

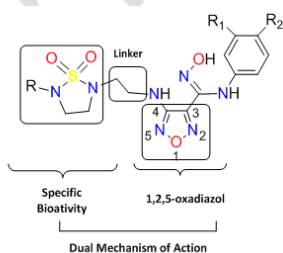
# ADVANCES IN THE SYNTHESIS, BIOLOGICAL ACTIVITIES AND APPLICATIONS OF 1,2,5-OXADIAZOL: A BRIEF REVIEW

## ABSTRACT

Oxadiazoles are five-membered heterocyclic compounds containing a nitrogen atom and at least one other noncarbon atom in the ring and belongs to azole class. ~~Oxadiazoles are five membered heterocyclic compounds containing a nitrogen atom and at least one other noncarbon atom in the ring and belongs to azole class.~~ Four isomers of oxadiazole are found. Among these, the three isomers 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole have a wide range of pharmaceutical applications. Among the immense class of heterocycle compounds with important biological activities already identified, 1,2,5-oxadiazoles have stood out for the wide variety of applications in medicinal chemistry, in the material chemistry and agricultural chemistry. In this work, the main synthesis methods and advances for obtaining 1,2,5-oxadiazoles and their derivatives reported in the literature over the years are reviewed, as well as the applications of these compounds in several branches of chemistry and their biological activities discovered until the moment.

*Keywords: 1,2,5-oxadiazoles, biological activities, medicinal chemistry, NO-donor.*

## Graphical Abstract



In this work, the main synthesis methods and advances for obtaining 1,2,5-oxadiazoles and their derivatives.

## 1. INTRODUCTION

Heterocyclics are an important class of organic compounds with a rich history with a huge impact on all areas of organic and medicinal chemistry [1-9]. On the other hand, natural products, drugs, and renewable resources prominently feature a great variety of heterocyclic moieties that are essential for their manifold properties. According to Cabrele and co-workers [10], the stereoselective synthesis, mediated by auxiliaries or catalysts, would not be possible without the electronic and steric control that can be enacted through heterocycles. Likewise, particularly stable entities such as C,H bonds can be often be activated through the combination of electronic and directing effects a heteroatom in the heterocycle might display, thus opening up versatile and efficient routes for their functionalization.

Oxadiazoles constitute a class of heterocyclic organic compounds that attracted attention due to their multiple applications in medicinal and materials chemistry [11]. Are heterocyclic compounds composed by two atoms of carbon, two atoms of nitrogen and one atom of oxygen. Oxadiazoles rings can exist in different regioisomeric forms (Figure 1) [12].

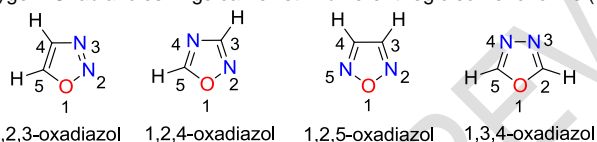


Fig. 1. Constitutional isomers of oxadiazoles.

According to Eicher and collaborator [13], except the 1,2,3-oxadiazole, which is unstable, the isomeric oxadiazoles (1,2,4-oxadiazol, 1,2,5-oxadiazol and 1,3,4-oxadiazol) can be encountered in molecules acting as drugs on the market or in final clinical trials (Figure 2), i.e. compound **1** named raltegravir [14], is an antiretroviral drug against HIV, while compound **2**, named ataluren is a good candidate for treatment of cystic fibrosis and zibotentan **3**, as an anticancer agent [15]. On the other hand, according to literature, compound **4** [16], it's used for construction of Organic Light Emitting Diodes (OLEDs) [17] or highly energetic materials[18] compounds of type **5** in the form of salts, just to name a few applications.

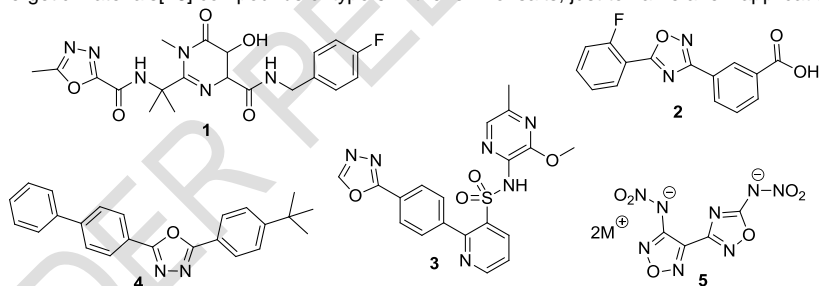
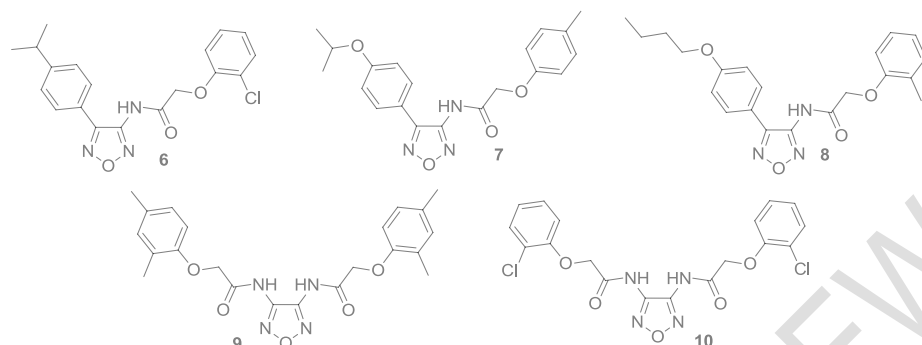


Fig. 2. Examples of oxadiazoles in drugs: zibotentan, ataluren and raltegravir.

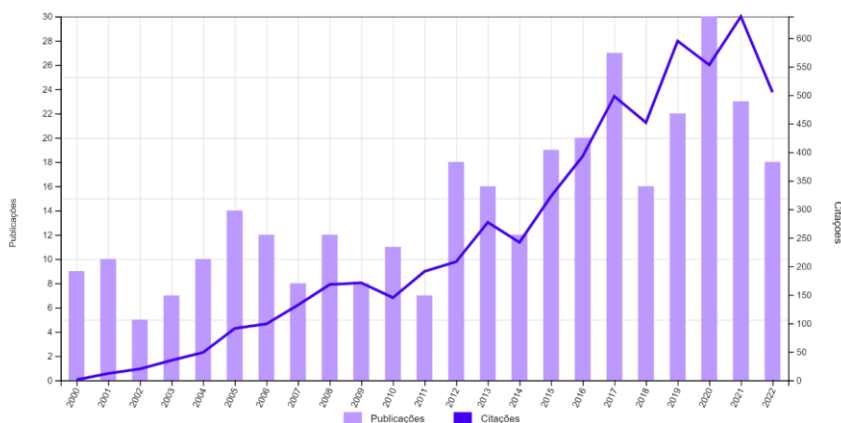
1,2,5-Oxadiazole derivatives are found to be potent inhibitors of indoleamine 2,3-dioxygenase and are useful for the treatment of cancer and other disorders. They are also useful as a new class of SENP2 inhibitors and can be used for the development of novel therapeutic agents for various diseases targeting SENPs [19-22]. In 2014, we report a new class of SENP2 inhibitors identified by a combination of structure based virtual screening and quantitative FRET based assay [23, 24]. The 1,2,5-oxadiazoles were utilized to check their ability to inhibit SENP2 activity at a lower concentration of 30  $\mu\text{M}$ . Five out of eight compounds tested contain a 1,2,5-oxadiazoles (compounds **6**, **7**, **8**, **9** and **10**) scaffold which represents a novel chemical class displaying potency against SENP2. The chemical structures of **6**, **7**, **8**, **9** and **10** are presented in Figure 3.



**Fig. 3.** 1,2,5-oxadiazoles scaffold which represents a novel chemical class displaying potency against SENP2.

1,2,5-oxadiazole-2-oxides represent an important class of NO donors [25]. Endogenous NO is a potent antimicrobial agent. Together with reactive oxygen intermediates (ROI), NO is one of the toxic mediators released by activated macrophages against pathogens. NO-mediated cellular toxicity is due to the generation of reactive species and/or inhibition of essential enzymes. Moreover, exogenous NO also displays cytotoxic and cytostatic effects against viruses and microbial agents including protozoa, for example, *Plasmodium falciparum*, a etiological agent of the most deadly form of human malaria [26]. On the other side, to a variety of NO-related bioactivities, 1,2,5-oxadiazoles also show cytotoxicity [27], mutagenicity, immunosuppression, central muscle relaxant properties, anticonvulsive effects, monoamine oxidase inhibition, and direct vasodilator and blood pressure lowering activities.

Based on data published in the years 2000-2022, it can be concluded that the synthesis and applications of 1,2,5-Oxadiazoles included in this review are of great importance for researchers who research Heterocyclic. A graph representing the number of 1,2,4-oxadiazoles citations in the literature and a series of reports published in the scope of time covered by this review (2010-2022) is shown in Figure 4.

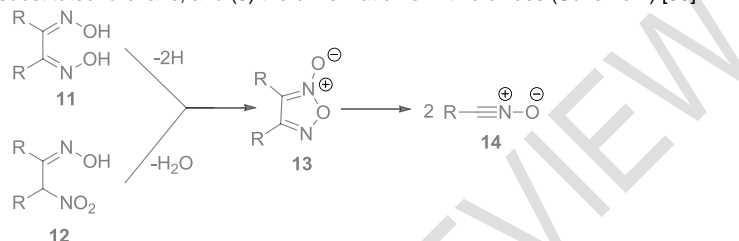


**Fig. 4.** Number of articles published and of citations on in application and synthesis of 1,2,5-oxadiazoles between 2000-2022.

We describe herein a survey of literature over the recent progress in application and synthesis of 1,2,5-oxadiazoles, their incorporation in bioactive molecules or functional scaffolds for preparation of materials.

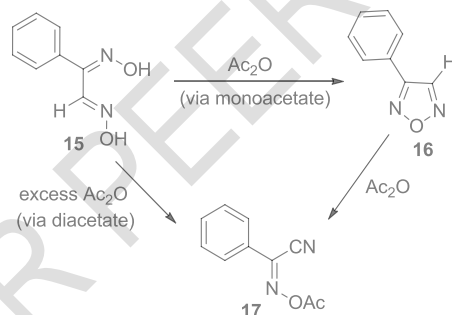
## 2. SYNTHESIS OF 1,2,5-OXADIAZOLE COMPOUNDS

Standard synthetic procedures for oxadiazole containing scaffolds usually utilizes the dehydrative cyclization of *bis*-oximes, which is performed at high temperatures [28] and often includes the introduction of different activating reagents [29]. The synthesis of new 2,5-disubstituted-1,3,4-oxadiazoles has attracted considerable attention. This interest stems largely from the fact that many 1,2,5-oxadiazole 2-oxide derivatives exhibit biological activities and from the ability of some of these derivatives to serve as donors of nitrogen oxide. The 1,2,5-oxadiazole 2-oxide ring can be constructed by various methods, the most synthetically useful of which are: (1) the oxidative cyclization of 1,2- dioximes; (2) the dehydration of nitroketoximes and symmetrically substituted furoxans; and (3) the dimerization of nitrile oxides (Scheme 1) [30].



**Scheme 1:** Synthetic ways of obtaining 1,2,5-oxadiazole.

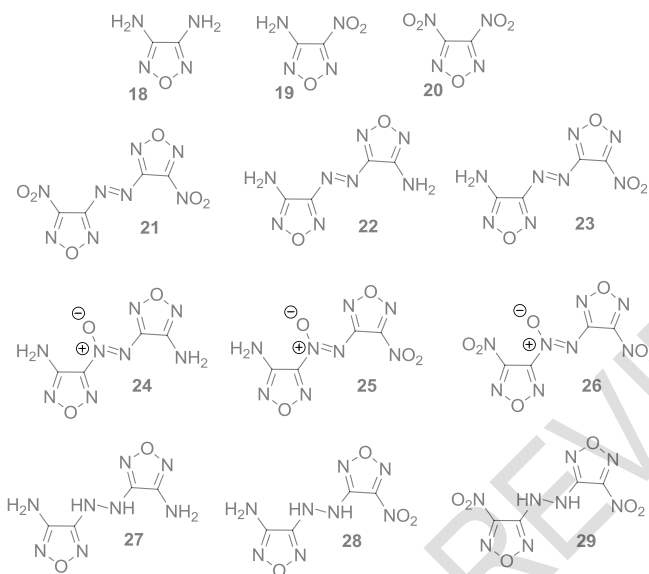
Though mono- and disubstituted 1,2,5-oxadiazoles have long been known, 1,2,5-oxadiazoles unsubstituted has resisted the synthetic efforts of organic chemists for 80 years. The synthesis of the unsubstituted heterocyclic 1,2,5-oxadiazoles unsubstituted, a stable liquid of b.p. 98°, was reported by Olofson and co-workers [31]. In fact, when phenylglyoxime is heated with 1 equiv. of acetic anhydride, the product in 87% yield is phenylfuzazan (Scheme 2). However, when phenylglyoxime is heated with 4 equiv. of acetic anhydride, the product mixture contains 27% phenylfuzazan and 58% of the oxime acetate (17).



