*Zibotentan*), and antihypertensive (*Tiodazosin* and *Nesapidil*) drugs. In the present review, we summarized the literature data about the main approaches for obtaining possible directions of structural modification and pharmacological activity of noncondensed heterocyclic systems based on the 1,3,4-oxadiazole ring as promising objects for modern bioorganic and medicinal chemistry.

INTRODUCTION

Molecular design and synthesis of new biologically active small molecules based on heterocyclic scaffolds are the important trends in modern organic and medicinal chemistry. The promising objects for drug discovery belong to quite a few oxygen- and nitrogen-containing five-membered heterocycles. In particular, 1,3,4-oxadiazole core is a known pharmacophore fragment, which possesses a wide range of opportunities for chemical modification and versatile pharmacological potential including anticancer (Ahsan *et al*., 2018; Rashid *et al*., 2012), antimicrobial (Bakht *et al*., 2010; Dhumal *et al*., 2016), antifungal (Naveena *et al*., 2010; Nimbalkar *et al*., 2016), antiviral (Albratty *et al*., 2019; Gan *et al*., 2016), antitubercular (Desai *et al*., 2018), anesthetic (Rajak *et al*., 2008), and anti-inflammatory and analgesic (Akhter *et al*., 2009; Rasheed *et al*., 2018) action.

Moreover, among 1,3,4-oxadiazole derivatives, the promising inhibitors of histone deacetylase (HDAC) **I** (Rajak *et al*., 2011), telomerase **II** (Zhang *et al*., 2012a), and focal adhesion kinase **III** (Zhang *et al*., 2013) have been identified as potential antitumor agents (Figure 1). Furthermore, oxadiazoles have been reported as the inductors of mitochondrial-mediated apoptosis (Kamal *et al*., 2010), inhibitors of α-glucosidase (Kashtoh *et al*., 2014), cathepsin K (Palmer *et al*., 2006), glycogen synthase kinase-3β (GSK-3β) (Tantray *et al*., 2018), tyrosinase (Khan *et al*., 2005), nucleotide pyrophosphatases/phosphodiesterases-1 NPP1 (Khan *et al*., 2009), urease (Abbasi *et al*., 2018), COX-2/5-LOX biosystem (Boschelli *et al*., 1993), and so forth. 1,3,4-oxadiazole derivatives belong to an antiretroviral drug—*Raltegravir*—being the first representative of the new class of HIV-1 integrase inhibitor (Cahn and Sued, 2007; Grinsztejn *et al*., 2007).

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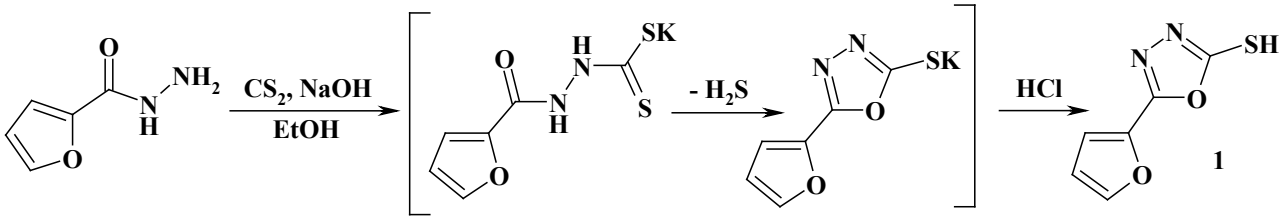
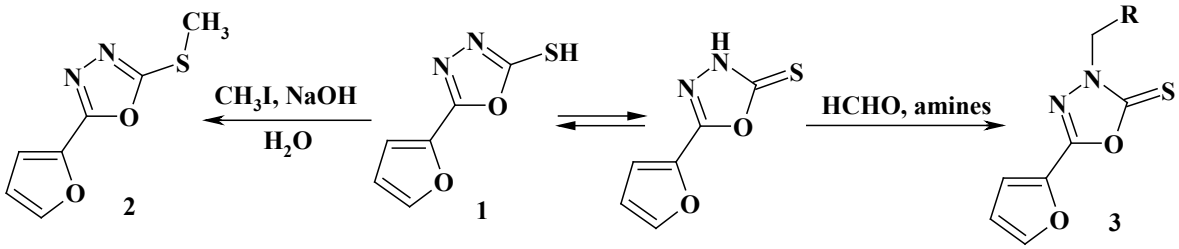
It is important to note that a combination of the 1,3,4-oxadiazole core with various heterocyclic fragments was accompanied by the emergence of a synergistic effect in many cases (Ahsan *et al*., 2011; Kotaiah *et al*., 2012; Padmavathi *et al*., 2011; Puthiyapurayil *et al*., 2012). Moreover, 1,3,4-oxadiazole cycle is a bioisostere for carboxylic, amide, and ester groups, which mostly contribute to the enhancement of the pharmacological activity by participating in the hydrogen bonding interactions with the receptors (Guimarães *et al*., 2005).

Synthetic approaches for the construction of 1,3,4-oxadiazole cycle and possible directions of chemical modification of its derivatives

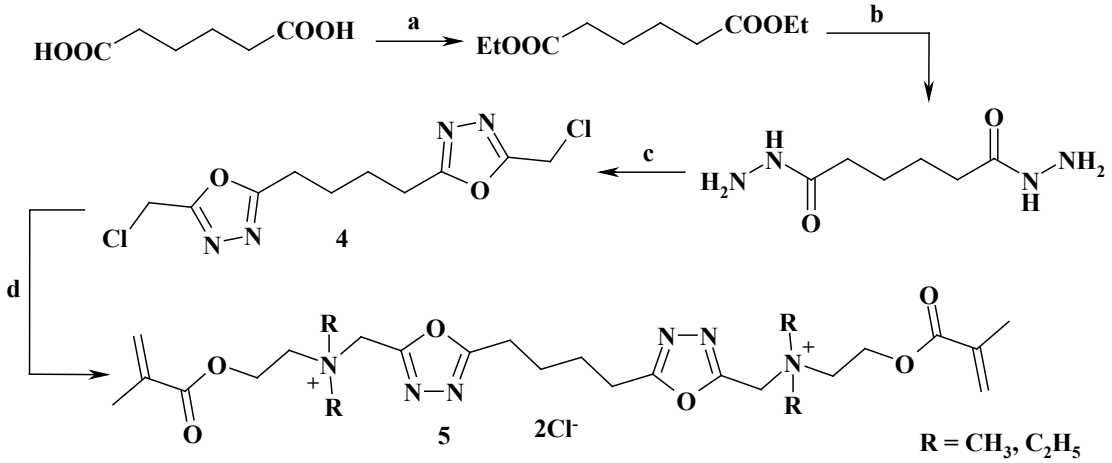
A known method for obtaining 2-mercapto-1,3,4-oxadiazole derivatives is based on the interaction of carboxylic acid hydrazides with carbon disulfide by heating in the alcoholic solution of alkali. Hence, the synthesis of furyl substituted 1,3,4-oxadiazole-2-thiol **1** was carried out starting from furan-2-carboxylic acid hydrazide in the abovementioned conditions (Koparir *et al*., 2010):



The presence of thiol-thione tautomerism caused a further chemical modification of compound **1** *via* *S*-alkylation reaction with methyl iodide and Mannich reaction with formaldehyde and aromatic or cyclic amines with the formation of the corresponding 2-methylmercapto-1,3,4-oxadiazoles **2** and 3*H*-1,3,4-diazoline-2-thiones **3** (Koparir *et al*., 2010).

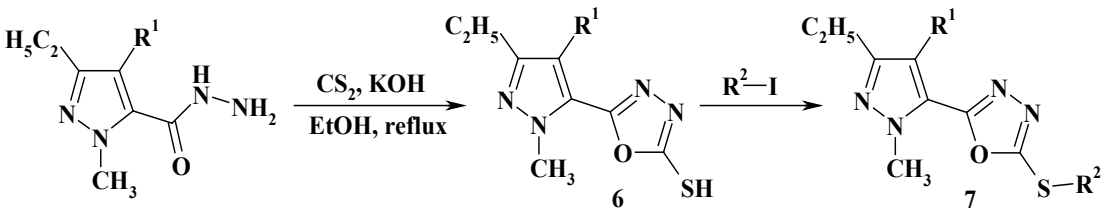


Following the ring-closure procedure, on treating hexanedioic acid dihydrazide with chloroacetic acid in refluxing phosphorus oxychloride, the corresponding 1,4-bis(1,3,4-oxadiazole-2-yl)butane **4** was synthesized. The target quaternary ammonium salts **5** were obtained by refluxing compound **4** in acetone medium with the appropriate tertiary amine, 2-(dimethylamino)ethyl methacrylate, or 2-(diethylamino)ethyl methacrylate, respectively (Rohand *et al*., 2019).

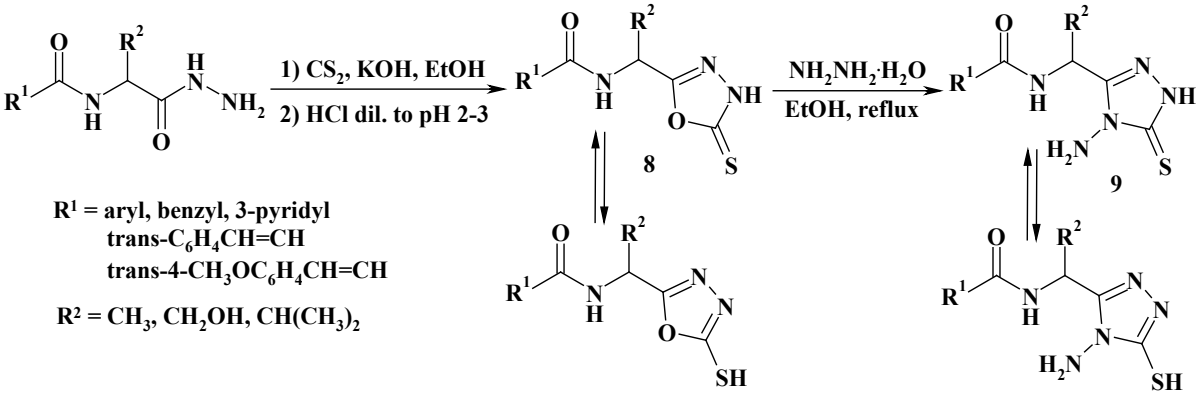


(a) C_2H_5OH, H_2SO_4 conc., reflux, 12h; (b) $NH_2NH_2{\cdot}H_2O$, C_2H_5OH, reflux, 8h;
(c) $POCl_3$, $ClCH_2COOH$, reflux, 8h; (d) DMAEMA/DEAEMA, acetone, reflux, 24h.

