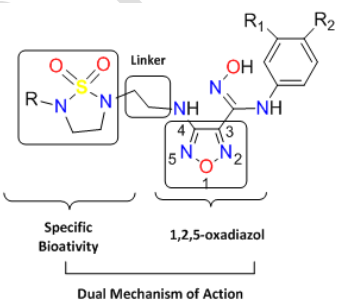
SYNTHESIS, BIOLOGICAL ACTIVITY AND APPLICATIONS OF 1,2,5-OXADIAZOL: A BRIEF REVIEW

ABSTRACT

Oxadiazoles are heterocyclic compounds that belong azole class which contain two nitrogen atoms and one oxygen, forming a five-membered heterocyclic ring. Four isomers of oxadiazole are found. Four isomers of oxadiazoles are described in the literature. Among these, 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole have several applications biological. Compounds of this type have been used in the treatment of various diseases in both humans and animals.Among the immense class of heterocycle compounds with important biological activities already identified, the 1,2,5-oxadiazoles have stood out for the wide variety of applications in medicinal chemistry, in material, 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.

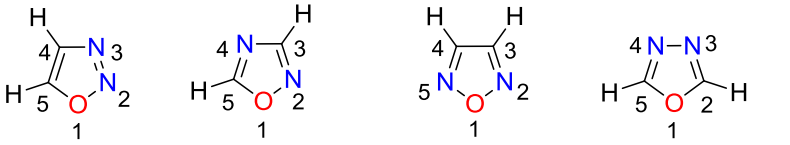
Graphical Abstract



1. INTRODUCTION

“Heterocyclics are an important class of organic compounds of great importance for organic and medicinal chemistry”. [1-9]. On the other hand, various products of natural origin, drugs, and medicines have heterocyclic moieties that are

essential for their manifold properties. According to Cabrele and Reiser [10], stereoselective synthesis, using auxiliaries or catalysts, is essential for electronic and steric control at the formation of the heterocyclic ring.
Oxadiazoles are a class of heterocyclic compounds that attracted attention due to their varieties of applications in medicinal and materials chemistry [11]. “Are heterocyclic compounds which contain two nitrogen atoms, one oxygen, and two carbon atoms. Oxadiazole rings can exist in different isomeric forms” (Figure 1) [12].



1,2,3-oxadiazole 1,2,4-oxadiazole 1,2,5-oxadiazole 1,3,4-oxadiazole

Fig. 1. Constitutional isomers of oxadiazoles.

According to Eicher and collaborators [13], the isomeric 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole can be encountered in molecules already marketed drugs 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 it is used at the treatment of cystic fibrosis and zibotentan **3**, as an anticancer agent [15]. On the other hand, according to literature, compound **4** [16], in the chemistry of materials for the construction of Organic Light Emitting Diodes (OLEDs) [17] or highly energetic materials [18] compounds of type **5** in the form of salts, is used in the form energetic organic salts. .

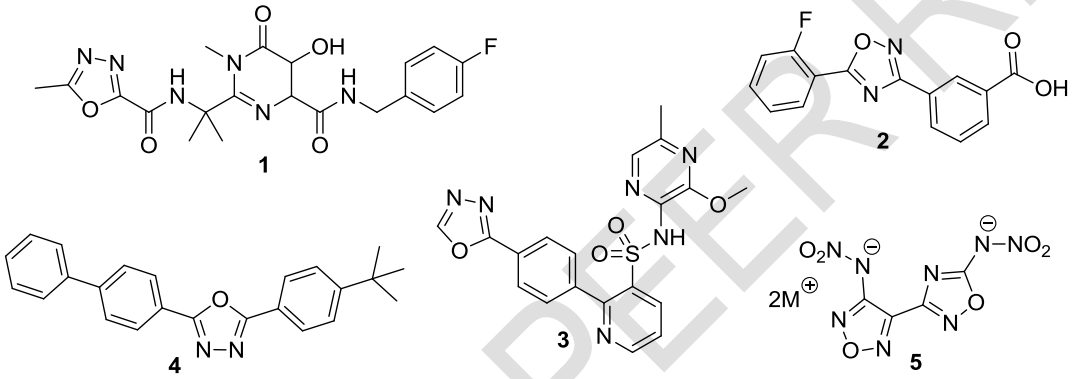


Fig. 2. Examples of oxadiazoles used as drugs and materials chemistry.

“1,2,5-Oxadiazole derivatives are found to be potent inhibitors of indoleamine 2,3-dioxygenase and are used in the treatment of cancer and other disturbance. They are also useful as a class of SENP2 inhibitors and can be used for the development of novel therapeutic agents for various diseases targeting SENPs” [19-23]. “In 2014, was reported a new class of SENP2 inhibitors identified by a combination of structure-based virtual screening and quantitative FRET-based assay” [24]. The 1,2,5-oxadiazoles were utilized to check their ability to inhibit SENP2 activity at a lower concentration of 30 μM. Among these five out of eight compounds tested to contain a ring of 1,2,5-oxadiazoles (compounds **6, 7, 8, 9,** and **10**) which represents a novel chemical class displaying activity against SENP2. The chemical structures of **6, 7, 8, 9,** and

10 are presented in Figure 3.