**Scheme 2.** Monosubstituted 1,2,5-oxadiazoles.

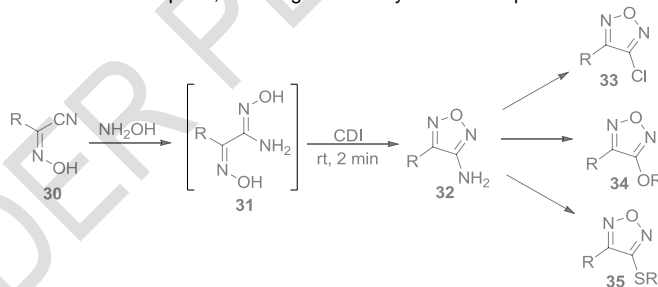
Ab initio calculations, correlations of molecules geometries, spectroscopic data with chemical properties, and quantitative structure–activity relationship have been conducted for both 1,2,5-oxadiazole 2-oxide ring. The latest investigations have shown that DFT methods can provide reliable tools for the prediction of geometries and energies of a wide variety of organic (and inorganic) compounds, especially in those cases where classical Hartree-Fock (HF) methods fail (e.g., for 1,2,5-oxadiazole 2-oxide ring and benzo 1,2,5-oxadiazole 2-oxide ring) [32-34]. The DFT method was used to study the static electronic dipole moments, polarizability anisotropies, and first- and second-order hyperpolarizabilities of azoles, including 1,2,5-oxadiazole [35].

DFT was used to calculate the heats of formation and infrared active vibrational frequencies of twelve 1,2,5-oxadiazole 2-oxide ring (Figure 5). The absolute values of the heats of formation are unreliable but the trends with systematic variations of the bridge and terminal groups are reasonable. The assignments of the vibrational motions to IR frequencies based on a force field analysis are given to clarify the complex coupling in these molecules [36, 37].



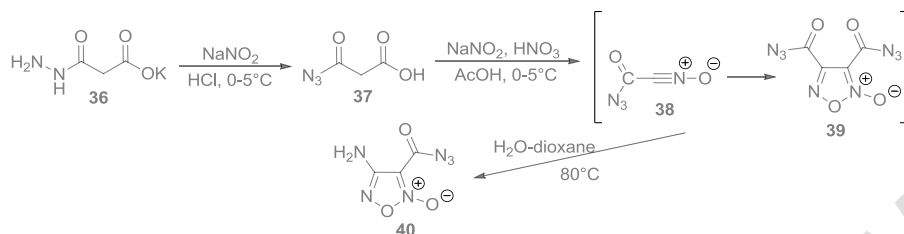
**Fig. 5.** 1,2,5-oxadiazole 2-oxide investigated by DFT computational methods.

According to Neel and Zhao [38], 1,1'-Carbonyldiimidazole was found to induce the formation of a variety of 3,4-disubstituted 1,2,5-oxadiazoles (fuzans) from the corresponding bisoximes at ambient temperature. Based on this observation, a two-step protocol was developed involving (1) hydroxylamine addition to readily prepared cyano-oximes to afford the corresponding bisoximes in situ and (2) CDI-induced cyclodehydration to form furazans. Cyano-oxime **30** underwent hydroxylamine addition and subsequent CDI-induced cyclization provided the 1,2,4-oxadiazoles in yield ranging from 56-85% (Scheme 3). According to the authors, this method was shown to be both more functional-group-tolerant and safer than its thermal alternatives. Conditions were developed that allowed for the first high-yielding synthesis of chlorofurazans from their amino counterparts, enabling the mild synthetic manipulation of these heterocycles.



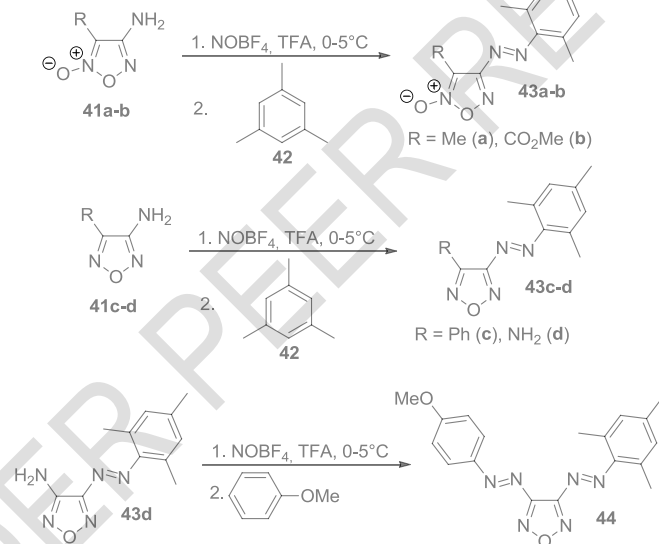
**Scheme 3.** Synthesis of 3,4-disubstituted 1,2,5-oxadiazoles.

The widely known methods for the 1,2,5-oxadiazole 2-oxide ring construction include cyclodimerization of nitrile oxides, oxidation of vic-glyoximes, and dehydration of  $\alpha$ -nitrooximes [39]. Several examples of alkene domino reactions resulting in the 1,2,5-oxadiazole 2-oxide ring formation are also known [40, 41]. In recent years, all these approaches received further development and new methods for the furazan ring construction were elaborated. 1,2,5-oxadiazole 2-oxide **39** was synthesized through the cycloaddition of azidocarbonylformonitrile oxide **38** generated via successive nitrosation of potassium monohydrazinyl malonate **36** to azidocarbonylmalonic acid **37** followed by its nitrosation/nitration/decarboxylation cascade under the action of  $\text{NaNO}_2$  in conc.  $\text{HNO}_3$ . However, 1,2,5-oxadiazole 2-oxide **39** is a very dangerous liquid to handle; therefore, it was quickly transformed into 1,2,5-oxadiazole 2-oxide derivatives **40** via the Curtius rearrangement [42] (Scheme 4).



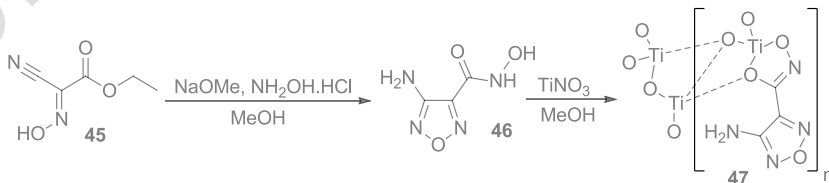
**Scheme 4.** Synthesis method of 1,2,5-oxadiazole 2-oxide.

To develop a method for the preparation of stable 1,2,5-oxadiazolyl diazonium salts various diazotization conditions were investigated per Zhilin et al [43]. The found mild optimal conditions were extended for a series of other amino-1,2,5-oxadiazoles **41a-d** resulting in the formation of azo compounds **43a-d**. The reaction proceeded successfully irrespective of the second substituent at 1,2,5-oxadiazole ring (either furazan or furoxan, Scheme 5). In addition, in the case of 3,4-diaminofurazan **41d** diazotization and subsequent azo coupling occurred chemoselectively remaining one of the amino groups unaffected and resulting in the formation of azo derivative **43d**. Amino group in compound **43d** was additionally involved in tandem diazotization/azo coupling sequence affording *bis*(aryldiazenyl)furazan **44** (Scheme 5).



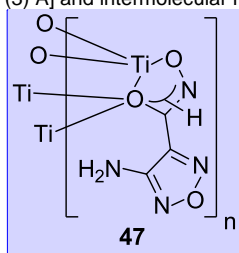
**Scheme 5.** Tandem diazotization/azo coupling of amino-1,2,5-oxadiazoles.

In 2018, poly[(1,3-4-amino-1,2,5-oxadiazole-3-hydroxamate) thallium(I)] was obtained according to a modification of the procedure reported by Neel and co-workers (Scheme 6).<sup>38</sup> The introduction of a hydroxamic group at the 1,2,5-oxadiazole ring allows the consideration of potentially interesting ligand systems for the synthesis of various polynuclear complexes [44].



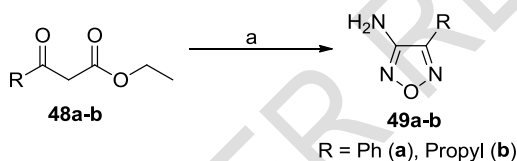
**Scheme 6.** Synthesis of 4-amino-1,2,5-oxadiazole-3-hydroxamate thallium(I).

The compound that represents the thallium(I) salt of a substituted 1,2,5-oxadiazole,  $[Ti(C_3H_3N_4O_3)]_n$ , with amino- and hydroxamate groups in the 4- and 3- positions of the oxa-diazole ring, respectively, was analyzed by X-ray crystallography [45]. In the crystal, the deprotonated hydroxamate group represent an intermediate between the keto/enol tautomers and forms a five-membered chelate ring with the thallium(I) cation. According to Safyanova et al [46]. the coordination sphere of the cation is augmented to a distorted disphenoid by two monodentately binding O atoms from two adjacent anions, leading to the formation of zigzag chains extending parallel to the b axis. The cohesion within the chains is supported by  $\pi$ - $\pi$  stacking [centroid-centroid distance = 3.746 (3) Å] and intermolecular N—H...N hydrogen bonds.



**Fig. 6.** Structure X-ray crystallography of substituted 1,2,5-oxadiazole.

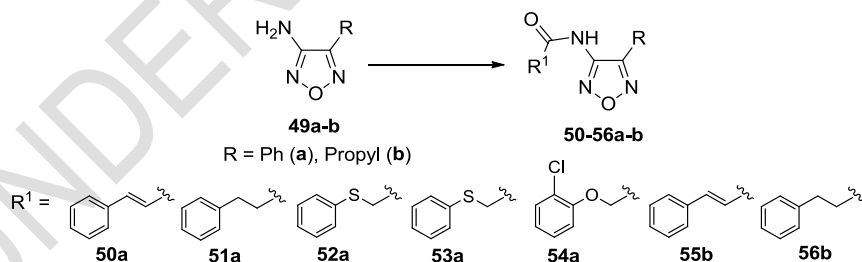
To explore the role of the methyl substituent on the oxadiazole, a small series of analogues were also prepared with alternative functionality on the heterocyclic ring was reported by Christoff et al [47]. 4-phenyl-1,2,5-oxadiazol-3-amine (**49a**) was synthesized from ethyl benzoylacetate in a one pot reaction as described by Sheremetev [48] (Scheme 7).



Reaction conditions: (a) One pot reaction over 3 days;  
 1. NaOH, H<sub>2</sub>O, 10 °C-rt.  
 2. NaNO<sub>2</sub>, 20% HClO<sub>4</sub>, 10 °C-rt.  
 3. NaOH, NH<sub>2</sub>OH.HCl, 90 °C, urea, reflux

**Scheme 7.** Synthesis of 4-phenyl-1,2,5-oxadiazol-3-amine from ethyl benzoylacetate.

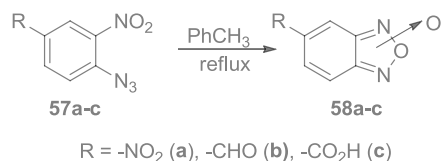
The same authors [47] developed a subsequent coupling of **49a** with five different acids, through the use of phosphorus pentachloride, produced the 4-phenyl compounds **50a–54a** (Scheme 7). Additionally, two 4-propyl oxadiazole analogues **55b** and **56b** were prepared to see if a longer chain would be tolerated if the 4-phenyl group was not accepted.



**Scheme 7.** Coupling 4-phenyl-1,2,5-oxadiazol-3-amine for produced the compounds **50a–54a**.

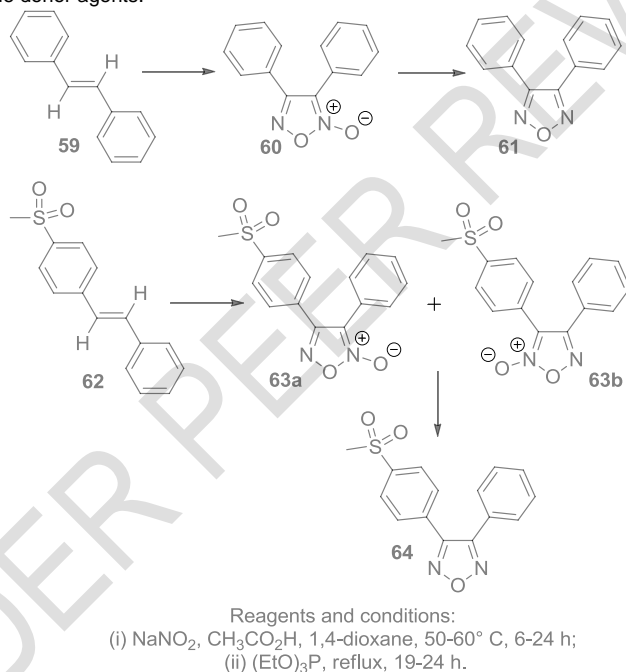
According to Aguirre et al [49], 1,2,5 oxadiazoles **58a**, **58b**, and **58c** were prepared, using the appropriate nitrophenyl azides reactants, by cyclocondensation in boiling toluene (Scheme 1). To the same authors described the results of a study on the use of Hanschs series design, cluster methodology, for the generation of new benzo[1,2-c][1,2,5-oxadiazole-*N*-oxide derivatives as antitrypanosomal compounds.

**Comment [Z1]:** Clarify Ti or Tl



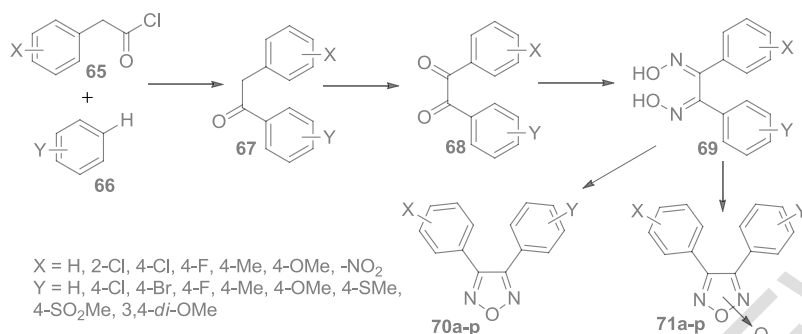
**Scheme 8.** Cyclocondensation in boiling toluene of appropriate nitrophenyl azides.