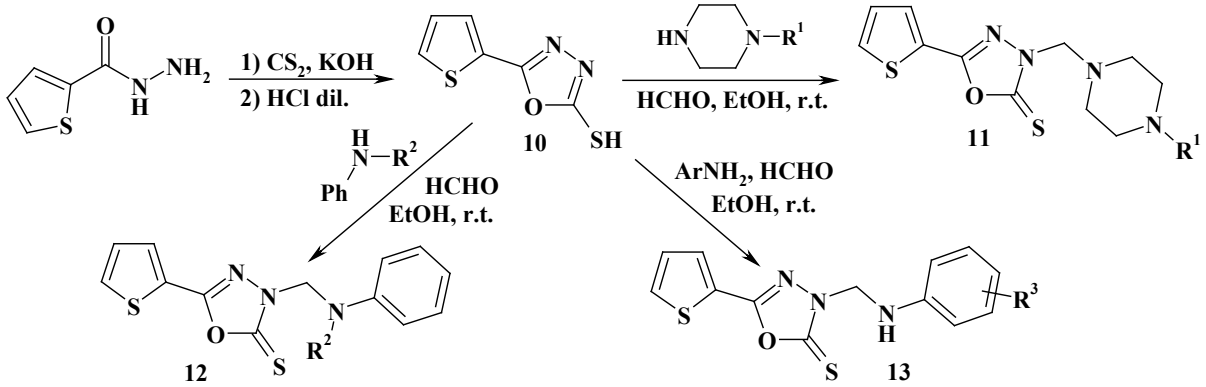
The synthesis of 2-mercapto-1,3,4-oxadiazoles **6** containing pyrazole moiety was proposed by Chen *et al*. (2000) starting from pyrazole-5-carboxylic acid hydrazides in the similar transformations. An interaction of compound **6** with alkyl iodides in the presence of tetrabutylammonium bromide resulted in the formation of the corresponding *S*-alkylated derivatives **7**.



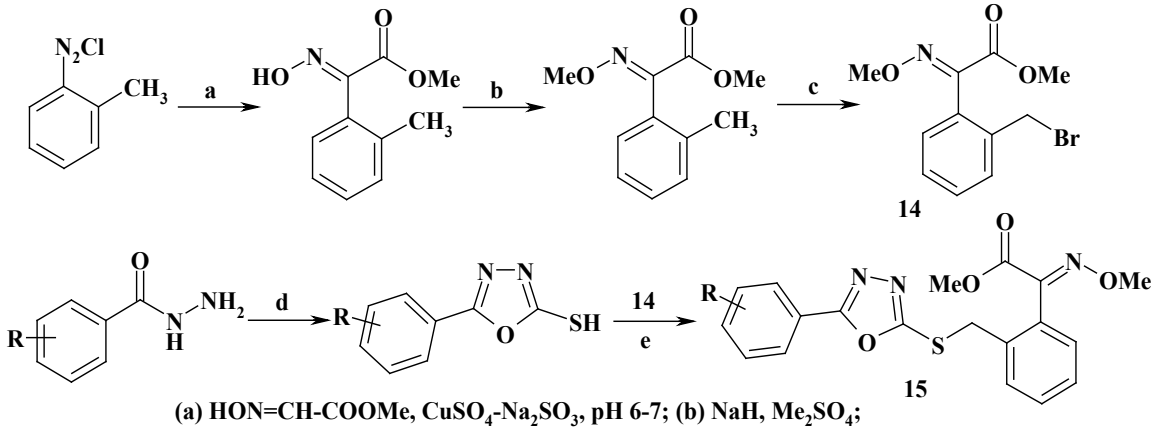
The cyclization of *N*-acylated aliphatic amino acid hydrazides with carbon disulfide in an ethanolic solution of potassium hydroxide resulted in 2,3-dihydro-1,3,4-oxadiazole-2-thiones **8**, which on reaction with hydrazine hydrate was subsequently modified with the formation of corresponding 1,2,4-triazole-5-thiones **9**. The existence of two tautomeric forms for compounds **8** and **9** (thione in solid state and thiol in solution) was confirmed by the presence of an absorption band at 1,240–1,142 cm^{-1} on Infrared (IR) spectra, which corresponds to the C=S group of thione form, and the characteristic signal at 14–15 ppm on ^1H Nuclear magnetic resonance (NMR) spectra due to SH-group (Feng *et al*., 2012).



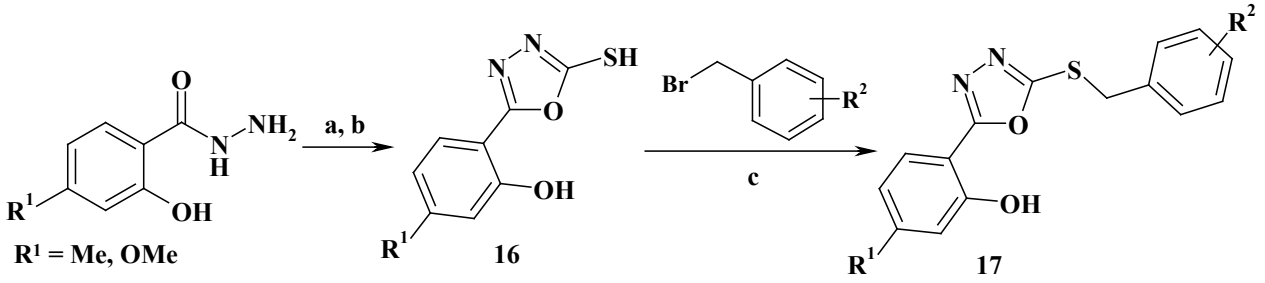
The synthesis of 3-arylamino(piperazinyl)methylene-substituted 1,3,4-oxadiazole-2-thiones **11–13** was carried out by the interaction of 5-(thiophene-2-yl)-1,3,4-oxadiazole-2-thiol **10** as a starting reagent with primary aromatic amines, *N*-substituted piperazine, or aniline derivatives according to the Mannich reaction procedure (Al-Omar, 2010):



Based on (*E*)-α-(methoxyimino)-[(2′-bromomethyl)phenyl]acetic acid methyl ester **14** as an alkylating agent, the synthesis of 5-aryl substituted 2-mercapto-1,3,4-oxadiazoles **15** was carried out (Li *et al*., 2006).

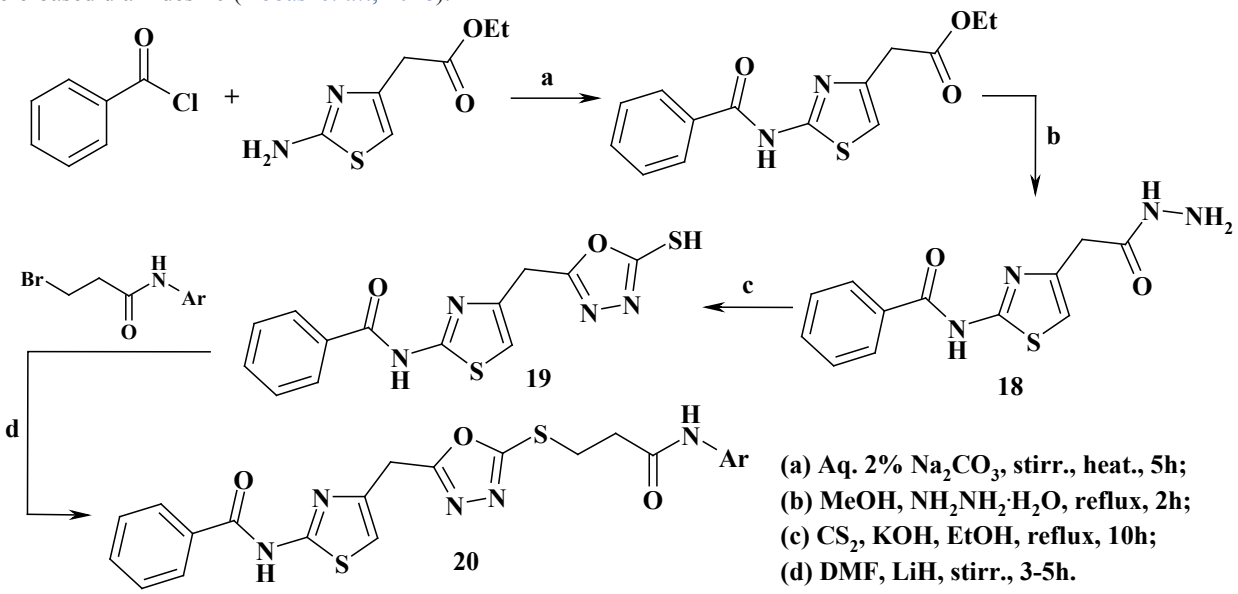


In similar transformations, the hydrazides of 4-substituted salicylic acids were used for the synthesis of corresponding 1,3,4-oxadiazole-2-thiols **16,** which on reaction with benzyl bromides afforded the group of *S*-alkylated derivatives **17** (Zhang *et al*., 2012b):

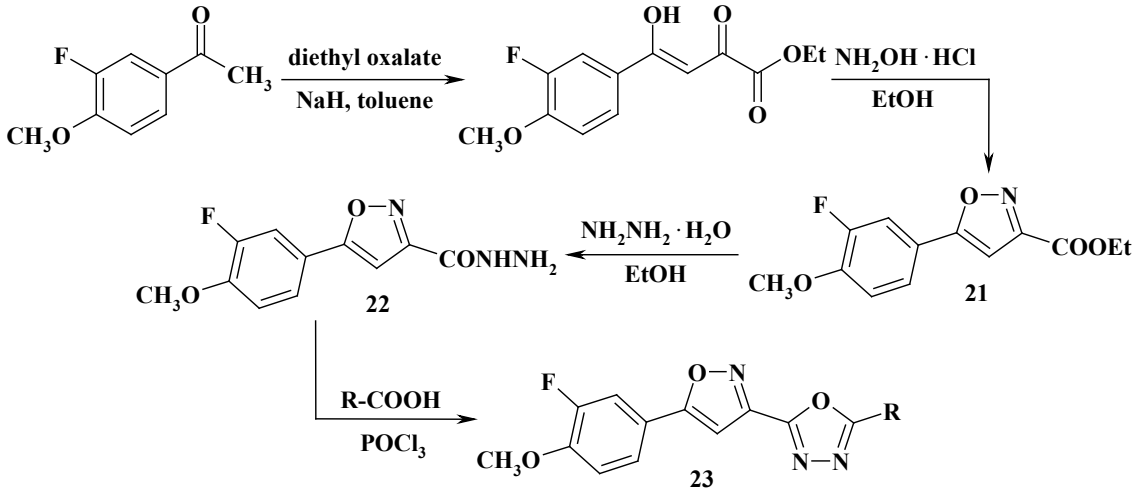


(a) CS_2/KOH, 95% ethanol, reflux, 24 h; (b) HCl, pH 5-6; (c) NaOH, acetonitrile, reflux, 8-24 h.

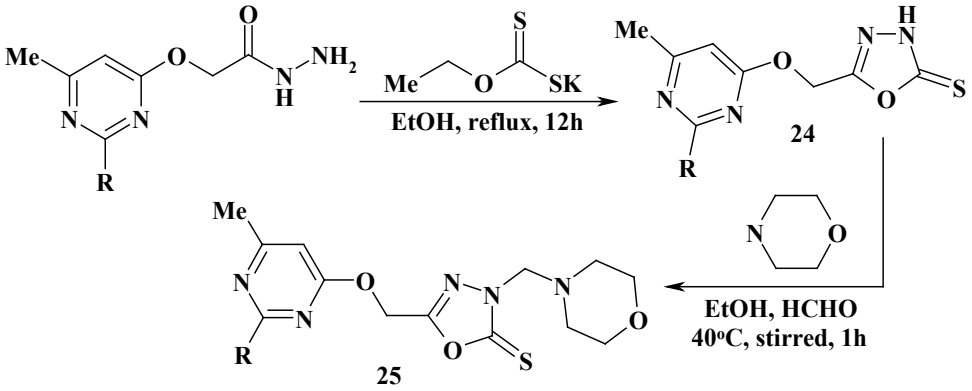
The synthesis of thiazole-substituted 1,3,4-oxadiazole-2-thiol **19** was performed by the cyclization reaction of 2-benzoylamino-1,3-thiazol-4-acetic acid hydrazide **18** with carbon disulfide in an ethanolic solution of alkali. The reaction of compound **19** with 3-bromo-N-(un/substituted-phenyl)propanamides in dimethylformamide medium using LiH as a basic catalyst gave the target thiazole-1,3,4-oxadiazole-based diamides **20** (Abbasi *et al*., 2018).