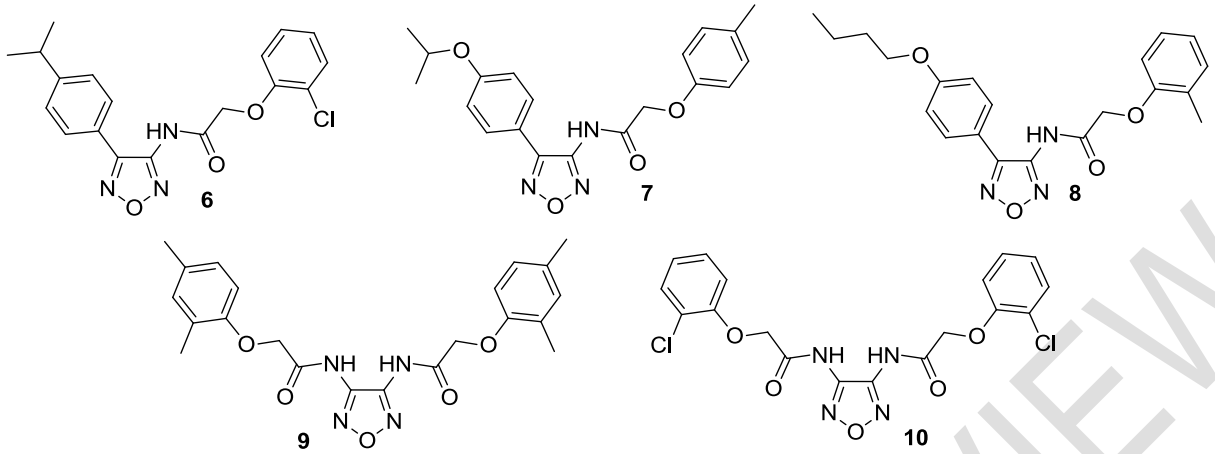


Fig. 3. Chemical structures of 1,2,5-oxadiazoles that present activities against SENP2.

"1,2,5-oxadiazole-2-oxides is a class of NO donors" [25]. "The NO donor is a potent antimicrobial agent. Together with ROI (reactive oxygen intermediates), NO is the toxic mediator released by macrophages against pathogens. NO-mediated cellular toxicity if you must 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, an etiological agent that causes human malaria" [26]. "On the other side, due to this 1,2,5-oxadiazoles also show cytotoxicity [27], mutagenicity, immunosuppression, muscle relaxant properties, anticonvulsive activity, oxidase inhibition, 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.

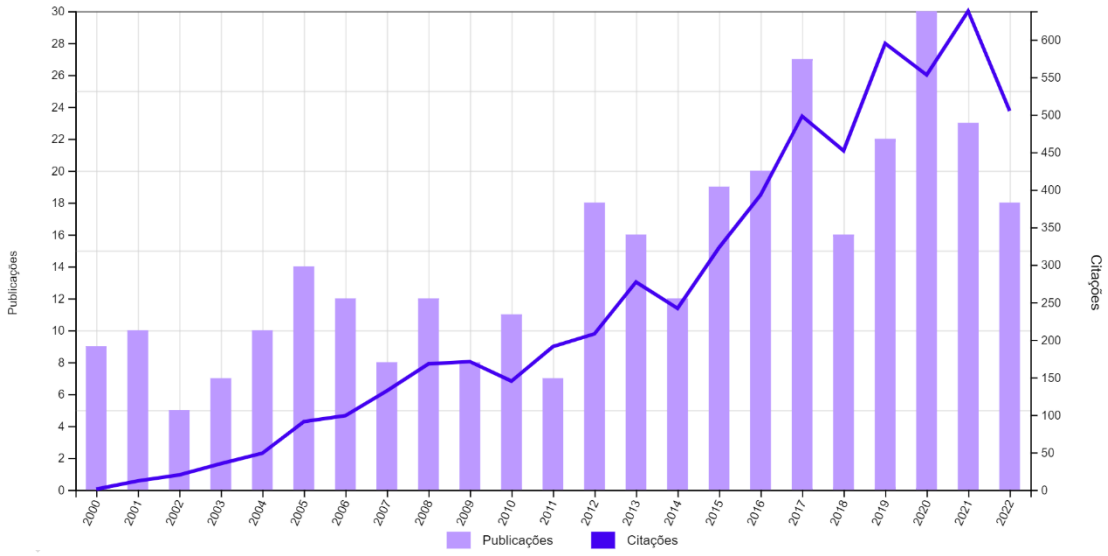
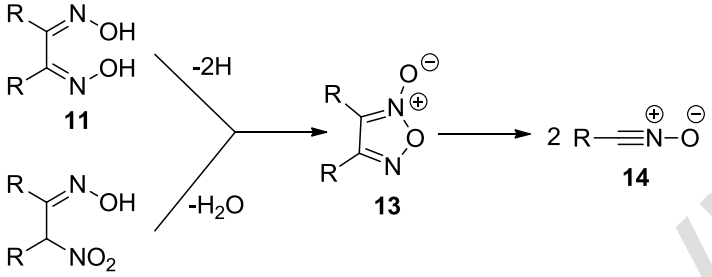


Fig. 4. Number of articles published and of citations on in application and synthesis of 1,2,5-oxadiazoles between 2000-2022.

We describe herein a survey of literature on the progress in the synthesis of 1,2,5-oxadiazoles and derivatives and your application in bioactive molecules or the chemistry of new functional materials.