Velázquez et al [50], reported the reaction of 1-[4-(methylsulfonyl)phenyl]-2-phenylethene with an aqueous sodium nitrite solution in acetic acid afforded a mixture (3:1 ratio) of the inseparable 4-[4-(methylsulfonyl)phenyl]-3-phenyl-1,2,5-oxadiazole-2-oxide (**63a**) and 3-[4-(methylsulfonyl)phenyl]-4-phenyl-1,2,5-oxadiazole-2-oxide (**63b**) regioisomers. According to the authors, reaction of furoxan **60**, or the regioisomers **63a,b**, with triethylphosphite at reflux for 19–24 h afforded the respective deoxygenated product 3,4-diphenyl-1,2,5-oxadiazole **61** (yield 70%), or 3-[4-(methylsulfonyl)phenyl]-4-phenyl-1,2,5-oxadiazole **64** in yield 84% (Scheme 9). Also according to the same authors, a group of 3,4-diphenyl-1,2,5-oxadiazole-2-oxides (3,4-diphenylfuroxans) and the corresponding *N*-desoxy 3,4-diphenyl-1,2,5-oxadiazoles (3,4-diphenylfurozans) analogs, were synthesized for *in vitro* evaluation as hybrid cyclooxygenase (COX) inhibitor/ nitric oxide donor agents.



**Scheme 9.** Synthesis 4-[4-(methylsulfonyl)phenyl]-3-phenyl-1,2,5-oxadiazole-2-oxide (**63a**) and 3-[4-(methylsulfonyl)phenyl]-4-phenyl-1,2,5-oxadiazole-2-oxide (**63b**) regioisomers.

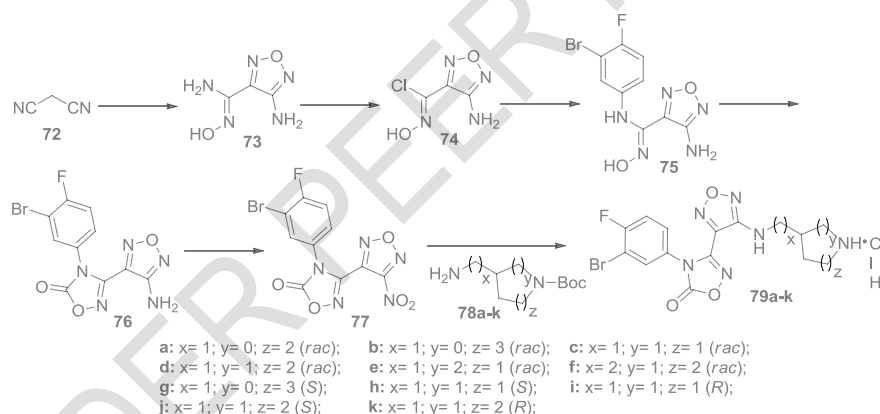
The general method employed for the preparation of 3,4-diaryl-1,2,5-oxadiazoles (**70a–p**) and 3,4-diaryl-1,2,5-oxadiazole *N*-oxides (**71a–p**) and important intermediates 1–3 is illustrated in Scheme 10. According to Yadav et al [51], acid chlorides of phenylacetic acid and substituted phenylacetic acids were obtained by refluxing the acid with thionyl chloride or phosphorous trichloride. Excess of thionyl chloride or phosphorous trichloride was removed under vacuum and the resulting acid chlorides were used as such in Friedel-Crafts acylation reaction with benzene and monosubstituted benzenes to yield 1,2-diaryl-1-ethanones (**1**). IR spectra of these ethanones showed the presence of characteristic carbonyl stretching peaks at 1690–1665 cm<sup>-1</sup>. Their <sup>1</sup>H NMR spectra showed characteristic signals for -CH<sub>2</sub>- at about 4.37 ppm.



**Scheme 10.** Synthesis 3,4-diaryl-1,2,5-oxadiazoles (**70a-p**) and 3,4-diaryl-1,2,5-oxadiazole N-oxides (**71a-p**).

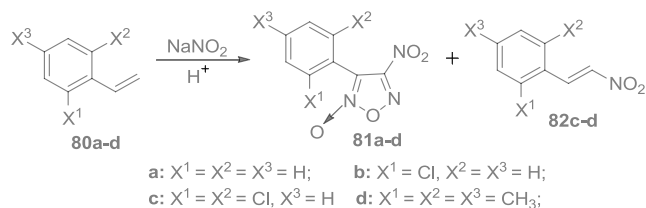
Song et al [52], described that malononitrile **72** was treated with sodium nitrite, hydroxylamine, and hydrochloric acid to afford hydroxyamidine **73** (Scheme 11). Then, it was diazotized under acidic condition and reacted with sodium chloride to provide the hydroximoyl chloride **74** in yield 48%, which was further transferred to compound **75** by coupling with 3-Br-4-phenylamine.

After that, compound **75** was treated with carbonyl diimidazole (CDI) to protect the oxime group, which resulted compound **76** in yield 74%. To introduce the side chain at oxadiazole, compound **76** was oxidized to nitro compound **77**. It was then substituted by a variety of amino compound (**78d**) and hydrolyzed under acidic condition to afford compounds **79d** in yield 90%.



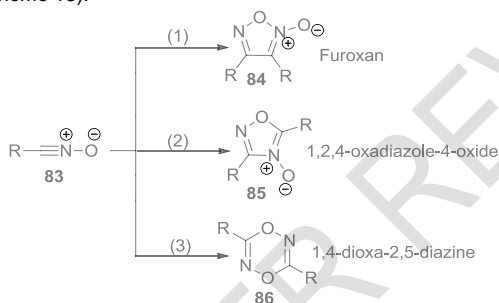
**Scheme 11.** Synthesis of 4-(4-Bromo-3-fluorophenyl)-3-(4-((piperidin-3-yl-methyl) amino)-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-5(4H)-one hydrochloride.

Takayama et al [53], reported the synthesis 4-aryl-1,2,5-oxadiazole-3-yl *N,N*-dialkylcarbamate derivatives was synthesized from styrene (**80a**) when they were treated with sodium nitrite under acidic conditions (acetic acid and aqueous hydrochloric acid) to yield 3-phenyl-4-nitrofuraxan (**81a**) as the sole isolatable product in 51% yield (Scheme 12). However, 2,6-dichlorostyrene afforded the furoxan derivative **81c** in 16% yield together with a non furoxanoid compound **82c** in 28% yield. <sup>1</sup>H-NMR spectrum and other spectroscopic data of (**82c**) revealed the structure of the major product to be *trans*-2-(2,6-dichlorophenyl) nitroethylene, which was confirmed by X-ray analysis. On the other hand, the 2,4,6-Trimethylstyrene (**80d**) also gave the furoxan (**81d**) and 2-nitrostyrene type compound (**82d**) in 16% and 30% yields, respectively. These results indicated that the existence of substituent at both the C2' and C6' positions on the benzene ring caused the steric hindrance that interfered with the formation of the furoxan derivatives.



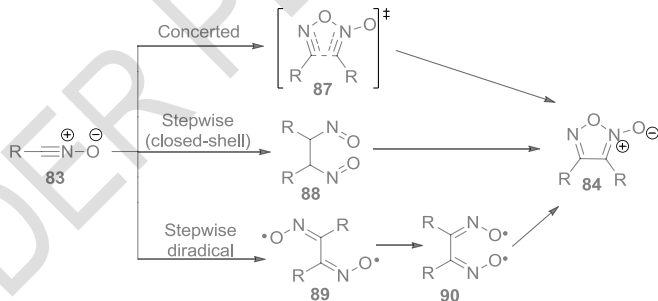
**Scheme 12.** Synthesis 4-aryl-1,2,5-oxadiazole-3-yl *N,N*-dialkylcarbamate derivatives .

According Yu and collaborators [54] nitrile oxides are widely used participants in 1,3-dipolar cycloadditions to generate five-membered ring heterocycles. Nitrile oxides (especially for lower aliphatic and acyl nitrile oxides) easily dimerize to form 1,2,5-oxadiazole-2-oxides, commonly known as furoxans or furazan oxides (reaction 1 in Scheme 13). Under acidic or basic conditions, nitrile oxides can also dimerize to give either 1,2,4-oxadiazole-4-oxides or symmetric 1,4-dioxa-2,5-diazines (reactions 2 and 3 in Scheme 13).



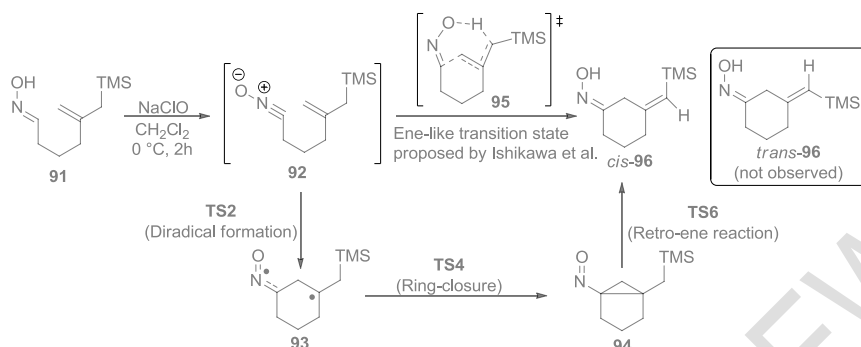
**Scheme 13.** The route by synthesis of 1,2,5-oxadiazole-2-oxides from nitrile oxides.

According to the same authors, two paths have been proposed for the dimerization of nitrile oxide to furoxans, but the detailed mechanism is not known. The most widely accepted mechanism is a concerted 1,3-dipolar cycloaddition process, where one nitrile oxide acts as a dipole while the C-N multiple bond in the other nitrile oxide acts as a dipolarophile (Scheme 14).



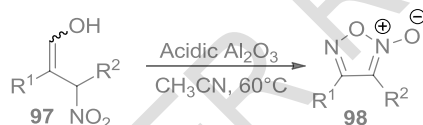
**Scheme 14.** Proposed mechanism for dimerization of nitrile oxide to 1,2,5-oxadiazole *N*-oxide.

According Yu and Houk [55], DFT calculations reveal that the intramolecular ene-like reaction between a nitrile oxide and an alkene is a three-step process involving a stepwise carbene-like 1,1-cycloaddition and a stereoselective retro-ene reaction. The stereoselective formation of one cyclic oxime product involving the TMS group is a steric effect. The achievement of the ene path is due to the ring strain in the competing (3+2) reaction path (Scheme 15). However, density functional theory studies of intramolecular ene-like (or the so-called 1,3-dipolar ene) reactions between nitrile oxides and alkenes described by Ishikawa et al [56] show that this reaction is a three-step process involving a stepwise carbenoid addition of nitrile oxide to form a bicyclic nitroso compound, followed by a retro-ene reaction of the nitrosocyclopropane intermediate.



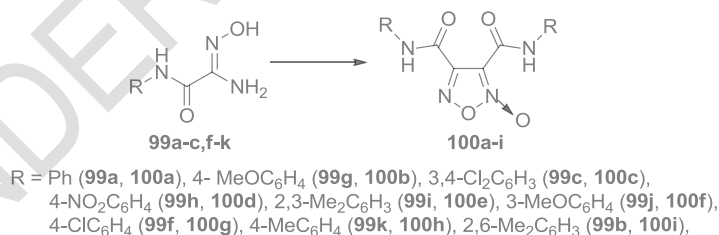
**Scheme 15.** 1,1-Cycloaddition mechanism to form bicyclic intermediate **94**, followed by a retro-ene reaction to furnish cyclic oxime *cis*-**7**.

Curini et al [56] described a convenient method for the synthesis of 1,2,5-oxadiazole-*N*-oxides from  $\alpha$ -nitro-ketoximes using acidic alumina as catalyst. According to the authors based previous experience in the use of alumina as the solid surface, found that acidic alumina is an excellent heterogeneous catalyst for the conversion of  $\alpha$ -nitro-oximes into their corresponding 1,2,5-oxadiazoles-*N*-oxides (Scheme 16). The reaction was carried out by adding a solution of the  $\alpha$ -nitro-oxime in acetonitrile to a suspension of acidic alumina in acetonitrile at 60°C. The reaction takes from 1 to 5 hours and after a simple work-up affords 1,2,5-oxadiazole-*N*-oxides derivatives in good yield from both cyclic and acyclic  $\alpha$ -nitro-oximes.



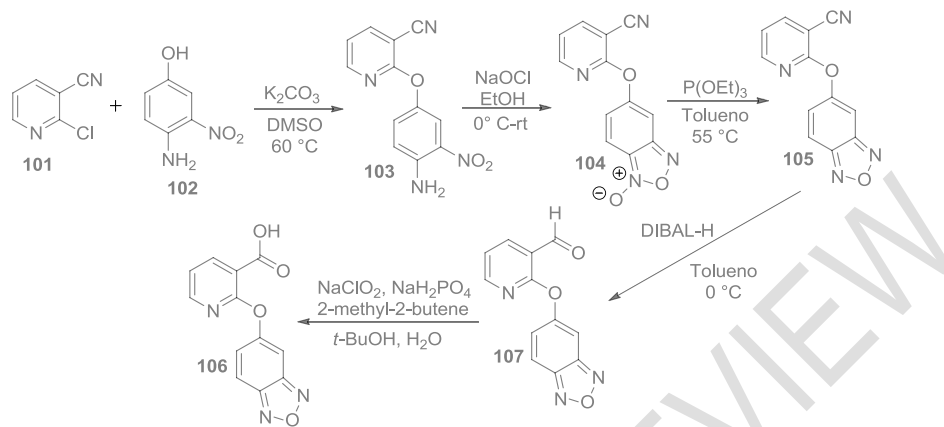
**Scheme 16.** Synthesis of 1,2,5-oxadiazole-*N*-oxides from  $\alpha$ -nitro-ketoximes.