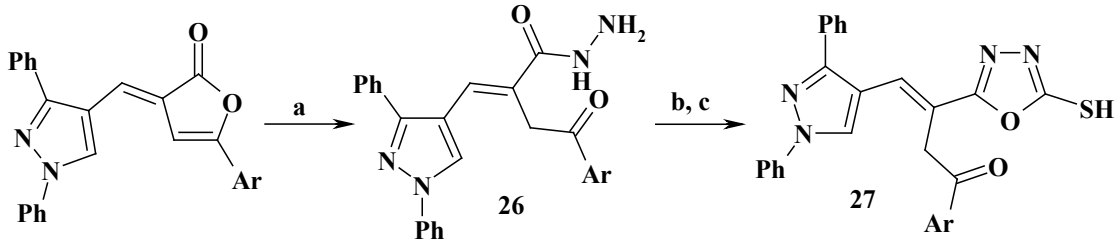
The sequential transformations of 3-fluoro-4-methoxyacetophenone with diethyl oxalate and hydroxylamine hydrochloride, respectively, gave ethyl isoxazole-3-carboxylate **21** which on hydrazinolysis procedure afforded the respective acid hydrazide **22**. The further cyclization of **22** with carboxylic acids in phosphorus oxochloride medium resulted in a series of isoxazole-substituted 1,3,4-oxadiazoles **23** with 3-fluoro-4-methoxyphenyl moiety (Shingare *et al*., 2018).



Jakubkiene *et al*. (2003) proposed a method for obtaining 1,3,4-oxadiazole-2-thiols **24**, based on cyclization of carboxylic acid hydrazides with potassium *O*-ethylxanthate in ethanol medium. By implementing this approach, a group of 3-morpholinomethylene-substituted 1,3,4-oxadiazole-2(3*H*)-thiones **25** with pyrimidine fragment was synthesized.

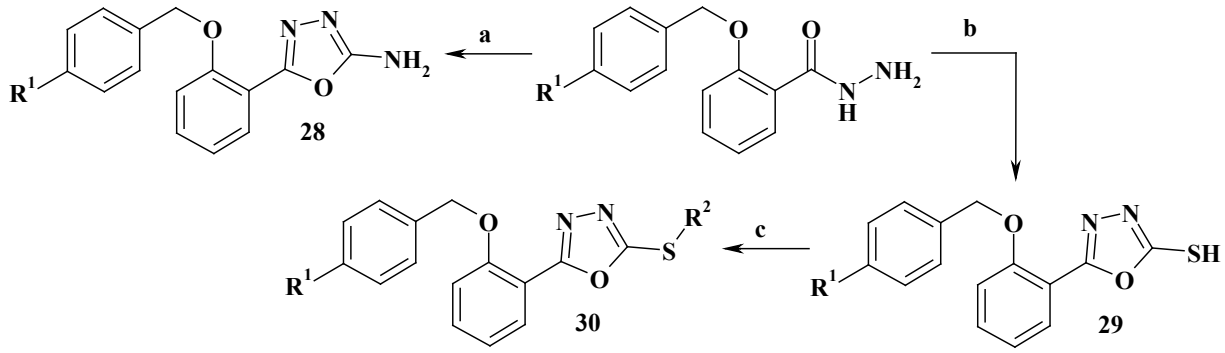


Following the hydrazinolysis of pyrazolyl-furan-2-one derivatives, the appropriate α-pyrazolyl-4-ylmethylidene-β-aroylpropionic acid hydrazides **26** were obtained and utilized for the synthesis of noncondensed 1,3,4-oxadiazole-substituted pyrazoles **27** (Hashem *et al*., 2007).



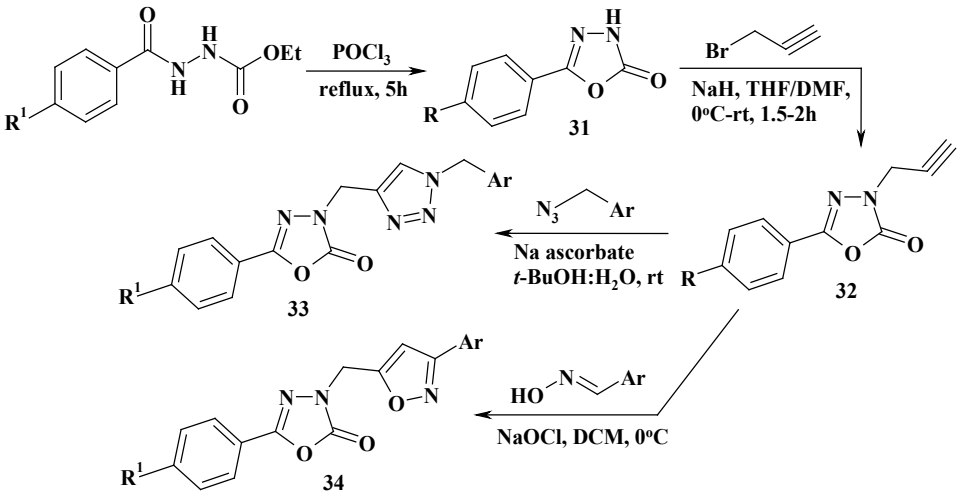
(a) NH_2NH_2, EtOH, r.t., stirring; (b) CS_2, NaOH, EtOH, reflux, 2h; (c) HCl dil.

A group of 2-amino-1,3,4-oxadiazoles **28** and 1,3,4-oxadiazole-2-thiols **29-30** with (benzyloxy)phenyl fragment were synthesized and evaluated as promising anticonvulsant agents (Zarghi *et al*., 2005).

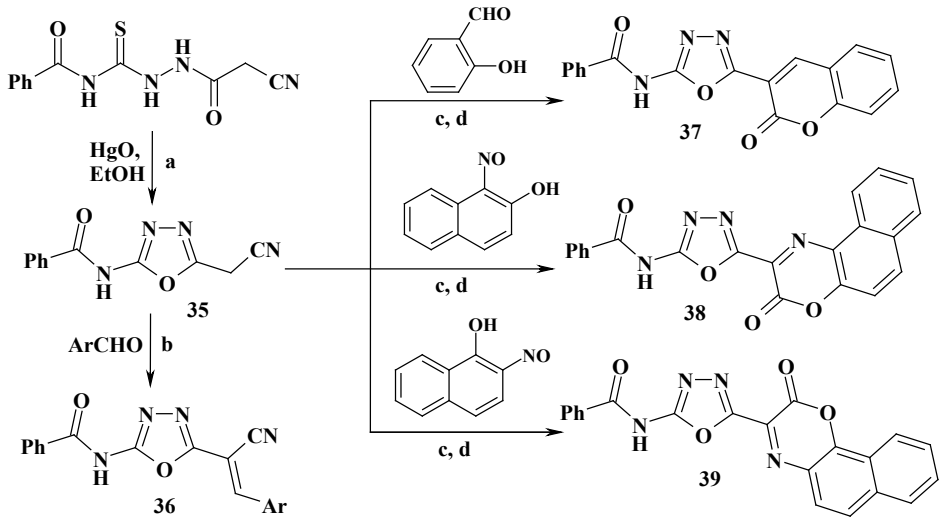


(a) BrCN, $NaHCO_3$, MeOH, rt, 3h; (b) CS_2, KOH, EtOH, reflux, 6h; (c) RI, NaOH, EtOH, sonication, 20 min.

According to the concept of hybrid-pharmacophore approach, a series of novel 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones with 1,2,3-triazole **33** and isoxazole **34** fragments as potential anticancer agents were synthesized by Madhavilatha *et al*. (2018). Thus, the starting 1,3,4-oxadiazole-2(3*H*)-ones **31** were modified by reacting with propargyl bromide in the presence of NaH into the corresponding *N*-propargylated derivatives **32** which reacted with various azides or aldoximes giving the target 1,3,4-oxadiazole containing 1,2,3-triazole **33** and isoxazole **34** derivatives.

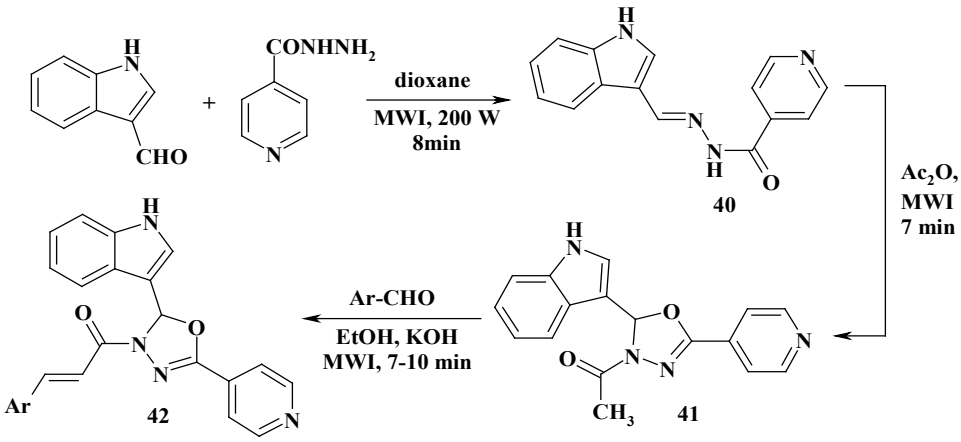


The cyclodesulfurization reaction of N^4-benzoyl-N^1-cyanoacetylthiosemicarbazide on boiling in ethanolic mercuric oxide solution provided 5-benzoylamino-2-cyanomethyl-1,3,4-oxadiazole **35** as a starting reagent for the synthesis of new compounds with a promising antitumor activity (Bondock *et al*., 2012). Furthermore, an interaction of compound **35** with aromatic aldehydes in ethanol medium resulted in the formation of a series of corresponding arylidene derivatives **36**. As an extension of the synthetic study, a new 1,3,4-oxadiazole-based coumarin **37** and naphtho[1,2-*b*]oxazines **38-39** were obtained by reacting compound **38** with salicylaldehyde, 1(2)-nitroso-2(1)-naphthols in ethanol solution using piperidine as the catalyst.