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

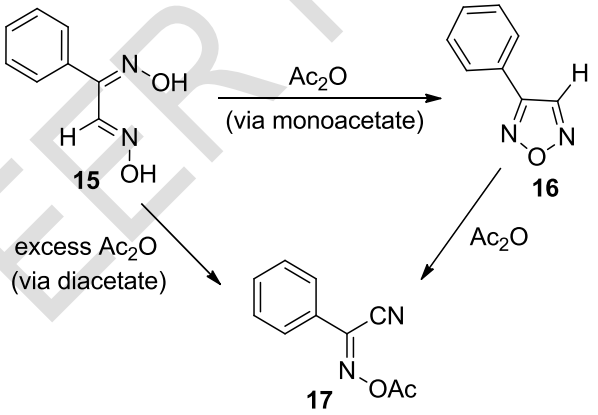
Synthetic procedures to obtain oxadiazole usually utilize the dehydrative cyclization of bis-oximes, at high temperatures [28] and often use different activating reagents [29]. The synthesis of new 1,3,4-oxadiazoles has attracted very researcher attention. This interest stems from the fact many 1,2,5-oxadiazole 2-oxide derivatives present 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 obter by various methods, such as: (1) the oxidative cyclization of 1,2-dioximes **11**; (2) the dehydration of nitroketoximes **12** and symmetrically substituted furoxans **13**; and (3) the dimerization of nitrile oxides**14** (Scheme 1)



[30].

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

Though mono- and disubstituted 1,2,5-oxadiazoles are well known, unsubstituted there are few synthesized. The synthesis of the 1,2,5-oxadiazoles unsubstituted was reported by Olofson and co-workers [31]. Its synthesis consisted of heating phenylglyoxime in acetic anhydride (1 equiv) to provide phenylfurazan with 87% yield (Scheme 2). However, when phenylglyoxime **15** was heated with 4 equiv of acetic anhydride, was produced a mixture of 27% phenylfurazan **16**



and 58% of oxime acetate (**17**).

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

"For oxadiazole 2-oxide rings were performed Ab initio calculations, correlations of molecules geometries, spectroscopic data with chemical properties, and quantitative structure-activity relationships. The latest investigations have shown that DFT methods can provide reliable tools for the prediction of geometries and energies of a variety of organic (and inorganic) compounds, especially in those cases where classical Hartree-Fock (HF) methods fail" [32-34]. "The DFT method was used to study the dipole moments, polarizability, and hyperpolarizabilities of azoles, including 1,2,5-oxadiazole" [35].

DFT was used to calculate the heat of formation and infrared vibrational frequencies of twelve 1,2,5-oxadiazole 2-oxide rings **18-29** (Figure 5). "The 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 coupling in a 1,2,5-oxadiazole 2-oxide rings" [36,37].

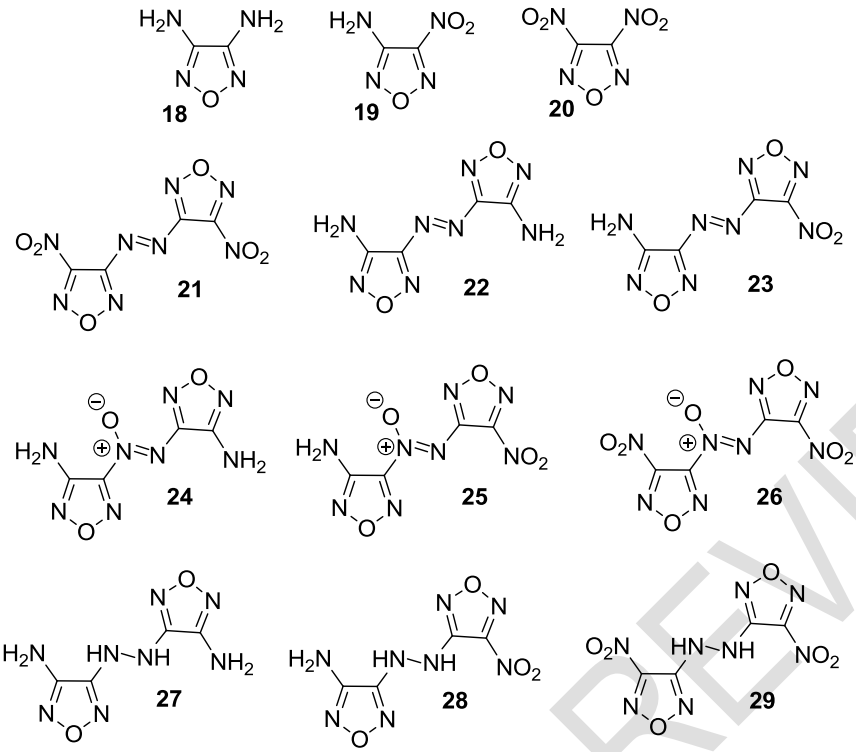
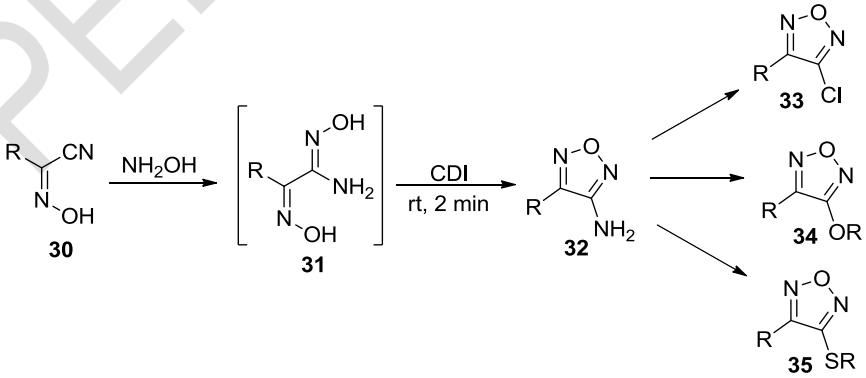


Fig. 5. Ab initio calculations, correlations of geometries, and spectroscopic data of oxadiazole 2-oxide rings..