According to Yarovenko et al [57], the 1,2,5-oxadiazole-*N*-oxides **100** can be prepared from amide oximes **1** in one step by nitrosation of compounds **99** in the presence of  $H_2SO_4$ . In these reactions, the sulfate anions act, apparently, as a weak base thus inducing elimination of HCl from intermediate hydroxymoyl chlorides **2** (Scheme 17). Hence, Yarovenko et al. <sup>57</sup> demonstrated for the first time that 1,2,5-oxadiazole-*N*-oxides can be prepared by nitrosation of amide oximes. This procedure allows one to synthesize *bis*-carbamoyl-furoxanes **100a-i** in good yields (60-91%) starting from available compounds.



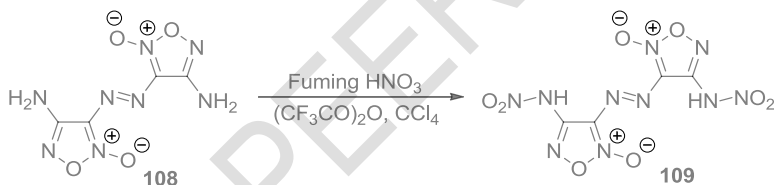
**Scheme 17.** 1,2,5-oxadiazole-*N*-oxides synthesis by one pot reaction.

According to Ruggeri et al [58] the 4-amino-3-nitrophenol couples with 2-chloronicotinonitrile very smoothly under mild conditions ( $K_2CO_3$ , DMSO, 60 °C). There was no evidence of competitive reaction with the electron-deficient amine. The product was easily isolated by filtration of the reaction mixture after precipitation with water, affording nitrile **103** in 77% yield (Scheme 18). The oxidative cyclization of nitroamine **103** in presence of EtOH and NaOCl provided benzofuroxan **104**. On the other hand, the reduction of benzofuroxan **104** to the desired benzofurazan **105** was run by treating **104** with a trialkyl phosphite at 55 °C. The desired nitrile **105** was isolated in 99% yield and has been reduced with DIBALH to provided intermediate aldehyde **107** in 97% yield. The compound **107** was oxidized with sodium chlorite to obtain acid **106** in 94% yield.



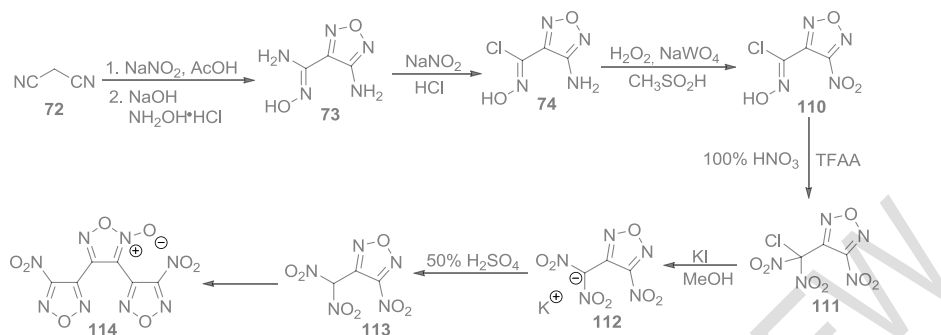
**Scheme 18.** Synthesis of 1,2,5-oxadiazoles from 4-amino-3-nitrophenol **102**.

The nitramine derivatives of 1,2,5-oxadiazole *N*-oxide are of specific interest as precursors for the preparation of high energy salts with nitrogen-rich cations. However, Larin et al [59], synthesized 3,3'-(diazene-1,2-diyl)-bis[4-(nitroamino)-1,2,5-oxadiazole 2-oxide], via nitration of available 4,40-diamino-3,30-diazenofuroxan the best yield of the target compound was achieved under the action of nitrating system  $\text{HNO}_3/(\text{CF}_3\text{CO})_2\text{O}$  in molar ratio 15:3 in  $\text{CCl}_4$  at  $-5^\circ\text{C}$  for 0.5 h (Scheme 19). The structure of 3,30-(diazene-1,2-diyl)-bis[4-(nitroamino)-1,2,5-oxadiazole 2-oxide] **109** was strictly confirmed by means of  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{N}$ -NMR, IR spectroscopy and high resolution mass spectra (HRMS).



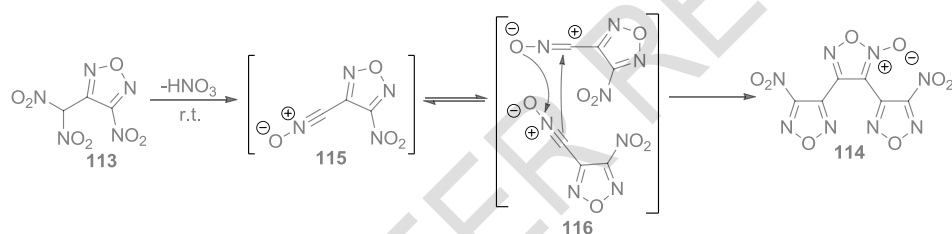
**Scheme 19.** Synthesis of 3,3'-(diazene-1,2-diyl)bis[4-(nitroamino)-1,2,5-oxadiazole 2-oxide] **109**.

In 2020, Shreeve et al [60] synthesized the compounds **110** and **111** according to previously reported method reported in the literature.<sup>60,61</sup> Then the reaction mixture was stirred at  $25^\circ\text{C}$ , and heated at  $50^\circ\text{C}$  for 2 h followed by an extractive workup to obtain **112** as a pale yellow liquid in yield of 70%. Compound **112** was nitrated with 100% nitric acid in trifluoroacetic anhydride (TFAA) at  $0^\circ\text{C}$  to give **113** as a pale yellow solid in yield of 60%. When compound **113** was treated with potassium iodide in methanol, the potassium salt **112** did not precipitate, but after the methanol was removed, the residue was washed with chloroform and recrystallized from acetone to provide **114** in yield of 70%. Compound **113** was obtained by acidification of **112** with 50% sulfuric acid. Recrystallization of **113** from dichloromethane at room temperature gave the unexpected crystalline compound **114** in yield of 86.5% (Scheme 20). Compounds **114** were fully characterized by infrared (IR),  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, and elemental analysis. Crystals of **114**, suitable for single-crystal X-ray diffraction structuring, were obtained at room temperature.



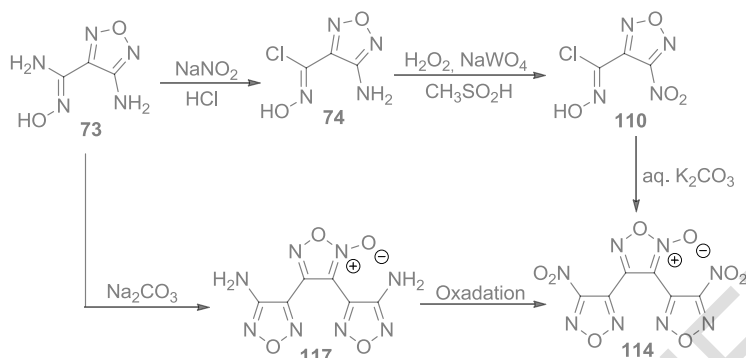
**Scheme 20.** Synthesis of 3,4-bis(4-nitro-1,2,5-oxadiazol-3-yl)-1,2,5-oxadiazole-*N*-oxide **114**.

Also, according to the same authors [60], a plausible mechanism for the formation of **114** is illustrated in Scheme 21. In this, an molecule of nitric acid is readily released by **113** at ambient temperature which leads to the extremely unstable isomers of alkyne and alkene-based nitrile oxide derivatives **115** and **116**. Later the two isomers undergo rapid cyclization to form stable 1,2,5-oxadiazole *N*-oxide **114** at 25 °C.



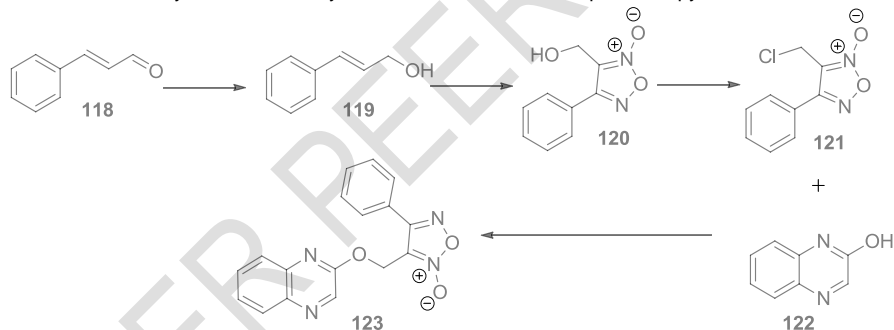
**Scheme 21.** Proposed of mechanism for formation of compound **114**.

The synthesis and characterization of 3-chlorocarbohydroxymoyl-4-nitro-1,2,5-oxadiazole and its transformation to dinitro trifurazanoxide were described for the first time by Duddu et al [61]. A careful analysis of literature reports revealed that all the synthetic approaches mainly involved oxidation of amino groups of diamino furazanofuroxan **117** to prepare **114** (Scheme 22). The initial attempts to oxidize the free amino group of **1** with H<sub>2</sub>O<sub>2</sub> in presence of sulfuric acid with or without catalyst yielded either a complex mixture of products or decomposed materials. Many attempts to obtain NCOF by using varying oxidation agent concentrations were not successful. Finally, compound **73** was subjected to oxidation by using aq. 70% H<sub>2</sub>O<sub>2</sub> in presence of tungsten based catalyst (Bmim)4W10O<sub>23</sub>, initially by stirring the reaction mixture at room temperature, and then heating it at 52°C for 4 h followed by an extractive work-up afforded compound **110** as a pale yellow liquid. Carbon NMR analysis of this liquid showed a resonance at 158.71 ppm as a triplet due to coupling of the nitro group nitrogen with aromatic ring carbon, suggesting the formation of the desired nitro compound **110**. In an effort to further confirm the identity of this liquid, an ethereal solution of **110** was reacted with an aq. potassium carbonate solution. Stirring the reaction mixture at room temperature for 2 h followed by an extractive workup and removal of solvent yielded the crude compound **114** in yield of 67%. Compound **114** was characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and elemental analysis.



**Scheme 22.** Synthesis of 3,4-Bis(4-nitro-1,2,5-oxadiazol-3-yl)-1,2,5-oxadiazole-*N*-oxide **114**.

El-Hamouly et al [62] reported that cinnamaldehyde (**118**) was treated with sodium borohydride in presence of methanol at 0°C after completion of addition, stirred at room temperature for 2 h to form cinnamyl alcohol (**119**). According Kumar et al [63] to a stirred solution of sodium nitrite in water was added dropwise cinnamyl alcohol in acetic acid and stirred at room temperature for 4 h to provide the compound 3-(hydroxymethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide **120**. To a stirred solution of (**120**) and pyridine in anhydrous dichloromethane was added thionyl chloride in an ice bath. The reaction mixture was stirred at room temperature for 3h followed by simple processing resulted in the formation of compound 3-(chloromethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide (**121**) already reported by Wang et al [64]. To a solution of the crude oil (**121**) and quinoxaline-2-ol (**122**) in acetone was added anhydrous K<sub>2</sub>CO<sub>3</sub> and maintain reflux condition for 5 h, followed by simple processing resulted in the formation to 4-phenyl-3-(quinoxalin-2-yloxy)-1,2,5-oxadiazole 2-oxide **123** (Scheme 23). Compounds **123** were fully characterized by infrared, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, and LC-MS m/z.



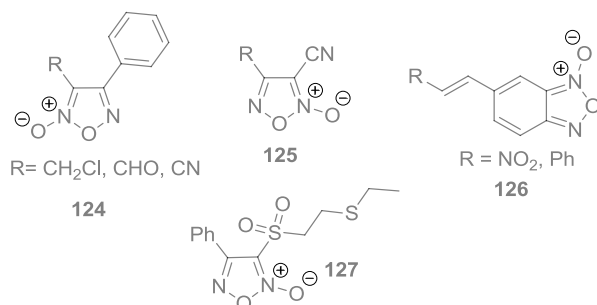
**Scheme 23.** Synthesis of 4-Phenyl-3-((Quinoxalin-2-yloxy) methyl)-1,2,5-Oxadiazole 2-Oxide **123**.

### 3. APPLICATIONS OF THE 1,2,5-OXADIAZOLE AND 1,2,5- OXADIAZOLE 2-OXIDE DERIVATIVES

Derivatives of 1,2,5-oxadiazole and 1,2,5-oxadiazole 2-oxide have a wide spectrum of applications. First they are used as starting materials in organic synthesis and medicinal chemistry. Particular attention has been focused on 1,2,5-oxadiazole 2-oxide as sources of NO in biological studies, biological markers, fluorescent and energetic materials (in materials chemistry). On the other hand, the applications of 1,2,5-oxadiazole *N*-oxide and benzo [c [1,2,5]-oxadiazole *N*-oxide derivatives as compounds which have agricultural activities are known.