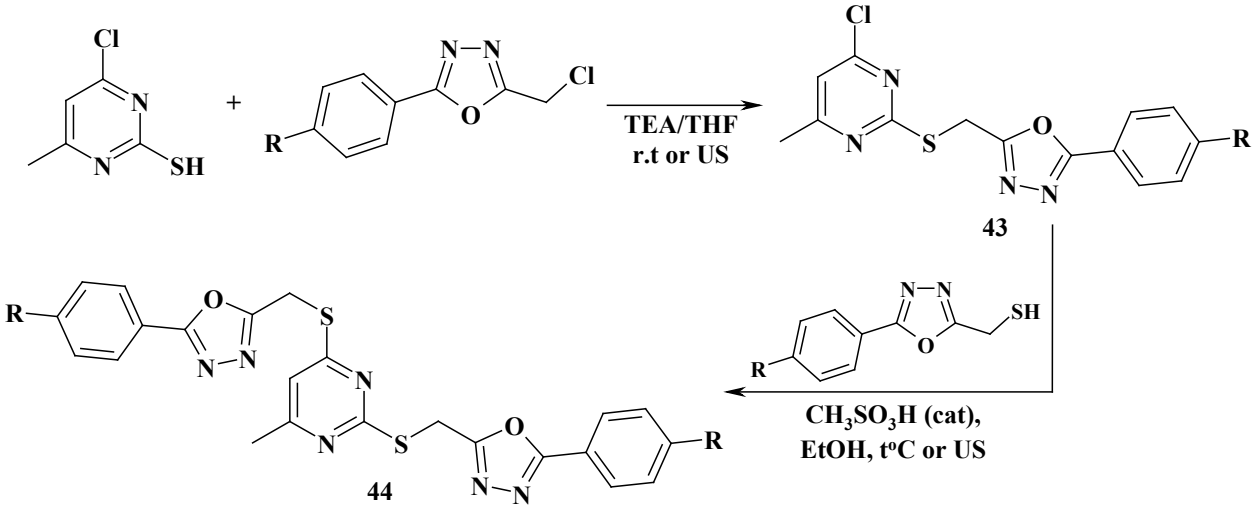


(a) EtOH, reflux, 4h; (b) triethylamine, EtOH, reflux, 6h; (c) piperidine, EtOH, reflux, 4h; (d) ice-water, HCl dil.

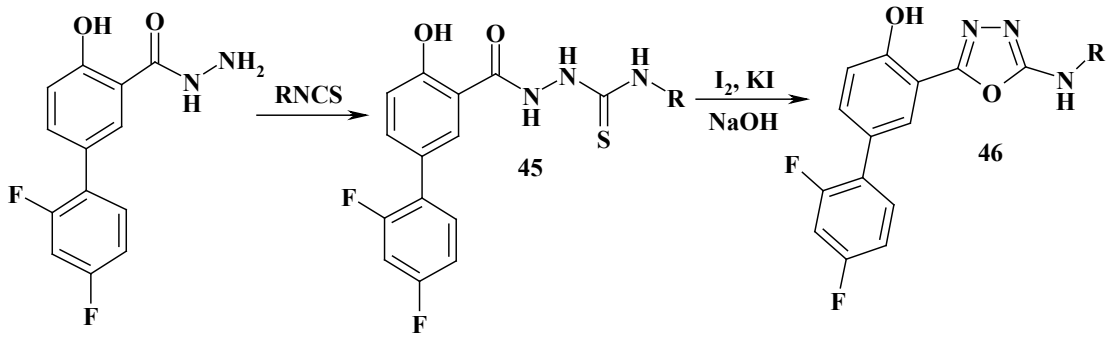
The interaction between indole-3-carbaldehyde and isoniazid yielded the isonicotinylhydrazide **40**, which cyclized with acetic anhydride with the formation of 3-acetyl-2,3-dihydro-1,3,4-oxadiazole **41**. The synthesis of target indole/pyridine containing 1,3,4-oxadiazoles **42** was carried out by heating of the compound **41** with appropriate arylcarbaldehydes in an ethanol solution of alkali (Desai *et al*., 2016).



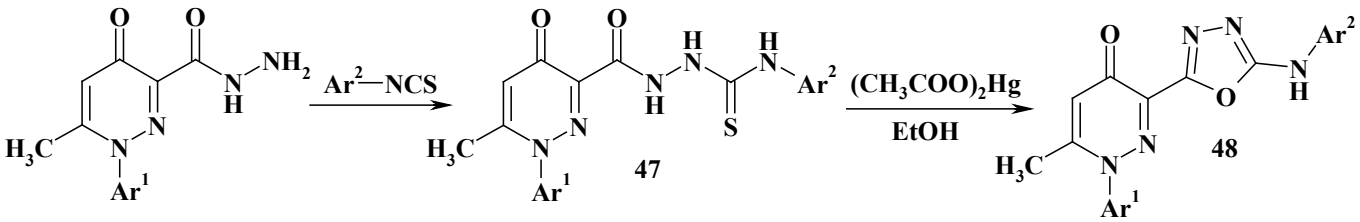
The *S*-alkylation reaction between 4-chloro-6-methylpyrimidine-2-thiol and 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole in tetrahydrofuran medium yielded the corresponding bis-heterocycle conjugate **43**. A series of new methylthio linked pyrimidinyl bis-1,3,4-oxadiazoles **44** were prepared by the reaction of compound **43** with (5-phenyl-1,3,4-oxadiazol-2-yl)methanethiol in the presence of a catalytic amount of methanesulfonic acid under conventional and ultrasound irradiation conditions (Madhu Sekhar *et al*., 2018).



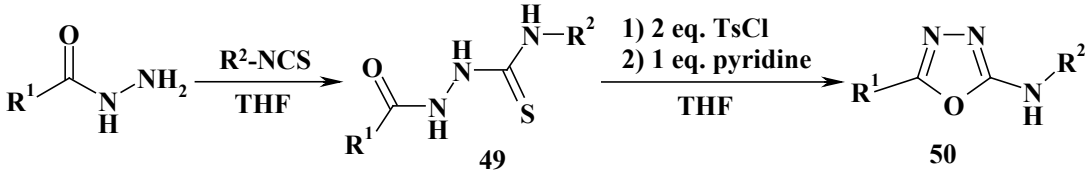
Reacting diflunisal hydrazide with alkyl/aryl isothiocyanates in ethanol resulted in the formation of *N*′-acylated 4-alkyl/arylthiosemicarbazides **45**. The cyclization of compounds **45** using iodine in alkaline medium afforded the corresponding 2-alkyl/arylamino-5-(2′,4′-difluoro-4-hydroxybiphenyl-5-yl)-1,3,4-oxadiazoles **46** (Küçükgüzel *et al*., 2007).



The interaction of 1-aryl-1,4-dihydro-6-methylpyridazine-4-on-3-carboxylic acid hydrazides with aryl isothiocyanates resulted in appropriate thiosemicarbazide derivatives **47** as key intermediates for the synthesis of pyridazinone substituted 1,3,4-oxadiazoles **48** (Zou *et al*., 2002).

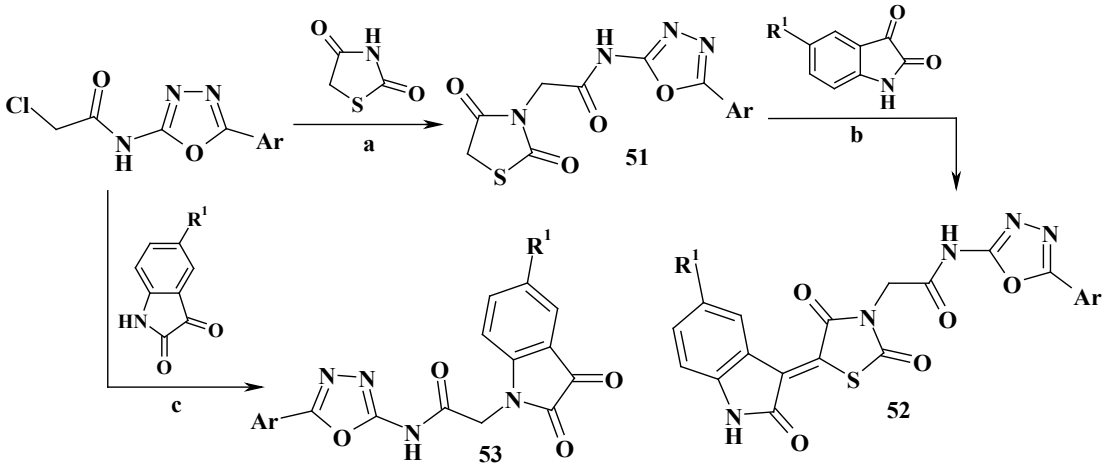


A similar approach for obtaining of 2,5-disubstituted 1,3,4-oxadiazoles was reported by Dolman *et al*. (2006). Thus, the target compounds **50** were prepared by the cyclodehydration of thiosemicarbazide precursors **49** mediated by tosyl chloride and organic base (pyridine) in tetrahydrofuran medium.



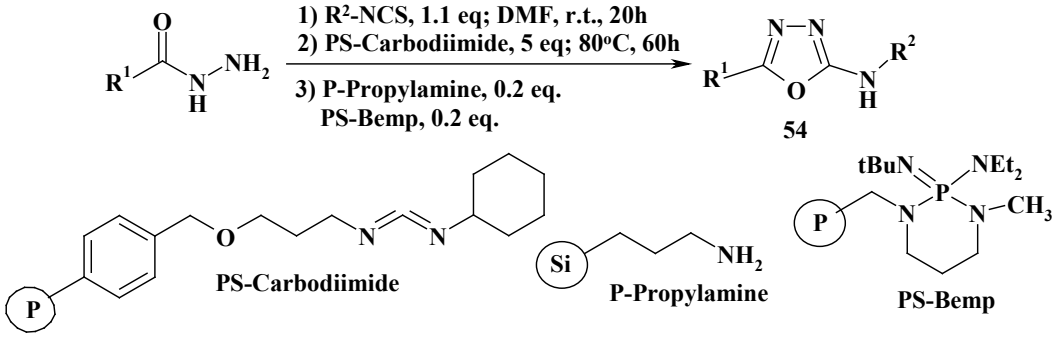
Based on the alkylation reaction of 2,4-thiazolidinedione potassium salt, generated *in situ*, and 1,3,4-oxadiazole substituted 2-chloroacetamides, a group of new bifunctional derivatives **51** were obtained. The synthesis of new 1,3,4-oxadiazole-, 4-thiazolidinone-, and indoline-based hybrids **52** was performed using standard Knoevenagel reaction procedure. Furthermore, the starting 1,3,4-oxadiazole-

substituted 2-chloroacetamides were reacted with isatin derivatives at room temperature in dimethylformamide medium giving the corresponding 1-[2-(1,3,4-oxadiazol-2-yl)-2-oxoethyl]-1*H*-indole-2,3-diones **53** (Lelyukh *et al*., 2015).

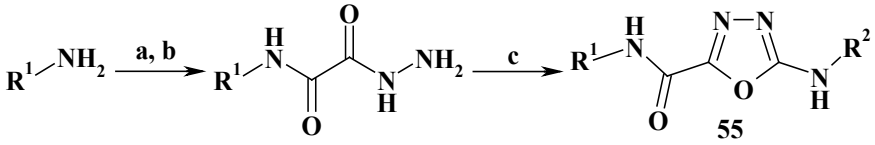


(a) KOH, KI, EtOH, reflux, 4-5h; (b) AcOH, AcONa, reflux, 3-4 h; (c) K_2CO_3, DMF, rt, 12h.

An effective one-pot synthesis of 1,3,4-oxadiazoles **54** from the acylhydrazines and isothiocyanates in dimethylformamide medium *via* polymer-supported (PS) reagents including PS-carbodiimide, P-propylamine, and PS-bemp had been reported by Coppo *et al*. (2004).