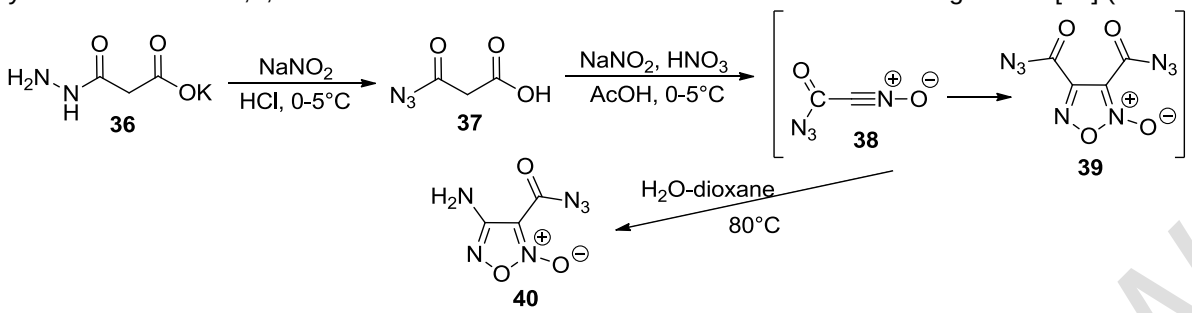
According to Neel and Zhao [38], "1,1′-Carbonyldiimidazole can be used to synthesize a variety of 3,4-disubstituted 1,2,5-oxadiazoles (furazans) from bisoximes at ambient temperature. The synthesis involves two steps (1) hydroxylamine addition a cyano-oximes to afford the bisoximes in situ and (2) CDI-induced cyclodehydration to provide furazans. Cyano-oxime **30** underwent hydroxylamine addition and subsequent CDI-induced cyclization of **31** to provide the 1,2,4-oxadiazoles **32** in yield ranging from 56-85% (Scheme 3)". According to the authors, the method was shown to be both more tolerant and safer. On the other hand, conditions were developed that allowed the synthesis of chlorofurazans in high-yielding from their amino counterparts.



Scheme 3. Synthesis of 1,2,5-oxadiazoles from Cyano-oxime **30**.

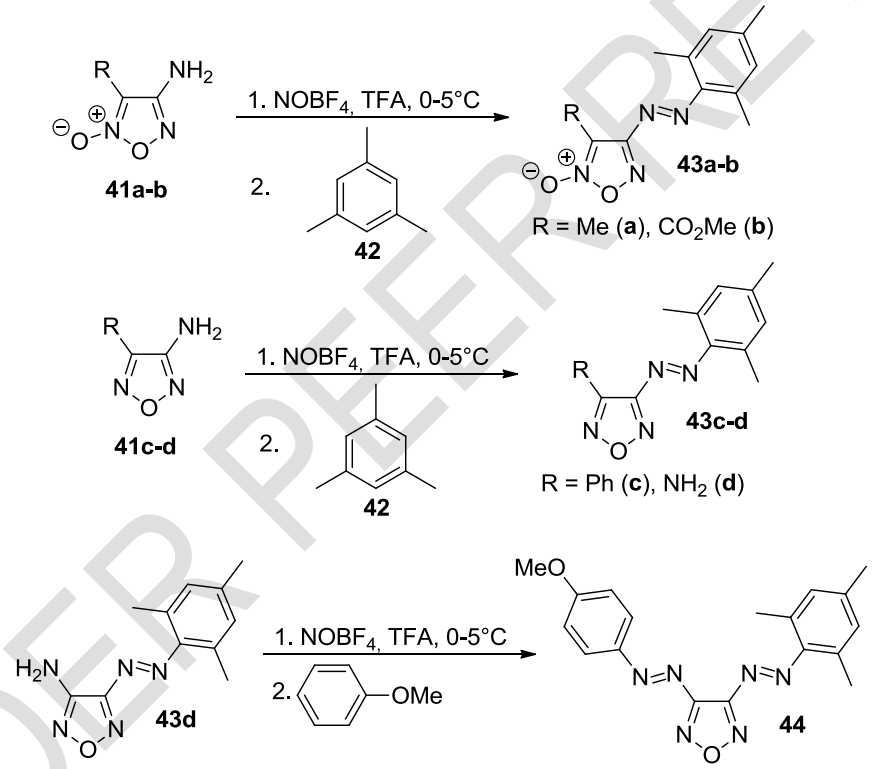
"The most known methods for the 1,2,5-oxadiazole 2-oxide ring construction consist of cyclodimerization of nitrile oxides, oxidation of vic-glyoximes, and dehydration of a-nitrooximes" [39]. "Several examples of alkene reactions result in the 1,2,5-oxadiazole 2-oxide ring formation" [40, 41]. "In recent years, new methods for furoxan synthesis were described. 1,2,5-oxadiazole 2-oxide 39 was synthesized through the cycloaddition of azido-carbonylformonitrile oxide **38** generated via nitrosation of potassium monohydrazinyl malonate **36** to azido-carbonylmalonic acid **37** followed of nitrosation/nitration/ decarboxylation under the action of $NaNO_2$ in HNO_3. However, 1,2,5-oxadiazole 2-oxide **39**, was

quickly transformed into 1,2,5-oxadiazole 2-oxide derivative **40** via the Curtius rearrangement" [42] (Scheme 4).