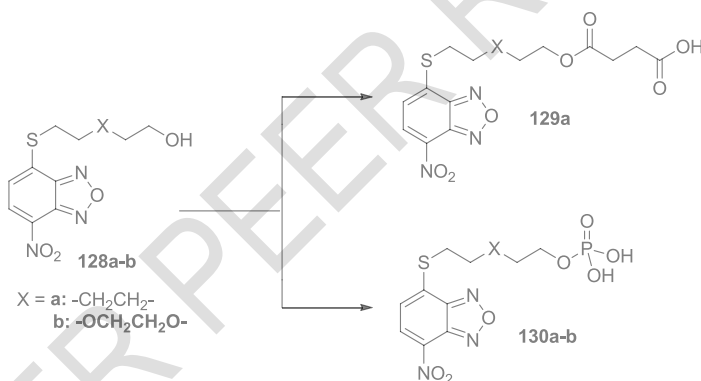
#### 3.1. Medicinal chemistry

1,2,5-Oxadiazole *N*-oxide derivatives are often tested as potential pharmaceuticals. For example, 1,2,5-oxadiazole and 1,2,5-Oxadiazole *N*-oxide derivatives have been tested as antitumor agents in vivo (compound **124**) [65], as potential anticancer agents (compound **125**) [66], as antitrypanosomal compounds (compound **126**) [67], and as antimalarial compound on the chloroquine sensitive D10 and the chloroquine-resistant W2 strains of *Plasmodium falciparum* (compound **4**) [68] (Figure 7).



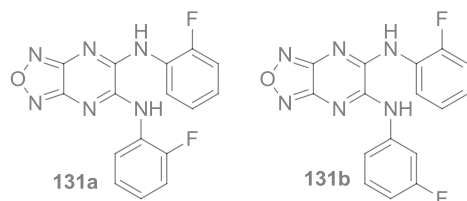
**Fig. 7.** 1,2,5-Oxadiazole *N*-Oxide derivatives as potential pharmaceuticals.

According to Di Paolo et al [69] the 7-nitrobenzo[*c*][1,2,5]oxadiazole (NBD) derivative NBDHEX (compound **128a**) and its analogue MC3181 (compound **128b**) have been found to be potent inhibitors of tumor cell growth in vitro and therapeutically active and safe in mice bearing human melanoma xenografts (Figure 8). To enhance the aqueous solubility of these compounds, we synthesized the hemisuccinate of **128a** (compound **129a**) and the phosphate monoesters of **128a** and **128b** (compound **130a** and **130b**, respectively). These novel NBD derivatives displayed a solubility in the conventional phosphate-buffered saline up to 150-fold higher than that of **128a**, and up to 4-fold higher than that of **128b**.



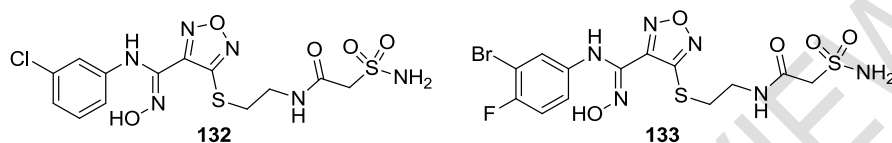
**Fig. 8.** Potent inhibitors of tumor cell growth in vitro and therapeutically active.

Kenwood et al [70] reported that BAM15 (Figure 9) compound as a new class of mitochondria selective uncouple prompted a medicinal chemistry campaign to garner a better understanding of the compound's structural properties and determine in vivo efficacy for this class of molecule in the STAM mouse model of NASH. However, Childress et al [71] proposed a study to make modification to structural changes on the 5- and 6-positions of the oxadiazolopyrazine core of BAM15. The investigations revealed that the aniline rings with electron withdrawing groups are preferred. Compared to symmetrical derivatives, unsymmetrical aniline analogs were significantly more potent, with **131a-b** bearing a 2-fluoro- and 3-fluoroaniline being the best. In particular, according to the authors compound **131a-b** is efficacious in a streptozotocin (STZ) induced mouse model of NASH demonstrating improvements in hepatocyte liver triglyceride content, inflammation, and fibrosis.



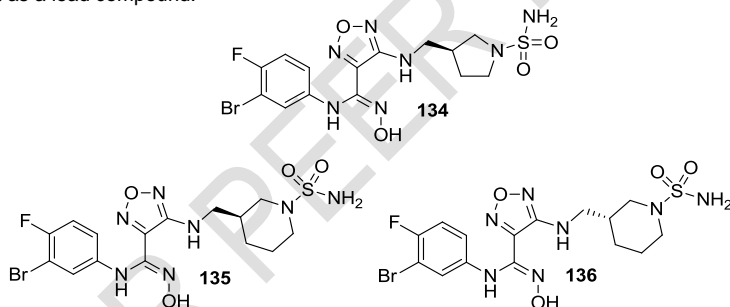
**Fig. 9.** Potential 1,2,4-oxadiazoles decoupling mitochondrial functions.

Recently Steeneck et al [72] reported the pharmacokinetics of compound **132** were investigated in more detail with a special emphasis on human glucuronidation (Figure 10). For this the PK in a humanized mouse liver model was studied using PXB mice (PhoenixBio). According Kato et al [73] these are chimeric mice with a humanized liver that is highly repopulated by human hepatocytes so that the major human drug-metabolizing enzymes and transporters are present in the liver. The use of these mice as animal models for predicting human drug metabolism and pharmacokinetics has been reported [74]. The authors used this model for compound 24 benchmarked against epacadostat (**133**). In a single dose PK (10 mg/kg, po), compound 24 displayed a more than 3-fold higher C<sub>max</sub> and more than 2-fold higher AUC compared to epacadostat (**133**). The ratio of AUC glucuronide/AUC parent is reduced from 3.6:1 for epacadostat (**133**) to 0.4:1 for 24.



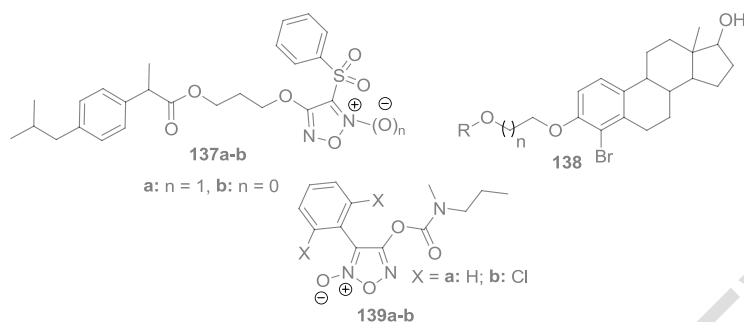
**Fig. 10.** Examples of IDO1 Inhibitors in clinical development: epacadostat (**132**) and linrodostat (**133**).

According Song et al [75] although epacadostat shows strong inhibitory activity against IDO1 and is further studied in clinic trials, its pharmacokinetic character is not satisfactory. To that point, the authors a cycle in the side chain of epacadostat was introduced aiming to increase the steric hindrance and improve the lipid solubility of the compound. Compounds **134**, **135**, and **136** (Figure 11) exhibited good potency against hIDO1 and IDO1-expressing HEK 293T cells, which were further investigated for their PK profiles. Compound **135** showed improved PK properties with longer half-life and better oral bioavailability compared with epacadostat. Finally, oral administration of compound **135** showed similar therapeutic efficacy with epacadostat in the CT-26 syngeneic xenograft model, which demonstrated that it was suitable for further development as a lead compound.



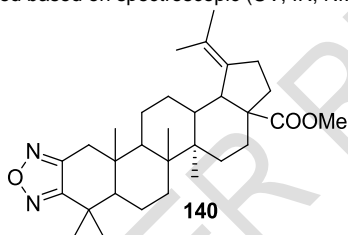
**Fig. 11.** 1,2,5-oxadiazoles com inhibitory activity against Indoleamine-2,3-dioxygenase-1 (IDO1).

A series of nonsteroidal anti-inflammatory drugs (NSAIDs) obtained by linking ibuprofen to selected 1,2,5-oxadiazole *N*-oxide moieties and to related 1,2,5-oxadiazole were tested for their anti-inflammatory, antiaggregatory, and ulcerogenic properties (Figure 12). However, benzenesulfonyl derivatives **137a** and **137b** elicited their action at the lower dose tested, and their effect was evident at 4 and 6 h. Biological evaluation of a series of 1,2,5-oxadiazole *N*-oxides has been described by Wan et al [76] and 4-bromo-3-((phenylsulfonyl)-1,2,5-oxadiazole 2-oxide)-oxy-propoxy-estradiol **138** exhibited the best activity with IC<sub>50</sub> values of 3.58–0.0008 μM. Preliminary pharmacological studies showed that **138** induced apoptosis and hardly affected the cell cycle of MDA-MB-231 cell line. 1,2,5-oxadiazole *N*-oxide **139a-b** exhibit potent anti-HIV-1 activity.



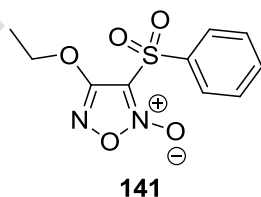
**Fig. 12.** 1,2,5-oxadiazoles with potential anti-inflammatory activity.

In 2019, Rasul [77] performed the introduction of oxadiazole moiety to ring A of the pentacyclic triterpenoid (triterpenoid betunilic acid) that enhanced the activity of the compound **140** obtained from natural sources (Figure 13). The compound presented antibacterial and fungicidal activity at different concentrations with respect to the parent compound. The structure of the compound was established based on spectroscopic (UV, IR, NMR) analysis.



**Fig. 13.** 1,2,5-oxadiazoles with potential antibacterial and fungicidal activity.

Cena et al [78] reported the potential antioxidant activity of furoxan derivatives. According to the authors, CHF 2363 in fact displays both a potent vasodilation activity and a 2-3 fold higher antioxidant action than *p*-cresol (Figure 14). This may be due to the product's ability to directly scavenge radicals and/or to small amounts of NO released by the product under the experimental conditions used for the evaluation of the antioxidant activity. It is known that low concentrations of NO display antioxidant actions.

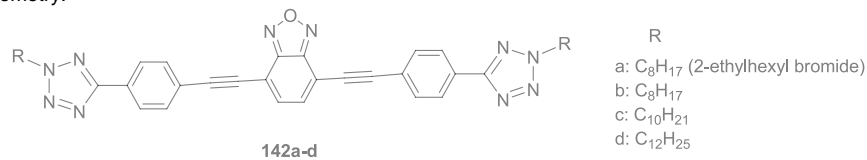


**Fig. 14.** 1,2,5-oxadiazoles with potent vasodilation activity and antioxidant action.

### 3.2. Material chemistry

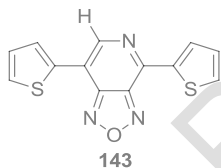
The application of compounds with 1,2,5-oxadiazole rings in materials chemistry is well known. Recently, Frizon et al [79] report the synthesis and characterization of fluorophores containing a 2,1,3-benzoxadiazole unit associated with a *p*-conjugated system (D-p-A-p-D) (Figure 15). The authors report the synthesis and characterization of BOX derivatives containing electron-donor groups (alkylated tetrazole rings) connected to the 2,1,3-BOX group as an electron-acceptor unit. These new fluorophores in solution exhibited an absorption maximum at around ~419 nm (visible region), as expected for electronic transitions of the *p*-*p*\* type ( $+ \sim 2.7 \times 10^7 \text{ L mol}^{-1} \text{ cm}^{-1}$ ), and strong solvent-dependent fluorescence emission ( $\Phi_{\text{FL}} \sim 0.5$ ) located in the bluish-green region. The Stokes' shift of these compounds is ca. 3,779  $\text{cm}^{-1}$ , which was attributed to an intramolecular charge transfer (ICT) state. In  $\text{CHCl}_3$  solution, the compounds exhibited longer and shorter lifetimes, which was attributed to the emission of monomeric and aggregated molecules, respectively.

All the final compounds **142a–d** synthesized were characterized by proton and carbon-13 NMR, IR spectroscopy, and mass spectrometry.



**Fig. 15.** 1,2,5-oxadiazoles with luminescence properties in their ground and excited electronic states.

The thienyl-substituted oxadiazolopyridine, 4,7-bis(2-thienyl)-1,2,5-oxadiazolo[3,4-c]pyridine (DTOP) (Figure 16) [80], is a newly designed material with a basic skeleton suitable for a red-emitting dye. The molecule possesses a widely conjugated  $\pi$ -electron system and therefore the excited singlet state emitting the fluorescence is expected to be shifted to a lower energy level. The red fluorescence of DTOP is recognized in the solid state and is expected to be a lead structure for molecules of great potential as red-emitting materials. The spectroscopic parameters of compound **143** were determined which was designed as a red-emitting dye for the electroluminescence (EL) device.



**Fig. 16.** 1,2,5-oxadiazole utilized as a red-emitting dye for the electroluminescence (EL) device.

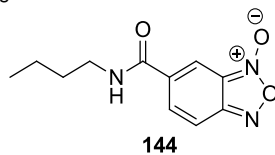
Šarlauskas and collaborator [81] prepared benzofuroxan (benzo[1,2-c]1,2,5-oxadiazole *N*-oxide) derivatives as potential energetic materials. Furthermore, the synthesis of some other benzofuroxan derivatives, potentially interesting as high energy, density materials (HEDMs), has been carried out. The densities of the compounds obtained were calculated using ACD Labs software (version 4.0). Based on the results obtained, it could be concluded that 5,6-DNBF is one of the densest nitro derivatives of the benzofuroxan series, comparable to CL-14, CL-17, CL-18, and thus could have potential applications as an HEDM.

### 3.3. Agricultural chemistry

According to Wilson co-workers, plant pathogenic fungi remain a serious and global problem for food security and human health. For example, fungus infection can cause severe crop yield reduction and results in dramatic economic losses in agriculture [82].