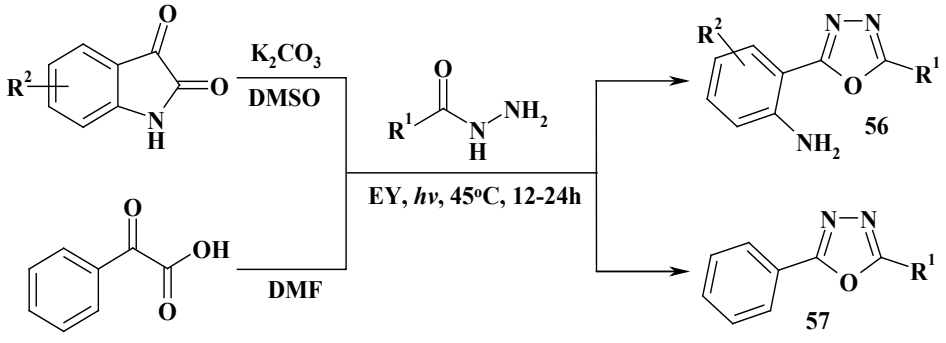


The synthesis of 2-arylamino-1,3,4-oxadiazole-5-carboxylic acid amides **55** as potential inhibitors of diacylglycerol acyl transferase-1 was carried out by McCoull *et al*. (2012). The library of target compounds was achieved through cyclocondensation of the corresponding acyl-hydrazines with various isothiocyanates using polymer-supported carbodiimide (PS-CDI) as a catalyst.

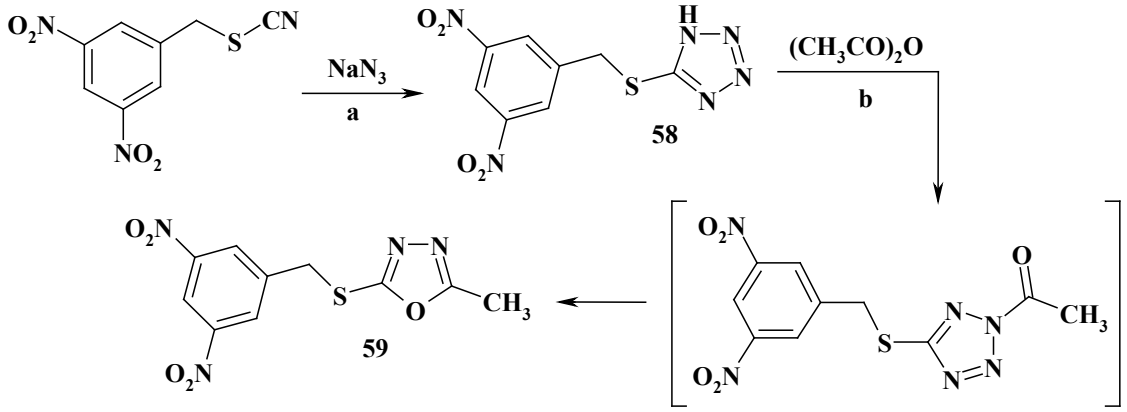


(a) MeOCOCOCl, pyridine, CH_2Cl_2; (b) NH_2NH_2, EtOH, reflux; (c) R^2NCS, PS-CDI.

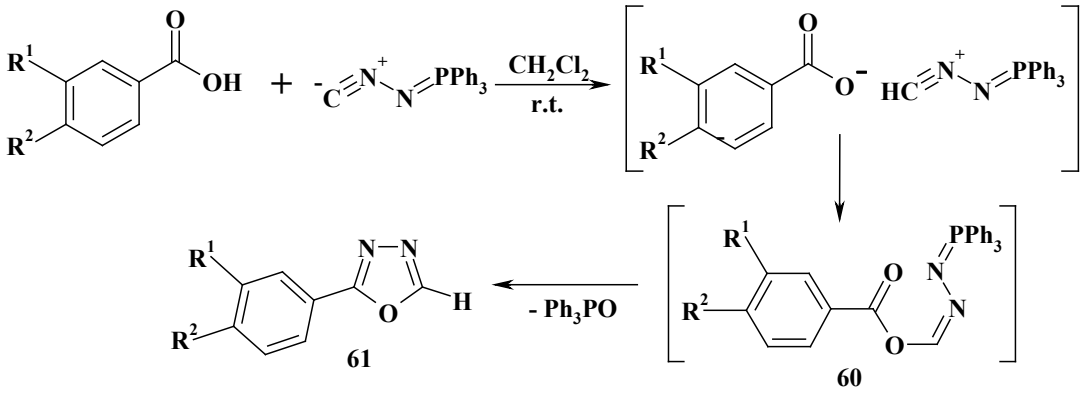
The synthesis of 1,3,4-oxadiazoles **56** and **57** by visible-light-mediated decarboxylation-cyclization of hydrazides with isatin derivatives or phenylglyoxylic acid under mild conditions with the assistance of the photocatalyst eosin Y had been discovered. Using a series of control experiments, it was established that the visible light, eosin Y, and base are essential conditions for the formation of the desired product in a good yield (Diao *et al*., 2018).



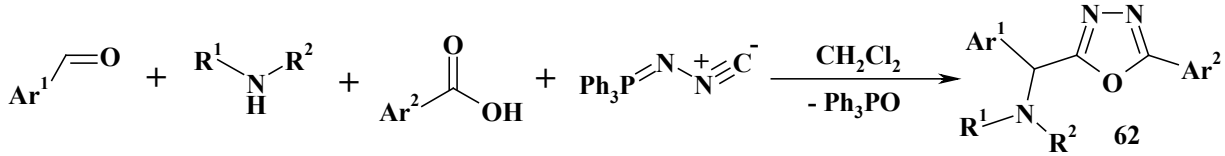
The interaction of 3,5-dinitrobenzyl isothiocyanate with sodium azide in toluene medium provided the corresponding *S*-substituted 1*H*-tetrazole-5-thiol **58**, which recyclized under the action of acetic anhydride into 5-methyl-1,3,4-oxadiazole **59** (Karabanovich *et al*., 2016).



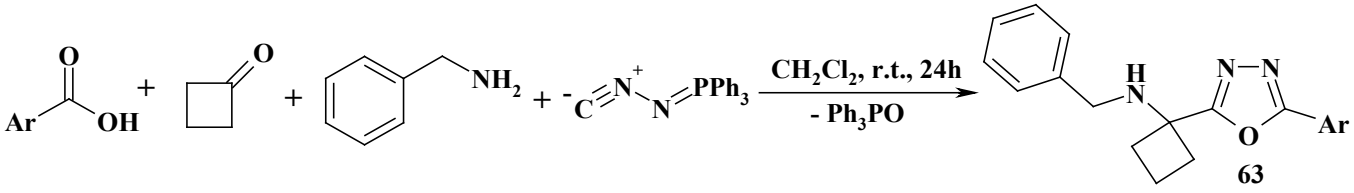
A convenient one-pot method for the synthesis of 2-aryl-1,3,4-oxadiazoles **61** was performed *via* a two-component reaction between benzoic acid derivatives with (*N*-isocyanimino)triphenylphosphorane at room temperature in dichloromethane medium (Souldozi and Ramazani, 2007). According to the authors, this interaction is accompanied by the formation of an intermediate adduct—iminophosphorane **60**—which then undergoes intramolecular *aza*-Wittig reaction, yielding the title compounds **59** and triphenylphosphine:



A fundamentally new approach for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **62** had been developed by Ramazani and Rezaei (2010). This procedure includes a one-pot four-component condensation reaction between (*N*-isocyanimino)triphenylphosphorane, secondary amines, arylcarboxylic acids, and aromatic aldehydes and is followed by intramolecular *aza*-Wittig ring closure without using any catalyst with stirring for 2 hours as shown as follows:



The synthesis of 2-[(1-benzylamino)cyclobutyl]-1,3,4-oxadiazoles **63** was performed according to the abovementioned multicomponent reaction condition using appropriate arylcarboxylic acids, cyclobutanone, benzylamine, and (*N*-isocyanimino) triphenylphosphorane (Ramazani *et al*., 2011).



Biological activity of heterocyclic systems based on functionally substituted 1,3,4-oxadiazoles

The analysis of the anti-inflammatory activity of 1,3-diarylpyrazole substituted 1,3,4-oxadiazoles allowed establishing their group selectivity for cyclooxygenase (COX)-2 compared with COX-1. Among these compounds, 1*H*-pyrazole-based 5-phenyl-1,3,4-oxadiazole **Ia** and its 5-pyridyl substituted analog **Ib** (Figure 2) were identified with the IC_{50} values of 0.31 and 0.5 μM, respectively. The selectivity indices SI (relation IC_{50} COX-1 to IC_{50} COX-2) exceeded 200 and are comparable to that of standard cyclooxygenase-2 inhibitor celecoxib (IC_{50} = 0.28 μM, SI > 357). The anti-inflammatory activity for both compounds was determined. As a result, the calculated values of effective concentration ED_{50} = 74.3 mg/kg (**Ia**) and 72.6 мг/кг (**Ib**) in comparison with celecoxib (ED_{50} = 81.7 mg/kg) and diclofenac (ED_{50} = 110.4 mg/kg) show a significant pharmacological potential of pyrazole-oxadiazoles as selective COX-2 inhibitors (Bansal *et al*., 2014).

The anti-inflammatory activity investigation of 2-[(2-phenylamino)benzoyl]-5-aryl-1,3,4-oxadiazoles allowed identifying two effective compounds **IIa** and **IIb** (Figure 2) with an inhibition value of 68.36% and 63.26%, respectively, at a dose of 100 mg/kg (Bala *et al*., 2013). The molecular docking studies for highly active compounds were performed to target COX-2. The scoring functional values of compounds **IIa** and **IIb** were much more than that of reference drug diclofenac but less than that of SC-S58 (selective COX-2 inhibitor).