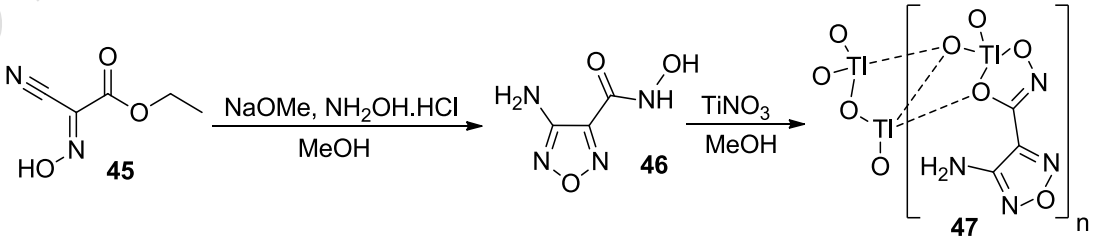
Scheme 4. Synthesis method of 1,2,5-oxadiazole 2-oxide.

To develop a method of preparation of stable 1,2,5-oxadiazolyl diazonium salts various diazotization conditions were investigated by Zhilin *et al* [43]. The optimal conditions were extended for a series of other amino-1,2,5-oxadiazoles **41a-d** which after reaction resulted in the formation of azo compounds **43a-d**. The reaction proceeded even with the addition of a second substituent at the 1,2,5-oxadiazole ring (either furazan or furoxan, Scheme 5). In addition, in the case of 3,4-diaminofurazan **41d**, a diazotization and subsequent azo coupling occurred resulting in the formation of azo derivative **43d.** The amino group in compound **43d** was involved in the Tandem diazotization/azo coupling sequence affording the formation of bis(aryldiazenyl)furazan **44** (Scheme 5).



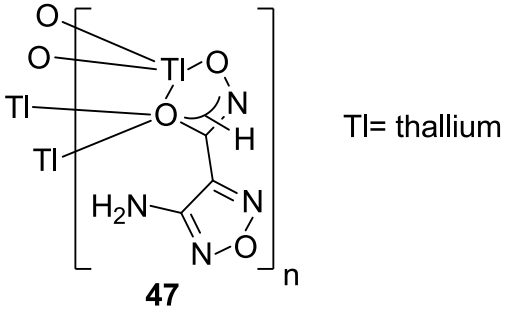
Scheme 5. Formation of bis(aryldiazenyl)furazan 44 from Tandem diazotization/azo coupling sequence.

In 2018, the compound poly[(3-4-amino-1,2,5-oxadiazole-3-hydroxamate) thallium(I)] **47** was obtained according to the procedure reported by Neel and co-workers (Scheme 6) [38]. The reaction of the introduction of a hydroxamic group of **45** at the 1,2,5-oxadiazole ring **46** allowed the synthesis of various polynuclear complexes [44].



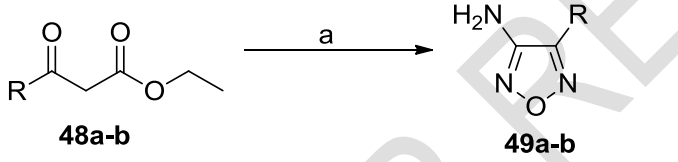
Scheme 6. Synthesis of various polynuclear complexes from **46**.

"The compound poly[(3-4-amino-1,2,5-oxadiazole-3-hydroxamate) thallium(I)], was analyzed by X-ray crystallography" [45]. In the crystal, the deprotonated hydroxamate group represents an intermediate between the keto/enol tautomers and forms a five-membered chelate ring with the thallium(I) cation. According to Safyanova et al [45], "the coordination sphere of the cation is augmented to a distorted disphenoid by two monodentate binding O atoms from two adjacent anions, leading to the formation of zigzag chains extending parallel to the b-axis. The consistency within the chains is supported by π–π stacking [centroid–centroid distance = 3.746 (3) Å] and intermolecular N—H···N hydrogen bonds"



47

Fig. 6. X-ray crystallography of substituted 1,2,5-oxadiazole.To explore the role of the methyl substituent on the oxadiazole, a series of analogs were prepared with alternative functionality on the heterocyclic [46]. The 4-phenyl-1,2,5-oxadiazol-3-amine (**49a-b**) was synthesized from ethyl benzoyl acetate **48a-b** in a one-pot reaction as described by Sheremetev [47] (Scheme 7).