On the other hand, the derivatives of benzo[1,2-c]1,2,5-oxadiazole *N*-oxide (benzofuroxans, BFXs) comprise an important class of pharmacologically active heterocyclic compounds, which possess, antifungal and insecticidal activities.

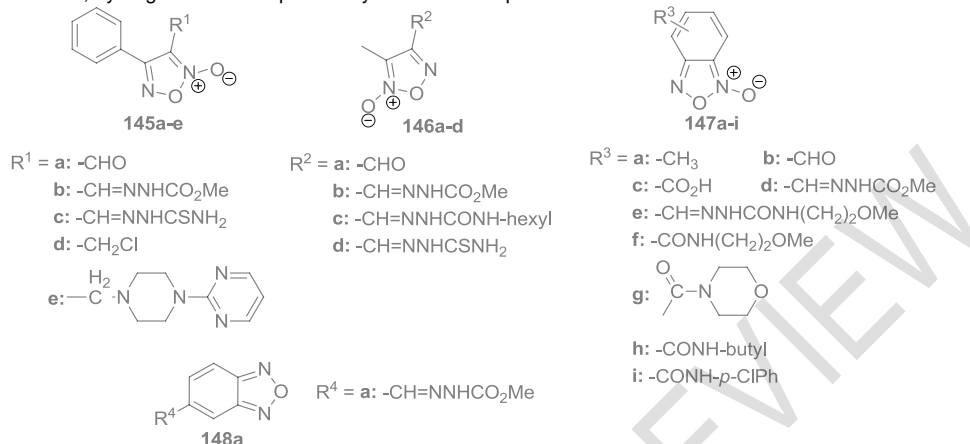
The applications of 1,2,5-oxadiazole *N*-oxide and benzo[1,2-c]1,2,5-oxadiazole *N*-oxide derivatives as compounds which have herbicidal activity are known. According to Cerecetto et al [83] a number of novel 1,2,5-oxadiazole *N*-oxide, benzo[1,2-c]1,2,5-oxadiazole *N*-oxide, and quinoxaline *N,N'*-dioxide derivatives were synthesized and evaluated for their herbicidal activity. Many of these compounds exhibited moderate to good herbicidal pre-emergence activity against *Triticum aestivum*. The most active compound, butylcarbamoylbenzo[1,2-c]1,2,5-oxadiazole *N*-oxide, **144**, displayed herbicidal activity at concentrations as low as 24 g/ha.



**Fig. 18.** 1,2,5-oxadiazoles *N*-oxides with potential herbicidal activity.

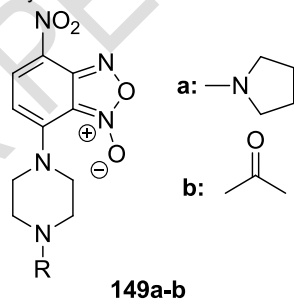
Fernandez et al [84] reported the relationship between the herbicidal activity of a number of novel 1,2,5-oxadiazole *N*-oxides and some physicochemical properties potentially related with this bioactivity, such as polarity, molecular volume, proton acceptor ability, lipophilicity, and reduction potential. According to the authors, the relationship between the phytotoxic activity of a number of novel 1,2,5-oxadiazole *N*-oxide with a variegated set of substituent (Figure 19) and

some physicochemical properties potentially related with such activity, such as lipophilicity descriptors, dipolar moment, molecular volume, hydrogen bond acceptor ability and reduction potential.



**Fig. 19.** 1,2,4-oxadiazoles *N*-oxide where herbicidal activity was related to some physicochemical properties.

Wang et al [85] reported forty-four benzofuroxan derivatives were designed and prepared as antifungal agents. Their structures were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS. Their antifungal activities were tested in vitro with four important phytopathogenic fungi, namely, *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, *Fusarium graminearum* and *Phytophthora capsici*, using the mycelium growth inhibition method. According to the authors their fungicidal activities were evaluated against four important plant pathogen strains including *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, *Fusarium graminearum*, and *Phytophthora capsici* in vitro, and the in vivo efficacies of **149a** and **149b** (Figure 20) against *S. sclerotiorum* infected cole leaves were evaluated. Compound **149b** displayed the maximum antifungal activity against *F. graminearum* (IC<sub>50</sub> = 1.1 µg/mL, which is about 2-fold higher than that of the well-known positive control carbendazim (IC<sub>50</sub> = 0.5 µg/mL). **149a** exhibited high antifungal effect against both *S. sclerotiorum* and *F. graminearum* Seh., with IC<sub>50</sub> values of 2.52 and 3.42 µg/mL, respectively.



**Fig. 20.** 1,2,4-oxadiazoles *N*-oxide with potential fungicidal activity.

In 2008, Yusupova et al [86] reported was also that benzofuroxan derivatives had fungicidal activity even though benzofuroxan derivatives as antifungal agents have not been systematically investigated. Finally, other relevant applications of 1,2,5-oxadiazoles are described in the literature [87-98]

#### 4. CONCLUSION

The field of the 1,2,5-oxadiazole and 1,2,5-oxadiazole *N*-oxide compounds has achieved a long transfer from the incipient studies regarding their synthesis to complex investigations regarding structural particularities and the consequences over the chemical reactivity and usefulness for a wide range of applications. Nowadays, we are dealing with numerous synthetic methods that have their advantages and drawbacks and are suitable for specific applications. Starting from the

early reported harsh dehydrative cyclization of the *N,N'*-diacylhydrazines and cycloaddition of tetrazoles to acid chlorides, we are now able to efficiently construct the heterocyclic core, by use of mild reagents, through oxidative cyclization of the convenient *N*-acylhydrazones or cross-coupling reactions of the already closed heterocycle with various electrophilic or nucleophilic reagents, under transition metal catalysis. Thus, a wide range of structures may be available for applications in different areas.

The biological activity of the 1,2,5-oxadiazole and 1,2,5-oxadiazole *N*-oxide has always been a subject of interest, evidenced by the commercially available antiviral drug on the market and a potent anticancer drug in the final phases of the clinical trials. Among the greatest achievements in the area of materials chemistry, one can note use of the compounds as electron transporting molecules for construction of fluorescent, phosphorescent or thermally-activated delayed fluorescence OLEDs. The field is under a continuous development and we expect to further open new ways in the chemistry of the oxadiazoles. Apart from these two great areas of research, the properties of the oxadiazoles were tuned to allow preparation of sensors for various cations and anions, useful both for chemical and biochemical systems, liquid crystals and coordination polymers, as well as the newly approached fields of solar cells and highly energetic materials.

We are, therefore, entitled to believe that the chemistry of the 1,2,5-oxadiazoles will continue to bring great achievements in various fields at the boundaries with biology and physics and to be encouraged that deeper and unlimited investigations will make this chemistry a pleasant and unforeseeable journey.

## REFERENCES

1. Taylor AP, Robinson RP, Fobian YM, Blakemore DC, Jones LH, Fadeyi O. *Modern advances in heterocyclic chemistry in drug DiscoverOrg. Biomol. Chem.* 2016, 14, 6611–6637. DOI [10.1039/c6ob00936k](https://doi.org/10.1039/c6ob00936k)
2. Ponra S, Majumdar KC. *Brønsted acid-promoted synthesis of common heterocycles and related bio-active and functional molecules. RSC Adv.* 2016, 6, 37784–37922. DOI: <https://doi.org/10.1039/C5RA27069C>
3. Sadjadi S, Heravi MM, Nazari N. *Isocyanide-based multicomponent reactions in the synthesis of heterocycles. RSC Adv.* 2016, 6, 53203–53272. DOI : <https://doi.org/10.1039/C6RA02143C>
4. Chen ZP, Zhou YG. *Asymmetric Hydrogenation of Heteroarenes with Multiple Heteroatoms. Synthesis* 2016, 48, 1769–1781. DOI: [10.1055/s-0035-1561622](https://doi.org/10.1055/s-0035-1561622)
5. Rohokale RS, Kshirsagar UA. *Advanced synthetic strategies for constructing quinazolinone scaffolds. Synthesis* 2016, 48, 1253–1268. DOI: <https://doi.org/10.1055/s-0035-1560413>
6. Ye ZS, Gettys KE, Dai MJ. *Opportunities and challenges for direct C–H functionalization of piperazines. Beilstein J. Org. Chem.* 2016, 12, 702–715. DOI: <https://doi.org/10.3762/bjoc.12.70>.
7. Kumari S, Kishore D, Paliwal S, Chauhan R, Dwivedi J, Mishra A. *Transition metal-free one-pot synthesis of nitrogen-containing heterocycles. Mol. Diversity.* 2016, 20, 185–232. DOI: <https://doi.org/10.1007/s11030-015-9596-0>.
8. Khan I, Ibrar A, Abbas N, Saeed A. *One-pot access to a privileged library of six membered nitrogenous heterocycles through multi-component cascade approach. Res. Chem. Intermed.* 2016, 42, 5147–5196. DOI: [https://DOI 10.1007/s11164-015-2354-1](https://doi.org/10.1007/s11164-015-2354-1)
9. He Q, Yin ZQ, Chen HB, Zhang ZM, Wang XX, Yue GZ. *Catalytic Asymmetric Syntheses of Indenes and Their Derivatives. Prog. Chem.* 2016, 28, 801–813. DOI: [https://DOI: 10.7536/PC160102](https://doi.org/10.7536/PC160102)

10. Cabrele C, Reiser O. *The Modern Face of Synthetic Heterocyclic Chemistry*. *J Org Chem*. 2016;81(21):10109-10125. DOI: <https://doi.org/10.1021/acs.joc.6b02034>
11. Pitasse-Santos P, Sueth-Santiago V, Marco E F, Lima J. 1, 2, 4-and 1, 3, 4-Oxadiazoles as Scaffolds in the Development of Antiparasitic Agents. *Braz. Chem. Soc.* 29, .3, 2018. DOI: <https://doi.org/10.21577/0103-5053.20170208>
12. Clapp LB. 1, 2, 4-Oxadiazoles. *Adv. Heterocycl. Chem.* **1976**, 20, 65. DOI: [https://doi.org/10.1016/S0065-2725\(08\)60852-1](https://doi.org/10.1016/S0065-2725(08)60852-1)
13. Eicher T, Hauptmann S, Speicher A. *The Chemistry of Heterocycles, Structure, Reactions, Syntheses, and Applications, Second Edition*, **2003** Wiley-VCH.
14. Clavel, F. HIV resistance to raltegravir. *Eur J Med Res.* 2009, **14** (Suppl 3), 47. <https://doi.org/10.1186/2047-783X-14-S3-47>
15. Glomb T, Szymankiewicz K, Świątek P. Anti-Cancer Activity of Derivatives of 1,3,4-Oxadiazole Molecules. 2018, 23, 2, 3361. DOI: [10.3390/molecules23123361](https://doi.org/10.3390/molecules23123361)
16. Barry PJ, Jones AM. *New and Emerging Treatments for Cystic Fibrosis Drugs* **2015**, 75, 1165. <https://doi.org/10.1007/s40265-015-0424-8>
17. Adachi C, Tsutsui T, Saito S. Blue light-emitting organic electroluminescent devices. *Appl. Phys. Lett.* 1990, 56, 799. DOI: <https://doi.org/10.1063/1.103177>
18. Paun A, Hadade ND, Paraschivescu CC, Matache M. 1,3,4-Oxadiazoles as luminescent materials for organic light emitting diodes via cross-coupling reactions. *J. Mater. Chem. C.* 2016, 4, 8596. DOI: <https://doi.org/10.1039/C6TC03003C>
19. Wei H, He C, Zhang J, Shreeve JM. Combination of 1,2,4-Oxadiazole and 1,2,5-Oxadiazole Moieties for the Generation of High-Performance Energetic Materials. *Angew. Chem. Int. Ed.* 2015, 54, 9367. DOI: <https://doi.org/10.1002/anie.201503532>
20. Bawa-Khalfe T, Cheng J, Lin SH, Ittmann MM, Yeh ET. *SENPI induces prostatic intraepithelial neoplasia through multiple mechanisms*. *J. Biol. Chem.* 2010, 285, 25859–25866. DOI: <https://doi.org/10.1074/jbc.M110.134874>
21. Cheng J, Kang X, Zhang S, Yeh ET. SUMO-specific protease 1 is essential for stabilization of HIF1alpha during hypoxia *Cell.* 2007, 131, 584–595. DOI: <https://doi.org/10.1016/j.cell.2007.08.045>
22. Yamaguchi T, Sharma P, Athanasiou M, Kumar A, Yamada S, Kuehn MR. Mutation of SENPI/SuPr-2 reveals an essential role for desumoylation in mouse development. *Mol. Cell. Biol.* 2005, 25, 5171–5182. DOI: <https://doi.org/10.1128/MCB.25.12.5171-5182.2005>
23. Cheng J, Bawa T, Lee P, Gong L, Yeh ET. Role of desumoylation in the development of prostate cancer. *Neoplasia* 2006, 8, 667–676. DOI: <https://doi.org/10.1593/neo.06445>
24. Kumar A, Ito A, Takemoto M, Yoshida M, Zhang KYJJ. Identification of 1,2,5-Oxadiazoles as a New Class of SENP2 Inhibitors Using Structure Based Virtual Screening. *Chem. Inf. Model.* 2014, 54, 870–880. DOI: <https://doi.org/10.1021/ci4007134>