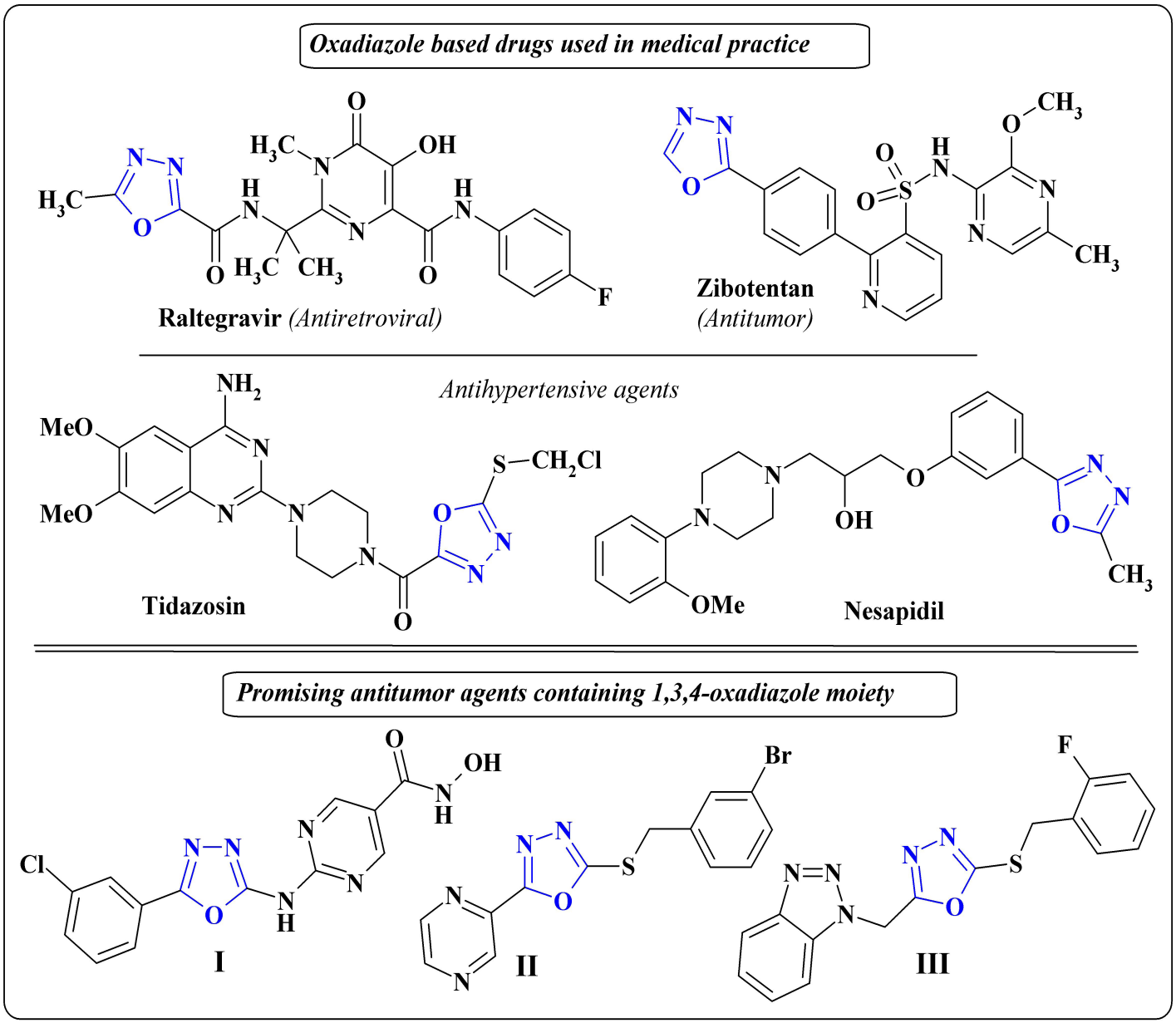


Figure 1. The pharmacological potential of 1,3,4-oxadiazole derivatives.

Among 1,3,4-oxadiazole derivatives with β-(benzoyl) ethyl fragment, two compounds—namely, 1-(4-bromophenyl)-3-[5-(4-chlorophenyl)-1,3,4-oxadiazole-2-yl]propan-1-on (**IIIa**) and 1-(4-bromophenyl)-3-[5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole-2-yl] propan-1-on (**IIIb**)—were found (Figure 2), which suppressed by 59.5% and 61.9%, respectively, the carrageenan-induced paw edema when administered orally at a dose of 100 mg/kg (Husain *et al*., 2009). The calculated SI (*severity index*) values were equal to 0.75 (**IIIa**) and 0.83 (**IIIb**), which are lower than that of the starting compound, β-(4-bromobenzoyl)propionic acid (SI = 1.17), and the reference drug indomethacin (SI = 2.67), indicating a low toxicity of the evaluable compounds **IIIa** and **IIIb**.

The antibacterial and antifungal activities of 5-(4-methoxy-3-fluorophenyl)isoxazole derivatives bearing 1,3,4-oxadiazole moiety were appraised against Gram-positive and Gram-negative microorganisms (*Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*) using ampicillin as the standard and several fungi strains including *Aspergillus niger*, *Aspergillus clavatus,* and *Candida albicans* using griseofulvin as the standard drug. As a result, a few compounds, namely, **IVa-e** (Figure 3), with promising antibacterial and antifungal action were identified (Shingare *et al*., 2018).

Based on the 3D QSAR analysis, the optimal structures were calculated, and the synthesis of 1,3,4-oxadiazoles as potential antibacterial agents was performed by Jha *et al*. (2010). For these compounds, the evaluation of antimicrobial activity against *E. coli*, *Staphylococcus epidermidis,* and *S. aureus* bacterial strains was carried out by disc diffusion method. According to the obtained results, two compounds, namely, 2-(2-acetoxyphenyl)-1,3,4-oxadiazole-2-thiol **V** and 2-phenyl-5-(3-pyridyl)-1,3,4-oxadiazole **VI** (Figure 3), exhibited the best activity with a range of growth inhibition zones of 24–26 mm (for comparison with standard drug ciprofloxacin, these parameters are 26, 30, and 29 mm, respectively).

The group of indole- and pyridine-substituted 1,3,4-oxadiazoles was evaluated for their *in vitro* antitubercular activity at the concentrations of 30, 10, and 3 lg/ml (Desai *et al*., 2016). The most active compounds **VIIa-d** (Figure 3) showed excellent MICs ranging from 0.94 to 5.17 μg/ml against Mycobacterium bovis bacillus Calmette-Guérin (BCG).

Among 2,5-disubstituted 1,3,4-oxadiazoles with 4-amino-2-methylpyrimidine fragment, compounds **VIIIa-f** (Figure 4) with a high *in vivo* activity level against *tobacco mosaic virus* had been identified. The EC_{50} value for the tested compound (246.48 μg/ml) was lower than that for standard antiviral drug ningnanmycin (EC_{50} = 301.83 μg/ml) (Wu *et al*., 2015).

The group of 1,3,4-oxadiazole substituted 5-aryl-8-hydroxy-1,6-naphthyridines was evaluated for their antiviral activity in a pseudotyped HIV cell-based assay (Johns *et al*., 2009a,

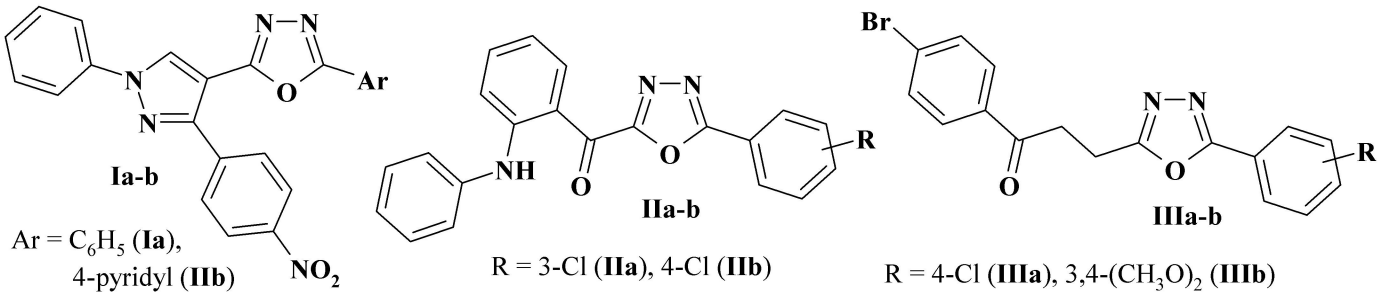


Figure 2. 1,3,4-Oxadiazole derivatives as potential anti-inflammatory agents.

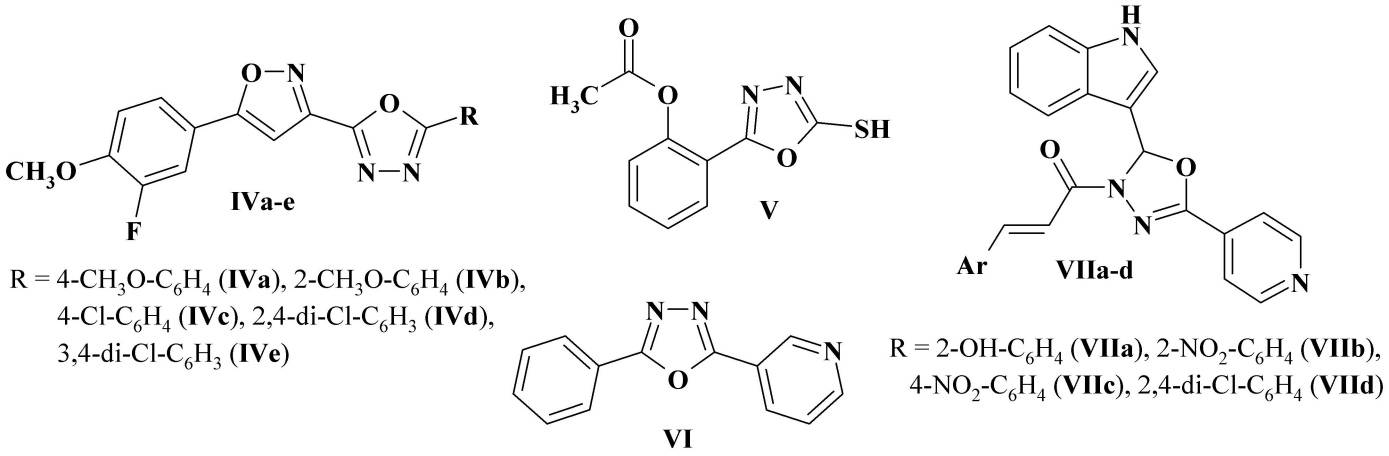


Figure 3. Effective antimicrobial, antifungal, and antimycobacterial compounds based on 1,3,4-oxadiazole core.

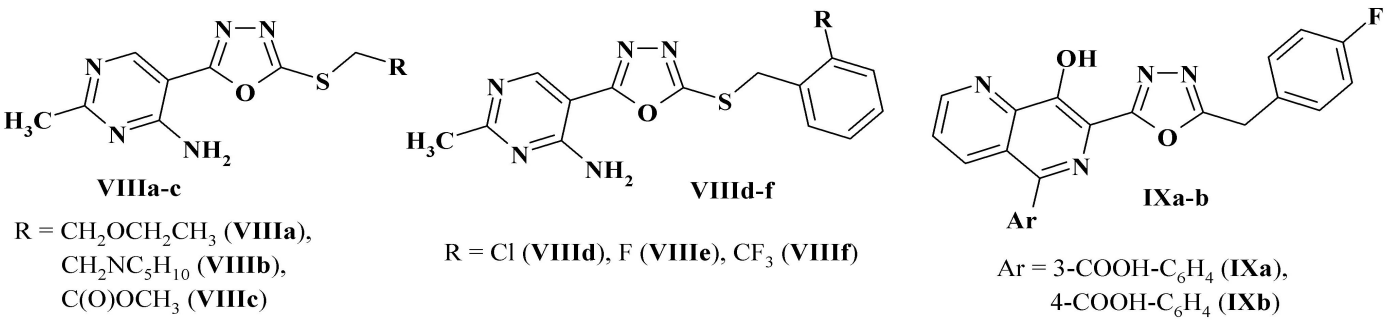


Figure 4. 1,3,4-Oxadiazole containing compounds with significant antiviral potential.

