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

Maryan Lelyukh1*, Marta Martynets2, Myroslava Kalytovska3, Iryna Drapak1, Stefan Harkov1, Taras Chaban4, Ihor Chaban1, Vasyl Matyiychuk5

1Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.
2Department of Oral Surgery and Prosthetic Dentistry FPGE, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.
3Department of Pharmacy and Biology, Stepan Gzhyskyi National University of Veterinary Medicine and Biotechnologies Lviv, Lviv, Ukraine.
4Department of General, Bioorganic, Physical and Colloidal Chemistry, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.
5Department of Pharmacy, Medical College of Burgas University “Prof. Dr. Asen Zlatarov”, Burgas, Bulgaria.

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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), antitumor (Zibotentan), and antihypertensive (Ilodazosin 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 (Kashioh 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-oxidazole 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).
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).

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, which on reaction with hydrazine hydrate was subsequently modified with the formation of corresponding 1,2,4-triazole-5-thiones. The existence of two tautomeric forms for compounds (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 \(^1\)H 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 was carried out by the interaction of 5-(thiophene-2-yl)-1,3,4-oxadiazole-2-thiol 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 \((E)\)-\(\alpha\)-(methoxyimino)-\([2'\text{-bromomethyl}]\)phenyl]acetic acid methyl ester as an alkylating agent, the synthesis of 5-aryl substituted 2-mercapto-1,3,4-oxadiazoles was carried out (Li et al., 2006):

\[(a) \text{HON}=\text{CH-COOMe, CuSO}_4\cdot\text{Na}_2\text{SO}_4, \text{pH} \; 6-7; \; (b) \text{NaH, Me}_2\text{SO}_4; \; (c) \text{NBS, CCl}_4, \text{reflux}; \; (d) \text{CS}_2, \text{KOH, reflux 8h; (e) CH}_3\text{ONa/DMF, overnight}\]
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):

\[
\text{R}^1 = \text{Me, OMe} \quad \text{a, b} \quad \text{CS}_2/\text{KOH, 95\% ethanol, reflux, 24 h; (b) HCl, pH 5-6; (c) NaOH, acetonitrile, reflux, 8-24 h.}
\]

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).
Jakubiene 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.

![Diagram](https://via.placeholder.com/150)

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

![Diagram](https://via.placeholder.com/150)

(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).

![Diagram](https://via.placeholder.com/150)

(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 arylidine 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)-naphtols 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 $N^1$-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]-1H-indole-2,3-diones \( 53 \) (Lelyukh et al., 2015).

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.

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 \( 1H \)-tetrazole-5-thiol 58, which recylized 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).

(a) \( \text{Et}_3\text{N-HCl}, \text{toluene}, 105^\circ \text{C}, 5\text{h}, 68\% \); (b) MW, 90^\circ \text{C}, 10\text{h}, 60\%.
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, 1H-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 mg/kg (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).

![Oxadiazole-based drugs used in medical practice](image1)

**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 VIIa-f (Figure 3) with a high in vivo activity level against tobacco mosaic virus had been identified. The EC₅₀ value for the tested compound (246.48 µg/ml) was lower than that for standard antiviral drug ningnanmycin (EC₅₀ = 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,
Among all compounds, the carboxylic acid analogs IXa and IXb (Figure 4) showed the most prominent HIV-1 integrase inhibitory activity with the IC₅₀ values of 0.002 μM. Thus, it was observed that the presence of carboxy group 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 GI₅₀) 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 GI₅₀ = −4.28),Xd (MID GI₅₀ = −4.25), and Xe (MID GI₅₀ = −4.13), showed a high activity but lower than that of the chlorosubstituted analogs.

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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 IC₅₀ = 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 IC₅₀ values of 10–16 μM than the comparison drug 5-fluorouracil (IC₅₀(K562) = 28 μM) and IC₅₀(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.

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

Figure 5. 1,3,4-Oxadiazole derivatives with a promising antitumor 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 ID₅₀ value of 12.5 μM when compared to its chemical precursor—appropriate 2-amino-1,3,4-oxadiazole (ID₅₀ = 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 N., 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 thiazole fragments to the benzodiazepine receptor 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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