25. Wang PG, Xian M, Tang X, Wu X, When Z, Cai T, Janczuk AJ. Nitric Oxide Donors: Chemical Activities and Biological Applications *Chem. Rev.* 2002, 102, 1091-1134. DOI: <https://doi.org/10.1021/cr000040l>
26. Galli U, Lazzarato L, Bertinaria M, Sorba G, Gasco A, Parapini S, Taramelli D. Synthesis and antimalarial activities of some furoxan sulfones and related furazans *Eur. J. Med. Chem.* 2005, 40, 1335-1340. DOI: <https://doi.org/10.1016/j.ejmech.2005.05.001>
27. Boiani M, Cerecetto H, González M. Cytotoxicity of furoxans: quantitative structure-activity relationships study. *Il Farmaco* 2004, 59, 405-412. DOI: <https://doi.org/10.1016/j.farmac.2003.12.011>
28. Fershtat LL, Makhova NN. Advances in the synthesis of non-annelated polynuclear heterocyclic systems comprising the 1,2,5-oxadiazole ring. *Russ. Chem. Rev.* 2016, 85, 1097-1145. DOI: <https://doi.org/10.1070/rcr4619>
29. Cerecetto H, González M. Benzofuroxan and Furoxan. *Chemistry and Biology. Top Heterocycl Chem.* 2007, 10, 265-308. DOI 10.1007/7081\_2007\_064
30. Butler RN, McMahon JM, McDonald PD, Pyne CS, Schambony S, McArdle P, Cunningham DJ. New phenanthrene systems: spiro-fused tricyclic phenanthro-1,2,4-triazolo-[4,3-d]-1,2,4-triazines and -[3,4-d]-1,2,5-oxadiazines: ring expansions of N-methylphenanthroazoliums. *Chem. Soc., Perkin Trans.* 1997, 1, 1047. DOI: <https://doi.org/10.1039/A605770E>
31. Telvekar VN, Takale BS. Reaction of Oximes of  $\alpha$ -Diketones with Diphosphorous Tetraiodide for Preparation of Oxadiazoles and Nitriles. *Synth. Commun.* 2013, 43, 221-227. DOI: <https://doi.org/10.1080/00397911.2011.595035>
32. Olofson RA, Michelman JS. Furazan<sup>8,1,2</sup>. *J Org Chem.* 1965, 30(6), 1854-1859. DOI: <https://doi.org/10.1021/jo01017a034>
33. Tselinsky IV, Melnikova SF, Pirogov SV, Shaposhnikov SD, Nather C, Traulsen T, Friedrichsen W. On the Interaction of 3,4-Dibenzoylfuroxan with Hydroxylamine. *Heterocycl. Commun.* 2000, 6, 35. DOI: <https://doi.org/10.1515/HC.2000.6.1.35>
34. Traulsen T, Friedrichsen WJ. Furo[3,4-b] benzofurans: synthesis and reactions *Chem. Soc., Perkin Transactions 1.* 2000, 1387 DOI: <https://doi.org/10.1039/B000619J>
35. Shaposhnikov SD, Pirogov SV, Mel'nikova SF, Tselinsky IV. Ring-opening and recyclization of 3,4-diacylfuroxans by nitrogen nucleophiles. *Tetrahedron*, 2003, 59, 1059. DOI: [https://doi.org/10.1016/S0040-4020\(02\)01633-2](https://doi.org/10.1016/S0040-4020(02)01633-2)
36. Jug K, Chiodo S, Calaminici P, Avramopoulos A, Papadopoulos MG. Electronic and Vibrational Polarizabilities and Hyperpolarizabilities of Azoles: A Comparative Study of the Structure-Polarization Relationship. *J. Phys. Chem. A*, 2003, 107, 4172. DOI: <https://doi.org/10.1021/jp022403m>
37. Beal RW, Brill TB. Thermal Decomposition of Energetic Materials 77. Behavior of N-N Bridged Bifurazan Compounds on Slow and Fast Heating. *Propellants, Explos., Pyrotech.*, 2000, 25, 247. DOI: [https://doi.org/10.1002/1521-4087\(200011\)25:5<241::AID-PREP241>3.0.CO;2-S](https://doi.org/10.1002/1521-4087(200011)25:5<241::AID-PREP241>3.0.CO;2-S)

38. Neel AJ, Zhao R. Mild Synthesis of Substituted 1,2,5-Oxadiazoles Using 1,1'-Carbonyldiimidazole as a Dehydrating Agent. *Org. Lett.* 2018, 20, 2024–2027. DOI: <https://doi.org/10.1021/acs.orglett.8b00568>
39. Nikonov, G.N. Bobrov, S. In: Black, D. (ed.) *Comprehensive heterocyclic chemistry*, 3rd ed.; Elsevier Ltd.: Oxford, UK, 2008; Vol. 5, p. 315.
40. Makhova N. N, Dubonos VG, Blinnikov AN, Ovchinnikov IV, Khmel'nitskii LI. Regiospecific and Regioselective Synthesis of Isomeric Nitrofuraxanes from Unsaturated Compounds. *Russ J Org Chem.* 1997, 33(8),1140.
41. Makhova NN, Fershtat LL. Recent advances in the synthesis and functionalization of 1,2,5-oxadiazole 2-oxides. *Tetrahedron Letters.* 2018, 59, 2317–2326. DOI: <https://doi.org/10.1016/j.tetlet.2018.04.070>
42. Guo T, Liu M, Huang X-C, Wang Z-J, Qiu S-J, Ge Z-X, Meng Z-H. Efficient preparation and comprehensive properties of thermal decomposition and detonation for 4,4'-dinitro-3,3'-azofuroxan. *J Anal Appl Pyrolysis.* 2017, 128 - 451. DOI: <https://doi.org/10.1016/j.jaap.2017.06.015>
43. Zhilin ES, Fershtat LL, Bystrov DM, Kulikov AS, Dmitrienko AO, Ananyev IV, Makhova NN. Renaissance of 1,2,5-Oxadiazolyl Diazonium Salts: Synthesis and Reactivity. *Eur. J. Org. Chem.* 2019, 4248–4259. DOI: <https://doi.org/10.1002/ejoc.201900622>
44. Ostrowska M, Golenya IA, Haukka M, Fritsky IO, Kontecka EG. Complex formation of copper(ii), nickel(ii) and zinc(ii) with ethylophosphonoacetohydroxamic acid: solution speciation, synthesis and structural characterization. *New J. Chem.* 2019, 43, 10237–10249. DOI: <https://doi.org/10.1039/C9NJ01175G>
45. Safyanova S, Bondar OA, Pavlishchuk AV, Omelchenko IV, Iskenderov TS, Kalibabchuk VA. Crystal structure of poly[ $\mu$ 3-4-amino-1,2,5-oxa-diazole-3-hydroxamato]thallium(I)]. *Acta Cryst. E.* 2020, 76, 328–331. DOI: <https://doi.org/10.1107/S2056989020001577>
46. Christoff RM, Murray GL, Kostoulias XP, Peleg AY, Abbott BM. Synthesis of novel 1,2,5-oxadiazoles and evaluation of action against *Acinetobacter baumannii*. *Bioorganic Med Chem.* 2017, 25(24), 6267-6272. DOI: <https://doi.org/10.1016/j.bmc.2017.08.015>
47. Sheremetev AB. One-pot synthesis of 3-amino-4-aryl- and 3-amino-4-hetarylfurazans. *Russ Chem Bull.* 2005, 54, 1057. DOI: <https://doi.org/10.1007/s11172-005-0359-4>
48. Aguirre G, Boiani L, Cerecetto H, Di Maio R, González M, Porcal W, Denicola A, Moller M, Thomson L, Tórtora V. Benzo[1,2-c]1,2,5-oxadiazole N-oxide derivatives as potential antitrypanosomal drugs. Part 3: Substituents-clustering methodology in the search for new active compounds. *Bioorg. Med. Chem.* 2005, 13, 6324–6335. DOI: [10.1016/j.bmc.2005.05.020](https://doi.org/10.1016/j.bmc.2005.05.020)
49. Velázquez C, Rao PNP, McDonald R, Knaus EE. Synthesis and biological evaluation of 3,4-diphenyl-1,2,5-oxadiazole-2-oxides and 3,4-diphenyl-1,2,5-oxadiazoles as potential hybrid COX-2 inhibitor/nitric oxide donor agents. *Bioorg Med Chem.* 2005, 13(8), 2749-2757. DOI [10.1016/j.bmc.2005.02.034](https://doi.org/10.1016/j.bmc.2005.02.034)
50. Yadav MR, Shirude ST, Puntambekar DS, Patel PJ, Prajapati HB, Parmar A, Balaraman R, Giridhar R. Studies in 3,4-diaryl-1,2,5-oxadiazoles and their N-oxides: Search for better COX-2 inhibitors. *Acta Pharm.* 2007, 57(1), 13-30. DOI: <https://doi.org/10.2478/v10007-007-0002-z>

51. Song X, Sun P, Wang J, Guo W, Wang Y, Meng L-H, Liu H. Design, synthesis, and biological evaluation of 1,2,5-oxadiazole-3-carboximidamide derivatives as novel indoleamine-2,3-dioxygenase 1 inhibitors. *Eur J Med Chem.* 2020, 189, 112059. DOI [10.1016/j.ejmech.2020.112059](https://doi.org/10.1016/j.ejmech.2020.112059)
52. Takayama H, Shirakawa S, Kitajima M, Aimi N, Yamaguchi K, Hanasaki Y, Ide T, Katsuura K, Fujiwara M, Ijichi K, Konno K, Sigeta S, Yokota T, Baba M. Utilization of Wieland Furoxan synthesis for preparation of 4-aryl-1,2,5-oxadiazole-3-yl carbamate derivatives having potent anti-HIV activity. *Bioorg. Med. Chem. Lett.* 1996, 6, 1993. DOI: [10.1016/0960-894X\(96\)00355-1](https://doi.org/10.1016/0960-894X(96)00355-1) 52
53. Yu Z-X, Caramella P, Houk KN. Dimerizations of Nitrile Oxides to Furoxans Are Stepwise via Dinitrosoalkene Diradicals: A Density Functional Theory Study. *J. Am. Chem. Soc.*, 2003, 125, 15420-15425. DOI: [10.1021/ja037325a](https://doi.org/10.1021/ja037325a)
54. Yu Z-X, Houk KN. Intramolecular 1,3-Dipolar Ene Reactions of Nitrile Oxides Occur by Stepwise 1,1-Cycloaddition/Retro-Ene Mechanisms. *J. Am. Chem. Soc.* 2003, 125, 13825-13830. DOI: [10.1021/ja0376487](https://doi.org/10.1021/ja0376487)
55. Ishikawa T, Urano J, Ikeda S, Kobayashi Y, Saito S. Novel Ene-Like Cycloisomerization Reaction of Nitrile Oxides with a Tethered Allyltrimethylsilyl Group. *Angew. Chem.* 2002, 41, 1586. DOI: [10.1002/1521-3773\(20020503\)41:9<1586::aid-anie1586>3.0.co;2-m](https://doi.org/10.1002/1521-3773(20020503)41:9<1586::aid-anie1586>3.0.co;2-m)
56. Curini M, Epifano F, Marcotullio MC, Rosati O, Ballini R, Bosica G. Alumina promoted cyclization of  $\alpha$ -nitro-oximes: a new entry to the synthesis of 1,2,5-oxadiazoles N-oxides (furoxans). *Tetrahedron Lett.* 2000, 41, 8817. DOI [10.1016/S0040-4039\(00\)01422-2](https://doi.org/10.1016/S0040-4039(00)01422-2)
57. Yarovenko VN, Zavarzin IV, Krayushkin MM. Synthesis of monothiooxamides of the thiazole series. *Russ. Chem. Bull.* 2002, 51, 1504. DOI: [10.1023/B:RUCB.0000030828.43955.7b](https://doi.org/10.1023/B:RUCB.0000030828.43955.7b)
58. Ruggeri S. G, Bill DR, Bourassa DE, Castaldi MJ, Houck TL, Ripin DHB, Wei L, Weston N. Safety vs Efficiency in the Development of a High-Energy Compound. *Org. Process Res. Dev.* 2003, 7, 1043. DOI: [10.1021/op0341059](https://doi.org/10.1021/op0341059)
59. Larin A, Ovchinnikov I, Fershtat L, Makhova N. 3,3'-(Diazene-1,2-diyl)bis[4-(nitroamino)-1,2,5-oxadiazole 2-oxide]. *Molbank.* 2018, 3, M1003. DOI: <https://doi.org/10.3390/M1003>
60. Shreeve JM, Yu Q, Chinnam AK, Yin P, Imler GH, Parrish DA. Finding furoxan rings. *Mater. J. Chem. A*, 2020, DOI: [10.1039/D0TA01538E](https://doi.org/10.1039/D0TA01538E).
61. Duddu R, Hoare J, Sanchez P, Damavarapu R, Parrish D. Synthesis of Nitro, Dinitro, and Polynitroalkylamino Derivatives of Trifurazanoxide. *J. Heterocycl. Chem.* 2017, 54, 3087-3092. DOI: [10.1002/jhet.2920](https://doi.org/10.1002/jhet.2920)
62. El-Hamouly WS, Abbas EMH, Tawfik, HA. One-pot synthesis of some (1H)-quinoxalin-2-ones. *Afr J Pure Appl Chem.* 2009, 4(1), 7-10. DOI [10.5897/AJPAC.9000102](https://doi.org/10.5897/AJPAC.9000102)
63. Kumar SN, Kumar CNSSP, Anudeep SRV, Sharma KK, Rao VJ, Babu NJ. An expedient synthesis of new 2-(furoxan-3-yl)thiazolidin-4-one derivatives. *ARKIVOC.* 2016, 32-49. DOI [10.3998/ark.5550190.p009.669](https://doi.org/10.3998/ark.5550190.p009.669)