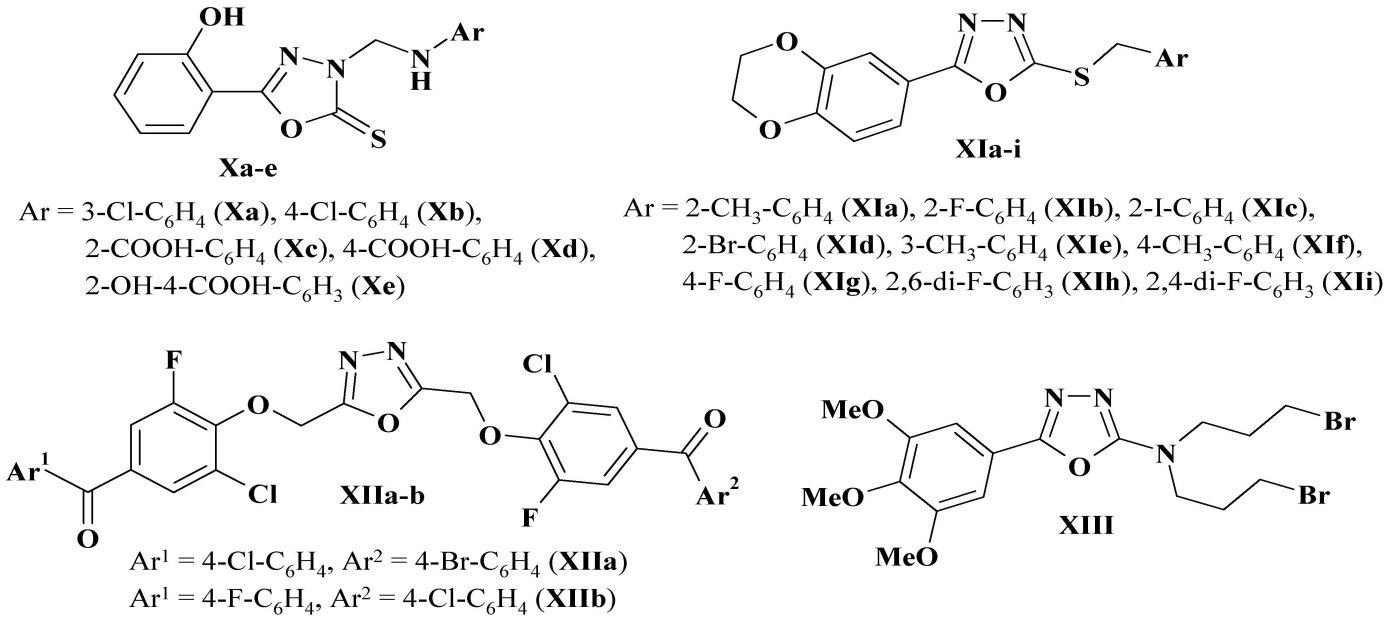


Figure 5. 1,3,4-Oxadiazole derivatives with a promising antitumor activity.

2009b). Among all compounds, the carboxylic acid analogs **IXa** and **IXb** (Figure 4) showed the most prominent HIV-1 integrase inhibitory activity with the IC_{50} values of 0.002 μM. Thus, it was observed that the presence of carboxygroup in the aryl fragment is most critical for the realization of HIV-1 inhibitory action.

The antiproliferative activity of 3-arylaminomethylene substituted 5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2-thiones was studied for a full 60-cell lines panel according to the National Cancer Institute (NCI, USA) methodology. The screening result data indicated that two active compounds, namely, **Xa** and **Xb** (Figure 5), exhibited a moderate cytotoxic effect and explicit selectivity against certain human cancer cell lines with a growth inhibitory values (MID GI_{50}) of −4.50 and −4.68, respectively (Aboraia *et al*., 2006). It was concluded that the chlorosubstituted arylamino derivatives are the most active (**Xa** and **Xb**). Furthermore, compounds with carboxylic function, namely, **Xc** (MID GI_{50} = −4.28), **Xd** (MID GI_{50} = −4.25), and **Xe** (MID GI_{50} = −4.13), showed a high activity but lower than that of the chlorosubstituted analogs.

The antitumor activity investigation of 1,3,4-oxadiazoles bearing 1,4-benzodioxan moiety **XIa-e** (Figure 5) demonstrated their effectiveness against HEPG2, HELA, SW1116, and BGC823 cancer cell lines at micromolar concentrations (range IC_{50} = 7.21–19.98 μM) compared with the 5-fluorouracil (Zhang *et al*., 2011).

Among 2,5-di-(4-aroylaryloxymethyl)-1,3,4-oxadiazoles, two highly active compounds **XIIa-b** (Figure 5) with high antiproliferative activities against human leukemic cell lines K562 and CEM were found (Gurupadaswamy *et al*., 2013). In particular, the mentioned compounds were more effective with a range of IC_{50} values of 10–16 μM than the comparison drug 5-fluorouracil (IC_{50} (K562) = 28 μM) and IC_{50} (CEM) = 32 μM)). Furthermore, it was established that the electron withdrawing halo groups at the para position in the benzophenone moieties are important for enhancing the inhibitory activity, whereas the electron releasing methyl group at the para position decreases the activity.

The evaluation of the antimitotic activity using *Onion Root Tip* method displayed that 2-[*N*,*N*-di-(3-bromopropyl)amino]-1,3,4-oxadiazole **XIII** (Figure 5) showed distinct antineoplastic effect with an ID_{50} value of 12.5 μM when compared to its chemical precursor—appropriate 2-amino-1,3,4-oxadiazole (ID_{50} = 34.5 μM). According to Lokanatha Rai *et al*. (2000), this effect may be due to the ability of compounds with *N*,*N*-di(bromopropyl) amino function to cyclization with the formation of a strained azetidinium ion, which further alkylates the NH, SH, or OH group of critical cell constituents, thereby blocking their function.

Besides, among oxadiazole derivatives, some hit compounds with antidiabetic (Taha *et al*., 2016), antioxidant (Patrao *et al*., 2013), and anticonvulsant (Rajak *et al*., 2013) activity were identified. The group of benzothiazole-substituted oxadiazoles was discovered as potential human protoporphyrinogen oxidase inhibitors (Jiang *et al*., 2010). An affinity of imidazo[1,2-*a*] pyrimidines with oxadiazole and related thiadiazole fragments to the benzodiazepine receptors was investigated (Tully *et al*., 1991). An immunosuppressive (Sun *et al*., 2011) and neuroprotective (Monte *et al*., 2013) activity evaluation for a group of 1,3,4-oxadiazoles with benzodioxan and benzodioxolane moieties was carried out.

CONCLUSION

In this review, we discuss the efforts to identify new promising compounds based on aryl/heteryl substituted noncondensed 1,3,4-oxadiazole derivatives, highlighting the main approaches for obtaining a chemical modification of the mentioned heterocycles and their pharmacological profile. 1,3,4-Oxadiazole heterocycle is a very interesting and important scaffold for modern organic and medicinal chemistry which demonstrated a wide range of biological activities including anticancer, antimicrobial, antitubercular, anti-inflammatory, and analgesic action. These ring systems are also featured in various approved drug structures such as *Raltegravir* (antiretroviral), *Zibotentan* (anticancer), and *Tiodazosin* and *Nesapidil* (antihypertensive). Thereby, the variety of the synthetic approaches of substituted 1,3,4-oxadiazoles and the widespread use of them in medicinal chemistry allow establishing this template as pharmacologically significant. All of the above can be considered as a background for further in-depth studies in the areas of chemistry and pharmacology of the mentioned heterocyclic systems with possible applications in medicine.

CONFLICT OF INTEREST

All authors confirmed that there is no conflict of interest.

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REFERENCES

Abbasi MA, Hassan M, Aziz-ur-Rehman, Siddiqui SZ, Raza H, Shah SAA, 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; 26:3791–804.

Aboraia AS, Abdel-Rahman HM, Mahfouz NM, EL-Gendy MA. Novel 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives: promising anticancer agents. Bioorg Med Chem, 2006; 14:1236–46.

Ahsan JA, Choupra A, Sharma RK, Jadav SS, Padmaja P, Hassan MZ, Al-Tamimi ABS, Geesi MH, Bakht MA. Rationale design, synthesis, cytotoxicity evaluation, and molecular docking studies of 1,3,4-oxadiazole analogues. Anticancer Agents Med Chem, 2018; 18:121–38.

Ahsan MJ, Samy JG, Khalilullah H, Nomani MdS, 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; 21:7246–50.

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; 44:2372–8.

Albratty M, El-Sharkawy KA, Alhazmi HA. Synthesis and evaluation of some new 1,3,4-oxadiazoles bearing thiophene, thiazole, coumarin, pyridine, and pyridazine derivatives as antiviral agents. Acta Pharm, 2019; 69:261–76.

Al-Omar MA. Synthesis and antimicrobial activity of new 5-(2-thienyl)-1,2,4-triazoles and 5-(2-thienyl)-1,3,4-oxadiazoles and related derivatives. Molecules, 2010; 15:502–14.

Bakht MA, Yar MS, Abdel-Hamid SG, Al Qasoumi SI, Samad A. Molecular properties prediction, synthesis and antimicrobial activity of some newer oxadiazole derivative. Eur J Med Chem, 2010; 45:5862–9.

Bala S, Kamboj S, Saini V, Prasad DN. Anti-inflammatory, analgesic evaluation and molecular docking studies of N-phenyl anthranilic acid-based 1,3,4-oxadiazole analogues. J Chem, 2013; 2013:6; doi:10.1155/2013/412053

Bansal S, Bala M, Suthar SK, 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; 80:167–74.

Bondock S, Adel S, Etman HA, Badria FA. Synthesis and antitumor evaluation of some new 1,3,4-oxadiazole-based heterocycles. Eur J Med Chem, 2012; 48:192–9.

Boschelli DH, Connor DT, Bornemeier DA, Dyer RD, Kennedy JA, Kuipers PJ, Okonkwo GC, Schrier DJ, Wright CD. 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; 36:1802–10.

Cahn P, Sued O. *Raltegravir*: a new antiretroviral class for salvage therapy. Lancet, 2007; 369:1235–6.

Chen H, Li Z, Han Y. Synthesis and fungicidal activity against rhizoctonia solani of 2-alkyl(alkylthio)-5-pyrazolyl-1,3,4-oxadiazoles (thiadiazoles). J Agric Food Chem, 2000; 48:5312–5.

Coppo FT, Evans KA, Graybill TL, Burton G. Efficient one-pot preparation of 5-substituted-2-amino-1,3,4-oxadiazole using resin-bound reagents. Tetrahedron Lett, 2004; 45:3257–60.

Desai NC, Somani H, Trivedi A, Bhatt K, Nawale L, Khedkar VM, Jha PC, 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; 26:1776–83.

Desai NC, Trivedi A, Somani H, Jadeja KA, Vaja D, Nawale L, Khedkar VM, Sarkar D. Synthesis, biological evaluation, and molecular docking study of pyridine clubbed 1,3,4-oxadiazoles as potential antituberculars. Synth Commun, 2018; 48(5):524–40.

Dhumal ST, Deshmukh AR, Bhosale MR, Khedkar VM, Nawale LU, Sarkar D, Mane RA. Synthesis and antitubercular activity of new 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffolds. Bioorg Med Chem Lett, 2016; 26:3646–51.

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; 59:767–70.

Dolman SJ, Gosselin F, O'Shea PD, Davies IW. Superior reactivity of thiosemicarbazides in the synthesis of 2-amino-1,3,4-oxadiazoles. J Org Chem, 2006; 71:9548–51.

Feng CT, Wang LD, Yan YG, Liu J, Li SH. Synthesis and antitumor evaluation of some 1,3,4-oxadiazole-2(3*H*)-thione and 1,2,4-triazole-5(1*H*)-thione derivatives. Med Chem Res, 2012; 21:315–20.

Gan X, Hu D, Li P, Wu J, Chen X, Xue W, Song B. Design, synthesis, antiviral activity and 3D-QSAR study of novel 1,4-pentadien-3-one derivatives containing the 1,3,4-oxadiazole moiety. Pest Manag Sci, 2016; 72(3):534–43.

Grinsztejn B, Nguyen B-Y, Katlama C, Gatell JM, Lazzarin A, Vittecoq D, Gonzalez CJ, Chen J, Harvey CM, Isaacs RD. Safety and efficacy of the HIV-1 integrase inhibitor *Raltegravir* (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet, 2007; 369:1261–9.