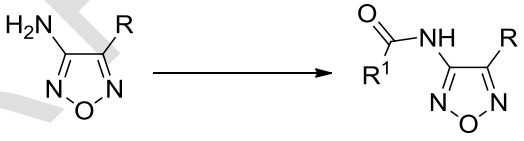
48a-b **49a-b**

R = Ph (**a**), Propyl (**b**)

Reaction conditions: (a) One pot reaction over 3 days;
1. NaOH, H2O, 10 °C-rt.
2. $NaNO_2$, 20% HClO4, 10 °C-rt.
3. NaOH, $NH_2OH.HCl$, 90 °C, urea, reflux

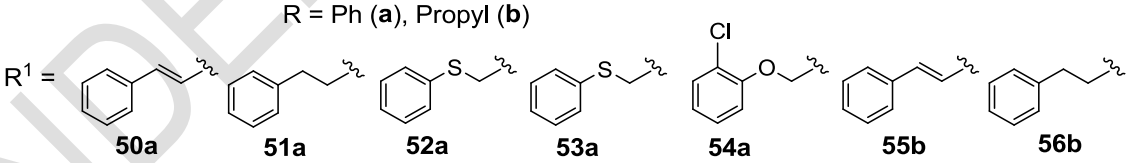
Scheme 7. Synthesis one-pot of 4-phenyl-1,2,5-oxadiazol-3-amine.

The same authors [47] reported the coupling of compound **49a** with five different acids, using of phosphorus pentachloride, produced the compounds **50a–54a** (Scheme 8). Additionally, two oxadiazole analogs **55b** and **56b** were prepared to check the influence of a long chain if the 4-phenyl group was not accepted.



49a-b **50-56a-b**

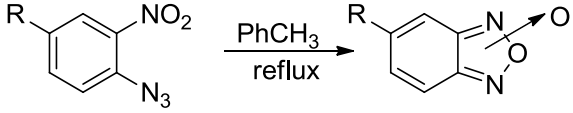
R = Ph (**a**), Propyl (**b**)



50a **51a** **52a** **53a** **54a** **55b** **56b**

Scheme 8. Coupling 4-phenyl-1,2,5-oxadiazol-3-amine for produced the compounds **50a–54a.**

According to Aguirre *et al* [48], 1,2,5 oxadiazoles **58a, 58b**, and **58c** were synthesized, using the nitrophenyl azides **57a-c** reactants, by condensation in reflux toluene (Scheme 1). To the same authors reported the results of a study on the use of Hanschs series, cluster methodology, for the formation of new benzo-[1,2-c]1,2,5-oxadiazole-*N*-oxide derivatives as antitrypanosomal compounds.

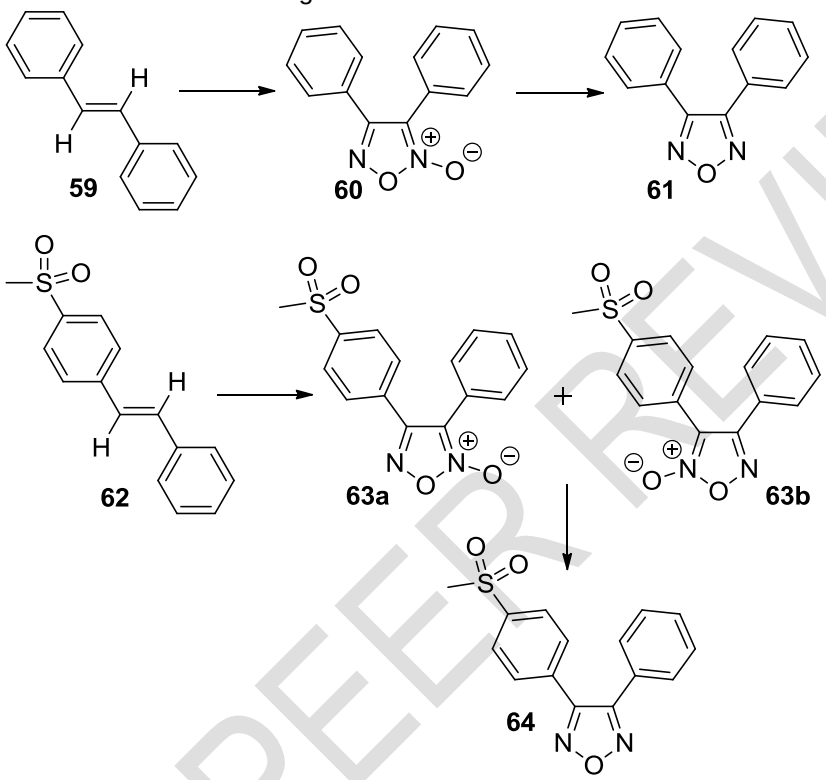


57a-c **58a-c**

R = -NO_2 (**a**), -CHO (**b**), -CO_2H (**c**)

Scheme 9. Synthesis of new benzo-[1,2-c]1,2,5-oxadiazole-*N*-oxide derivatives by cyclocondensation.