64. Wang YD, Bao XQ, Xu S, Yu WW, Cao SN, Hu JP, Li Y, Wang XL, Zhang D, Yu SS. A Novel Parkinson's Disease Drug Candidate with Potent Anti-neuroinflammatory Effects through the Src Signaling Pathway. *J Med Chem.* 2016, 59(19), 9062-9079. DOI: <https://doi.org/10.1021/acs.jmedchem.6b00976>
65. Aguirre G, Boiani M, Cerecetto H, Fernandez M, Gonzalez M, Leon E, Pintos C, Raymondo, S, Arredondo C, Pacheco JP, Basombrio MA. Furoxan derivatives as cytotoxic agents: preliminary in vivo antitumoral activity studies. *Die Pharmazi*, 2006, 61, 54-59.
66. Boiani M, Cerecetto H, González M, Risso M, Olea-Azar C, Piro OE, Castellano EE, Lopez de Cerain A, Ezpeleta O, Monge-Vega A. 1,2,5-oxadiazole N-oxide derivatives as potential anti-cancer agentes : synthesis and biological evaluation. Part IV. *Eur. J. Med. Chem.*, 2001, 36, 771. DOI doi: 10.1016/s0223-5234(01)01265-x.
67. Aguirre G, Boiani L, Cerecetto H, Di Maio R, Gonzalez M, Porcal W, Denicola A, Moeller M, Thomson L, Tortora V. Benzo[1,2-c]1,2,5-oxadiazole N-oxide derivatives as potential antitrypanosomal drugs. Part 3: Substituents-clustering methodology in the search for new active compounds. *Bioorg. Med. Chem.*, 2005, 13, 6324-6335. DOI : <https://doi.org/10.1016/j.bmc.2005.05.020>
68. Galli U, Lazzarato L, Bertinaria M, Sorba G, Gasco A, Parapini S, Taramelli D. Synthesis and antimalarial activities of some furoxan sulfones and related furazans. *Eur. J. Med. Chem.*, 2005, 40, 1335. DOI [10.1016/j.ejmech.2005.05.001](https://doi.org/10.1016/j.ejmech.2005.05.001)
69. Di Paolo V, Fulci C, Rotili D, De Luca A, Tomassi S, Serra M, Scimeca M, Geroni C, Quintieri L, Caccuri A. M. Characterization of water-soluble esters of nitrobenzoxadiazole-based GSTP1-1 inhibitors for cancer treatment. *Biochem. Pharm.* 2020, 78, 114060. DOI [10.1016/j.bcp.2020.114060](https://doi.org/10.1016/j.bcp.2020.114060)
70. Kenwood BM, Weaver J L, Bajwa A, Poon IK, Byrne FL, Murrow BA, Calderone JA, Huang L, Divakaruni AS, Tomsig JL, Okabe K, Lo RH, Coleman GC, Columbus L, Yan Z, Saucerman JJ, Smith JS, Holmes JW, Lynch KR, Ravichandran KS, Uchiyama S, Santos WL, Rogers GW, Okusa MD, Bayliss DA, Hoehn KL. Identification of a novel mitochondrial uncoupler that does not depolarize the plasma membrane. *Mol. Metab.* 2014, 3, 114–123. DOI: <https://doi.org/10.1016/j.molmet.2013.11.005>
71. Childress ES, Salamoun JM, Hargett SR, Alexopoulos SJ, Chen S-Y, Shah DP, Santiago-Rivera J, Garcia CJ, Dai Y, Tucker SP, Hoehn KL, Santos WL. [1,2,5]Oxadiazolo[3,4-b]pyrazine-5,6-diamine Derivatives as Mitochondrial Uncouplers for the Potential Treatment of Nonalcoholic Steatohepatitis. *J Med Chem.* 2020, 63(5), 2511-2526. DOI: <https://doi.org/10.1021/acs.jmedchem.9b01440>
72. Steeneck C, Kinzel O, Anderhub S, Hornberger M, Pinto S, Morschhaeuser B, Braun F, Kleymann G, Hoffmann T. Discovery of Hydroxyamidine Based Inhibitors of IDO1 for Cancer Immunotherapy with Reduced Potential for Glucuronidation. *ACS Med Chem Lett.* 2020, 11(2), 179-187. DOI: <https://doi.org/10.1021/acsmchemlett.9b00572>
73. Katoh M, Matsui T, Okumura H, Nakajima M, Nishimura M, Naito S, Tateno C, Yoshizato K, Yokoi T. Expression of human phase ii enzymes in chimeric mice with humanized liver. *Drug Metab. Dispos.* 2005, 33, 1333–1340. DOI: [10.1124/dmd.105.005157](https://doi.org/10.1124/dmd.105.005157)

74. Sanoh S, Ohta S. Chimeric mice transplanted with human hepatocytes as a model for prediction of human drug metabolism and pharmacokinetics. *Biopharm. Drug Dispos.* 2014, 35, 71–86. DOI [10.1002/bdd.1864](https://doi.org/10.1002/bdd.1864)
75. Song X, Sun P, Wang P, Guo W, Wang Y, Meng L-H, Liu H. Design, synthesis, and biological evaluation of 1,2,5-oxadiazole-3-carboximidamide derivatives as novel indoleamine-2,3-dioxygenase 1 inhibitors. *Eur. J. Med. Chem.* 2020, 189, 112059. DOI [10.1016/j.ejmech.2020.112059](https://doi.org/10.1016/j.ejmech.2020.112059)
76. Wan Q, Deng Y, Huang Y, Yu Z, Wang C, Wang K, Dong J, Chen Y. Synthesis and Antitumor Evaluation of Novel Hybrids of Phenylsulfonylfuroxan and Estradiol Derivatives. *Chem. Open.* 2020, 9(2), 176-182. DOI: <https://doi.org/10.1002/open.201900228>
77. Rasul MG. Synthesis of Oxadiazole Derivative of Pentacyclic Triterpenoid and Its Biological activity. *Orient J Chem.* 2019, 35(3), 1143-1147. DOI [10.13005/ojc/350331](https://doi.org/10.13005/ojc/350331)
78. Cena C, Bertinaria M, Boschi D, Giorgis M, Gasco A. Use of the furoxan (1,2,5-oxadiazole 2-oxide) system in the design of new NO-donor antioxidant hybrids. *ARKIVOC.* 2006, 7, 301-309. DOI [10.3998/ark.5550190.0007.722](https://doi.org/10.3998/ark.5550190.0007.722)
79. Frizon TEA, Vieira AA, da Silva FN, Saba S, Farias G, de Souza B, Zapp E, Lôpo MN, Braga HC, Grillo F, Curcio SF, Cazati T. Synthesis of 2,1,3-Benzoxadiazole Derivatives as New Fluorophores-Combined Experimental, Optical, Electro, and Theoretical Study. *Front Chem.* 2020, 12,360. DOI: <https://doi.org/10.3389/fchem.2020.00360>.
80. Gorohmaru H, Thiemann T, Sawada T, Takahashi K, Nishi-i K, Ochi N, Kosugi Y, Mataka S. Preparation of 4,7-Dihetaryl-1,2,5-oxadiazolo[3,4-c]pyridines as Red Fluorescent Materials. *Heterocycles.* 2002, 56, 421. DOI [10.3987/COM-01-S\(K\)64](https://doi.org/10.3987/COM-01-S(K)64)
81. Sarlauskas J, Anusevicius Z, Misiunas A. Benzofuroxan (Benzo[1,2-c]1,2,5-oxadiazole N-oxide) Derivatives as Potential Energetic Materials: Studies on Their Synthesis and Properties. *C. Eur. J. Ener. Mat.*, 2012, 9(4), 365-386. ISSN 1733-7178
82. Wilson RA, Talbot NJ. Fungal physiology – a future perspective. *Microbiology.* 2009, 155, 3810–3815. DOI: <https://doi.org/10.1099/mic.0.035436-0>
83. Cerecetto H, Dias E, Di Maio R, Gonzalez M, Pacce S, Saenz P, Seoane G, Suescun L, Mombro A, Fernandez G, Lema M, Villalba J. Synthesis and Herbicidal Activity of N-Oxide Derivatives. *J. Agric. Food Chem.* 2000, 48, 2995. DOI [10.1021/jf9904766](https://doi.org/10.1021/jf9904766)
84. Fernandez LA, Santo MR, Reta M, Giacomelli L, Cattana R, Silber JJ, Risso M, Cerecetto H, Gonzalez M, OleaAzar C. Relationship Between Physicochemical Properties and Herbicidal Activity of 1,2,5-Oxadiazole N-Oxide Derivatives. *Molecules* 2005, 10, 1197-1208. DOI [10.3390/10091197](https://doi.org/10.3390/10091197)
85. Wang L, Cong L, Zhang Y, Qiao C, Ye Y. Synthesis and Biological Evaluation of Benzofuroxan Derivatives as Fungicides against Phytopathogenic Fungi. *J. Agric. Food Chem.* 2013;61:8632–8640. DOI: <https://doi.org/10.1021/jf402388x>
86. Yusupova LM, Garmonov YS, Zakharov MI, Bykov RA.; Falyakhov, F. I.; Garipov, V. T. Fungicidal and toxicological properties of functionally substituted nitrobenzofuroxanes. *Pharm. Chem. J.* 2008, 42 (4), 183–185. DOI [10.1007/s11094-008-0097-7](https://doi.org/10.1007/s11094-008-0097-7)

87. Koga T, Takase A, Yasuda S, Yamashita S, Gorohmaru H, Thiemann T, Mataka H. Fluorescence spectroscopic characterization of 4,7-bis(2-thienyl)-1,2,5-oxadiazolo[3,4-c]pyridine; lead structure of new red-emitting EL material. *Chem. Phys. Letters*. 2002, 354, 173-178. DOI [10.1016/S0009-2614\(02\)00147-1](https://doi.org/10.1016/S0009-2614(02)00147-1)
88. Klapötke TM, Witkowski TG. Nitrogen-Rich Energetic 1,2,5-Oxadiazole-Tetrazole – Based Energetic Materials. *Propellants, Explosives, Pyrotechnics*. 2015, 40(3), 366-373. DOI [10.1002/prop.201400294](https://doi.org/10.1002/prop.201400294)
89. Zhao Z, Yin Z, Chen H, Guo Y, Tang Q, Liu Y. Novel benzo[c][1,2,5]oxadiazole-naphthalenediimide based copolymer for high-performance air-stable n-type field-effect transistors exhibiting high electron mobility of  $2.43 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ . *J. Mater. Chem. C*. 2017, 5, 2892-2898. DOI [10.1039/C6TC05659H](https://doi.org/10.1039/C6TC05659H)
90. Xu Z, Yang H. Novel Energetic Compounds Based on 3-Methyl-1,2,5-Oxadiazole 2-Oxide *Journal of Energetic Materials*. 2018, 36, 29-35. DOI [10.1080/07370652.2017.1302519](https://doi.org/10.1080/07370652.2017.1302519)
91. Fershtat LL, Makhova NN. 1,2,5-Oxadiazole-Based High-Energy-Density Materials: Synthesis and Performance. *Chempluschem*. 2020, 85(1), 13-42. DOI: [10.1002/cplu.201900542](https://doi.org/10.1002/cplu.201900542)
92. Yu Q, Chinnam AK, Yin P, Imler GH, Parrish DA, Shreeve JM. Finding furoxan rings. *J Mater Chem A*. 2020, 8(12), 5859-5864. DOI: [10.1039/D0TA01538E](https://doi.org/10.1039/D0TA01538E)
93. Zhu W, Ye Z, Dong Z. Nitramino-furazan-functionalized fused high-nitrogen backbones as energetic materials with high detonation performance and good molecular stabilities. *New J. Chem*. 2019, 43(41), 16300-16304. DOI: [10.1039/C9NJ03636A](https://doi.org/10.1039/C9NJ03636A)
94. Xue Q, Bi F-Q, Zhang J-L, Wang Z-J, Zhai L-J, Huo H, Wang B-Z, Zhang S-Y. A Family of Energetic Materials Based on 1,2,4-Oxadiazole and 1,2,5-Oxadiazole Backbones With Low Insensitivity and Good Detonation Performance. *Front. Chem*. 2020, 1-10. DOI: [10.3389/fchem.2019.00942](https://doi.org/10.3389/fchem.2019.00942)
95. Gospodinov I, Hermann TB, Klapötke TM, Stierstorfer J. Energetic Compounds Based on 3,4-Bis(4-nitramino-1,2,5-oxadiazol-3-yl)-1,2,5-furoxan (BNAFF). *Propellants, Explosives, Pyrotechnics*. 2018, 43, 4, 355-363. DOI: [10.1002/prop.201700289](https://doi.org/10.1002/prop.201700289)
96. Hermann TS, Klapötke TM, Krumm B. Formation and Characterization of Heavy Alkali and Silver Salts of the 4-Nitro-pyrazolo-(3,4-c)-furazan-5-N-oxide Anion. *Propellants, Explosives, Pyrotechnics*, 2017, 42, 1-9. DOI: <https://doi.org/10.1002/prop.201700170>
97. Chen P, Dou H, He C, Pang S. Boosting the Energetic Performance of Trinitromethyl-1,2,4-oxadiazole Moiety by Increasing Nitrogen-Oxygen in the Bridge. *Int. J. Mol. Sci*. 2022, 23(17), 10002; <https://doi.org/10.3390/ijms231710002>
98. Liu L, Yao Z, Wang S, Xie T, Wu G, Zhang H, Zhang P, Wu Y, Yuan H, Sun H. Syntheses, Biological Evaluations, and Mechanistic Studies of Benzo[c][1,2,5]oxadiazole Derivatives as Potent PD-L1 Inhibitors with In Vivo Antitumor Activity. *J Med Chem*. 2021, 64(12):8391-8409. doi: [10.1021/acs.jmedchem.1c00392](https://doi.org/10.1021/acs.jmedchem.1c00392).