Guimarães CRW, Boger DL, Jorgensen WL. Elucidation of fatty acid amide hydrolase inhibition by potent α-ketoheterocycle derivatives from Monte Carlo simulations. J Am Chem Soc, 2005; 127:17377–84.

Gurupadaswamy HD, Girish V, Kavitha CV, Raghavan SC, Kharum SA. Synthesis and evaluation of 2,5-di(4-aryloylaryloxymethyl)-1,3,4-oxadiazole as anticancer agents. Eur J Med Chem, 2013; 63:536–43.

Hashem AI, Youssef ASA, Kandeel KA, Abou-Elmagd WSI. Conversion of some 2(3*H*)-furanones bearing a pyrazolyl group into other heterocyclic systems with a study of their antiviral activity. Eur J Med Chem, 2007; 42:934–9.

Husain A, Ajmal M. Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties. Acta Pharm, 2009; 59:223–33.

Jakubkiene V, Burbuliene MM, Mekuskiene G, Udrenaite E, Gaidelis P, Vainilavicius P. Synthesis and anti-inflammatory activity of 5-(6-methyl-2-substituted 4-pyrimidinyloxymethyl)-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives. Il Farmaco, 2003; 58:323–8.

Jha KK, Samad A, Kumar Y, Shaharyar M, Lal Khosa R, Jain J, Kumar V, Singh P. Design, synthesis and biological evaluation of 1,3,4-oxadiazole derivatives. Eur J Med Chem, 2010; 45:4963–7.

Jiang L-L, Tan Y, Zhu X-L, Wang Z-F, Zuo Y, Chen Q, Xi Z, Yang G-F. Design, synthesis and 3D-QSAR analysis of novel 1,3,4-oxadiazol-2(3*H*)ones as protoporphyrinogen oxidase inhibitors. J Agric Food Chem, 2010; 58:2643–51.

Johns BA, Weatherhead JG, Allen SH, Thompson JB, Garvey EP, Foster SA, Jeffrey JL, Miller WH. The use of oxadiazole and triazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 1: establishing the pharmacophore. Bioorg Med Chem Lett, 2009a; 19:1802–6.

Johns BA, Weatherhead JG, Allen SH, Thompson JB, Garvey EP, Foster SA, Jeffrey JL, Miller WH. 1,3,4-Oxadiazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 2: SAR of the C5 position. Bioorg Med Chem Lett, 2009b; 19:1807–10.

Kamal A, Dastagiri D, Ramaiah MJ, Bharathi EV, Reddy JS, Balakishan G, Sarma P, Pushpavalli SNCVL, 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; 18:6666–77.

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 ST, 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; 59:2362–80.

Kashtoh H, Hussain S, Khan A, Saad SM, Khan JAJ, Khan KM, Perveen S, Choudhary MI. Oxadiazoles and thiadiazoles: novel α-glucosidase inhibitors. Bioorg Med Chem, 2014; 22:5454–65.

Khan KM, Fatima N, Rasheed M, Jalil S, Ambreen N, Perveen S, Choudhary MI. 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; 17:7816–22.

Khan MTH, Choudhary MI, Khan KM, 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; 13:3385–95.

Koparir M, Cetin A, Cansiz A. 5-Furan-2-yl-1,3,4-oxadiazole-2-thiol, 5-furan-2-yl-4H-1,2,4-triazole-3-thiol and their thiol-thione tautomerism. Molecules, 2005; 10:475–80.

Kotaiah Y, Harikrishna N, Nagaraju K, Rao CV. Synthesis and antioxidant activity of 1,3,4-oxadiazole tagged thieno[2,3-*d*]pyrimidine derivatives. Eur J Med Chem, 2012; 58:340–5.

Küçükgüzel ŞG, Küçükgüzel I, Tatar E, Rollas S, Şahin F, Güllüce M, De Clercq E, Kabasakal L. Synthesis of some novel heterocyclic compounds derived from diflunisal hydrazide as potential anti-infective and anti-inflammatory agents. Eur J Med Chem, 2007; 42:893–901.

Lelyukh M, Havrylyuk D, Lesyk R. Synthesis and anticancer activity of isatin, oxadiazole and 4-thiazolidinone based conjugates. Chem Chem Technol, 2015; 9(1):29–36.

Li Y, Liu J, Zhang H, Yang X, Liu Z. Stereoselective synthesis and fungicidal activities of (*E*)-α-(methoxyimino)-benzeneacetate derivatives containing 1,3,4-oxadiazole ring. Bioorg Med Chem Lett, 2006; 16:2278–82.

Lokanatha Rai KM, Linganna N. Synthesis and evaluation of antimitotic activity of alkylated 2-amino-1,3,4-oxadiazole derivatives. Il Farmaco, 2000; 55:389–92.

Madhavilatha B, Bhattacharjee D, Sabitha G, Reddy BVS, Yadav JS, Jain N, Reddy BJM. Synthesis and *in vitro* anticancer activity of novel 1,3,4-oxadiazole-linked 1,2,3-triazole/isoxazole hybrids. J Heterocycl Chem, 2018; 55(4):863–70.

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.

McCoull W, Addie MS, Birch AM, Birtles S, Buckett LK, Butlin RJ, Bowker SS, Boyd S, Chapman S, Davies RDM, Donald CS, Green CP, Jenner C, Kemmit PD, Leach AG, Moody GC, Gutierrez PM, Newcombe NJ, Nowak T, Packer MJ, Plowright AT, Revill J, Schofield P, Sheldon C, Stokes S, Turnbull AV, Wang SJY, Whalley DP, Wood JM. Identification, optimisation and *in vivo* evaluation of oxadiazole DGAT-1 inhibitors for the treatment of obesity and diabetes. Bioorg Med Chem Lett, 2012; 22:3873–8.

Monte FL, Kramer T, Gu J, Brodrecht M, Pilakowski J, Fuertes A, Dominguez JM, Plotkin B, Eldar-Finkelman H, Schmidt B. Structure-based optimization of oxadiazole-based GSK-3 inhibitors. Eur J Med Chem, 2013; 61:26–40.

Naveena CS, Boja P, Kumari NS. Synthesis, characterization and antimicrobial activity of some disubstituted 1,3,4-oxadiazoles carrying 2-(aryloxymethyl)phenyl moiety. Eur J Med Chem, 2010; 45:4708–19.

Nimbalkar UD, Tupe SG, Vazques JAS, Khan FAK, Sangshetty JN, Nikalje APG. 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(5), 484.

Padmavathi V, Reddy GD, Reddy SN, Malesh K. Synthesis and biological activity of 2-(bis((1,3,4-oxadiazolyl/1,3,4-thiadiazolyl) methylthio)methylene)malononitriles. Eur J Med Chem, 2011; 46:1367–73.

Palmer JT, Hirschbein BL, Cheung H, McCarter J, Janc JW, Yu ZW, Wesolowski G. Keto-1,3,4-oxadiazoles as cathepsin K inhibitors. Bioorg Med Chem Lett, 2006; 16:2909–14.

Patrao P, Khader AMA, Kalluraya B, Vinayachandra. Synthesis of new 5-naphthyl substituted 1,3,4-oxadiazole derivatives and their antioxidant activity. Der Pharm Chem, 2013; 5(2):24–32.

Puthiyapurayil P, Poojary B, Chikkanna C, Buridipad SK. Design, synthesis and biological evaluation of a novel series of 1,3,4-oxadiazole bearing *N*-methyl-4-(trifluoromethyl)phenyl pyrazole moiety as cytotoxic agents. Eur J Med Chem, 2012; 53:203–10.

Rajak H, Agarawal A, Parmar P, Thakur BS, Veerasamy R, Sharma PC, Kharya MD. 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; 21:5735–8.

Rajak H, Kharya MD, 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; 341:247–61.

Rajak H, Thakur BS, Singh A, Raghuvanshi K, Sah AK, Veerasamy R, Sharma PC, Pawar RS, Kharya MD. 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; 23:864–8.

Ramazani A, Rezaei A. Novel one-pot, four-component condensation reaction: an efficient approach for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives by Ugi-4CR/*aza*-Wittig sequence. Org Lett, 2010; 12:2852–5.

Ramazani A, Shajari N, Mahyari A, Ahmadi Y. A novel four-component reaction for the synthesis of disubstituted 1,3,4-oxadiazole derivatives. Mol Divers, 2011; 15:521–7.

Rasheed H, Afridi R, Khan AU, Ullah MZ, Khalid S, Atiq A, Kashif H, Ahmed MN, Kim YS, Khan S. Anti-inflammatory, anti-rheumatic and analgesic activities of 2-(5-mercapto-1,3,4-oxadiazol-2-yl)-*N*-propylbenzenesulphonamide (MOPBS). Inflammopharmacology, 2018; 26(4):1037–49.

Rashid M, Husain A, Mishra R. Synthesis of benzimidazole bearing oxadiazole nucleus as anticancer agents. Eur J Med Chem, 2012; 54:855–66.

Rohand T, Ramli Y, Baruah M, Budka J, Das AM. Synthesis, structure elucidation and antimicrobial properties of new bis-1,3,4-oxadiazole derivatives. Pharm Chem J, 2019; 53(2):150–4.

Shingare RM, Patil YS, Sangshetty JN, Patil RB, Rajani DP, Madje BR. Synthesis, biological evaluation and docking study of some novel isoxazole clubbed 1,3,4-oxadiazoles derivatives. Med Chem Res, 2018; 27(4):1283–91.

Souldozi A, Ramazani A. The reaction of (*N*-isocyanimino) triphenylphosphorane with benzoic acid derivatives: a novel synthesis of 2-aryl-1,3,4-oxadiazole derivatives. Tetrahedron Lett, 2007; 48:1549–51.

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 against RAW246.7 cells. Bioorg Med Chem, 2011; 19:4895–902.

Taha M, Ismail NH, Jamil W, Imran S, Rahim F, Kashif SM, Zulkefeli M. Synthesis of 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives and evaluation of their antiglycation potential. Med Chem Res, 2016; 25:225–34.

Tantray MA, Khan I, Hamid H, Alam MS, 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.

Tully WR, Gardner CR, Gillespie RJ, Westwood R. 2-(Oxadiazolyl)- and 2-(thiazolyl)imidazo[1,2-*a*]pyrimidines as agonists and inverse agonists at benzodiazepine receptors. J Med Chem, 1991; 34:2060–7.

Wu W, Chen Q, Tai A, Jiang G, Ouyang G. Synthesis and antiviral activity of 2-substituted methylthio-5-(4-amino-2-methylpyrimidin-5-yl)-1,3,4-oxadiazole derivatives. Bioorg Med Chem Lett, 2015; 25:2243–6.

Zarghi A, Tabatabai SA, 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; 15:1863–5.

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; 21:3723–9.

Zhang X-M, Qiu M, Sun J, Zhang Y-B, Yang Y-S, Wang X-L, Tang J-F, Zhu H-L. Synthesis, biological evaluation, and molecular docking studies of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan moiety as potential anticancer agents. Bioorg Med Chem, 2011; 19:6518–24.

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, 2012a; 20:6356–65.

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 potent immunosuppressive agents. Bioorg Med Chem, 2012b; 20:3359–67.

Zou X-J, Lai L-H, Jin G-Y, Zhang Z-X. Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. J Agric Food Chem, 2002; 50:3757–60.

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