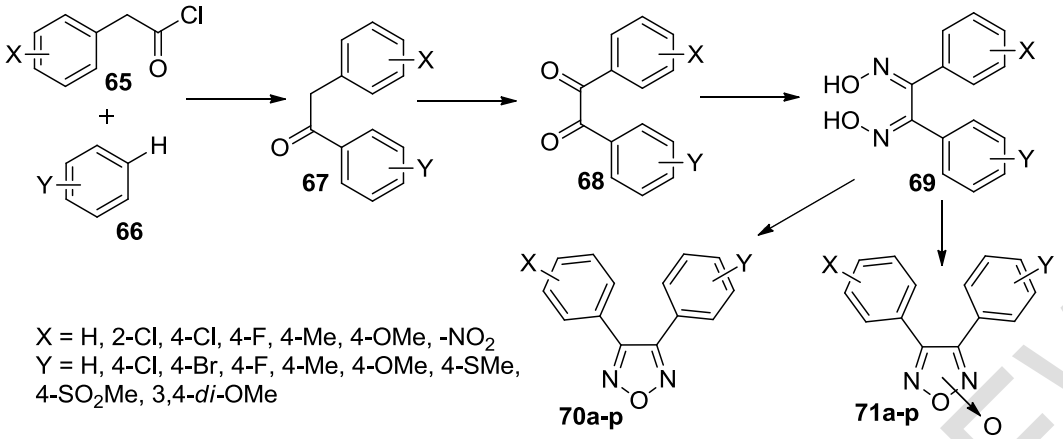
Velázquez *et al* [49], reported "the reaction of (*E*)-1,2-diphenylethene **59** with a saturated aqueous solution of sodium nitrite in a mixture of acetic in 1,4-dioxane, afforded 3,4-diphenyl-1,2,5-oxadiazole-2-oxide **60** in 26% yield (Scheme 1). Similarly, the reaction using (*E*)-1-[4-(methylsulfonyl)phenyl]-2-phenylethene **62** provided a mixture of the 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, the reaction of compound **60**, or the regioisomers **63a,b**, with triethylphosphite at reflux for 19–24h afforded the deoxygenated product 3,4-diphenyl-1,2,5- oxadiazole **61** in yield 70% or 3-[4-(methylsulfonyl)phenyl]-4-phenyl-1,2,5-oxadiazole **64** in yield 84%". Also according to the authors, the 3,4-diphenylfuroxans and the 3,4-diphenylfurazans analogs, were synthesized for in vitro evaluation as hybrid cyclooxygenase (COX) inhibitor/nitric oxide donor agents..



Reagents and conditions:
(i) $NaNO_2$, CH_3CO_2H, 1,4-dioxane, 50-60° C, 6-24 h;
(ii) $(EtO)_3P$, reflux, 19-24 h.

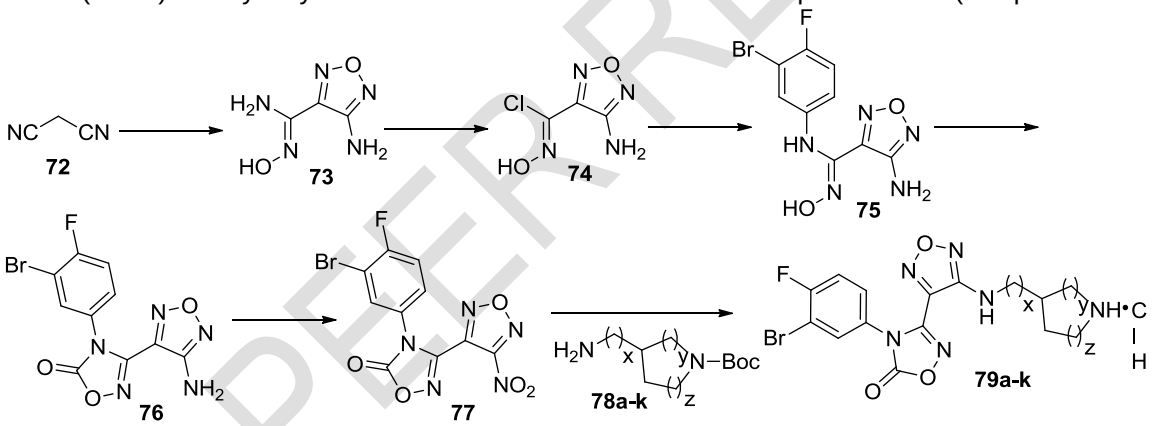
Scheme 10. Synthesis of1,2,5-oxadiazoles from (*E*)-1,2-diphenylethene **59** and (*E*)-1-[4-(methylsulfonyl)phenyl]-2-phenylethene **62**. .

Scheme 10 demonstrates the steps of the synthesis of compounds 3,4-diaryl-1,2,5-oxadiazoles (**70a–p**), 3,4-diaryl-1,2,5-oxadiazole *N*-oxides (**71a–p),** and intermediates **65-69**. According to Yadav *et al* [50], the cyclization of compound **69** to 3,4-diaryl-1,2,5-oxadiazoles (**70a–p**) was realized using different acidic/basic dehydrating agents using succinic anhydride under heating at 180–185 °C. On the other hand, oxidation of **69** was carried out with aqueous sodium hypochlorite solution (20%) to provide 3,4-diaryl-1,2,5-oxadiazole *N*-oxides (**71a–p**).



Scheme 11. Synthesis 1,2,5-oxadiazoles (**70a–p**) and derivatives (**71a–p**).

Song *et al* [51], described that compound **72** was treated with sodium nitrite, hydroxylamine, and hydrochloric acid to provide compound 73 (Scheme 12). Then, a diazotization reaction was performed under acidic conditions using sodium chloride to produce compound **74** in 44% yield. In sequence compound, **74** reacted with 3-Br-4-phenylamine to provide compound **75**. After that, the oxime group of **75** was protected with carbonyl diimidazole (CDI) which resulted in compound **76** in 74% yield. Then, compound **76** was oxidized to compound **77**. In sequence compound **77** reacted with a variety of amino compounds (**78a-k**) and hydrolyzed under acidic conditions to afford compound **79a-k** (compound **79d**

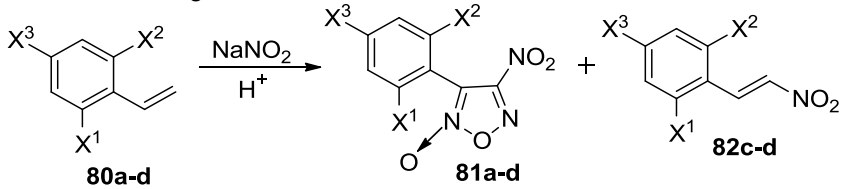


a: x= 1; y= 0; z= 2 (*rac*); **b:** x= 1; y= 0; z= 3 (*rac*); **c:** x= 1; y= 1; z= 1 (*rac*);
d: x= 1; y= 1; z= 2 (*rac*); **e:** x= 1; y= 2; z= 1 (*rac*); **f:** x= 2; y= 1; z= 2 (*rac*);
g: x= 1; y= 0; z= 3 (*S*); **h:** x= 1; y= 1; z= 1 (*S*); **i:** x= 1; y= 1; z= 1 (*R*);
j: x= 1; y= 1; z= 2 (*S*); **k:** x= 1; y= 1; z= 2 (*R*);

obtained in 90% yield).

Scheme 12. Synthesis of 1,2,5-oxadiazole-3-carboximidamide derivatives.

Takayama *et al* [52], reported the synthesis 4-aryl-l,2,5-oxadiazole-3-yl *N,N*-dialkylcarbamate derivatives from styrene (**80a-d**) and sodium nitrite under acidic conditions to yield 3-phenyl-4-nitrofuroxan (**81a**) in 51% yield (Scheme 13). However, compound **80d** provided the furoxan derivative **81c** in 16% yield and compound **82c** (non furoxanoid) in 28% yield. ^{1}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, compound 80d provided compounds **81d** and **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

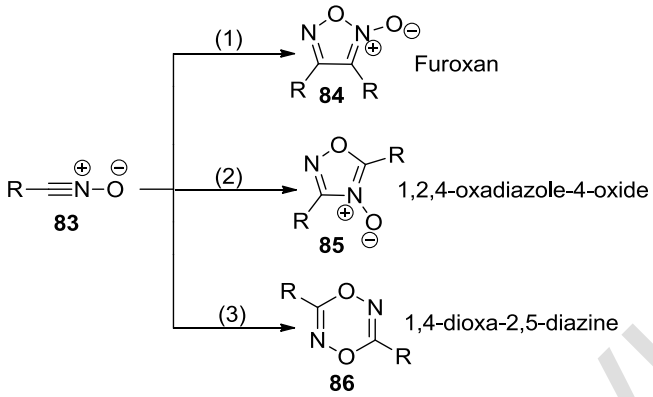


a: $X^1 = X^2 = X^3 = H$; **b:** $X^1 = Cl$, $X^2 = X^3 = H$;
c: $X^1 = X^2 = Cl$, $X^3 = H$ **d:** $X^1 = X^2 = X^3 = CH_3$;

furoxan derivatives.

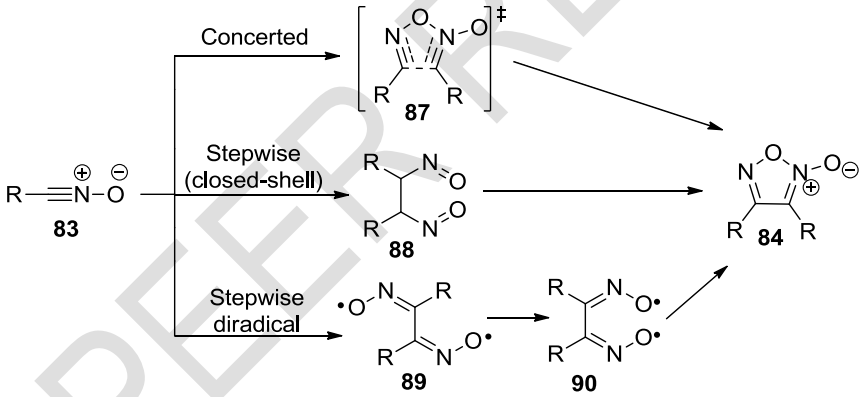
Scheme 13. Synthesis of 1,2,5-oxadiazole derivatives from styrene.

According to Yu and collaborators [53], “nitrile oxides are used in 1,3-dipolar cycloadditions to provide five-membered ring heterocycles. Nitrile oxides (mainly aliphatic nitrile oxide and acyl nitrile oxide) dimerize to form 1,2,5-oxadiazole-2-oxides, known as furoxans or furazan oxides (reaction 1 in Scheme 14). Under acidic or basic conditions, nitrile oxides can also dimerize to provide either 1,2,4-oxadiazole-4-oxides or symmetric 1,4-dioxa-2,5-diazines (reactions 2 and 3 in Scheme 14).



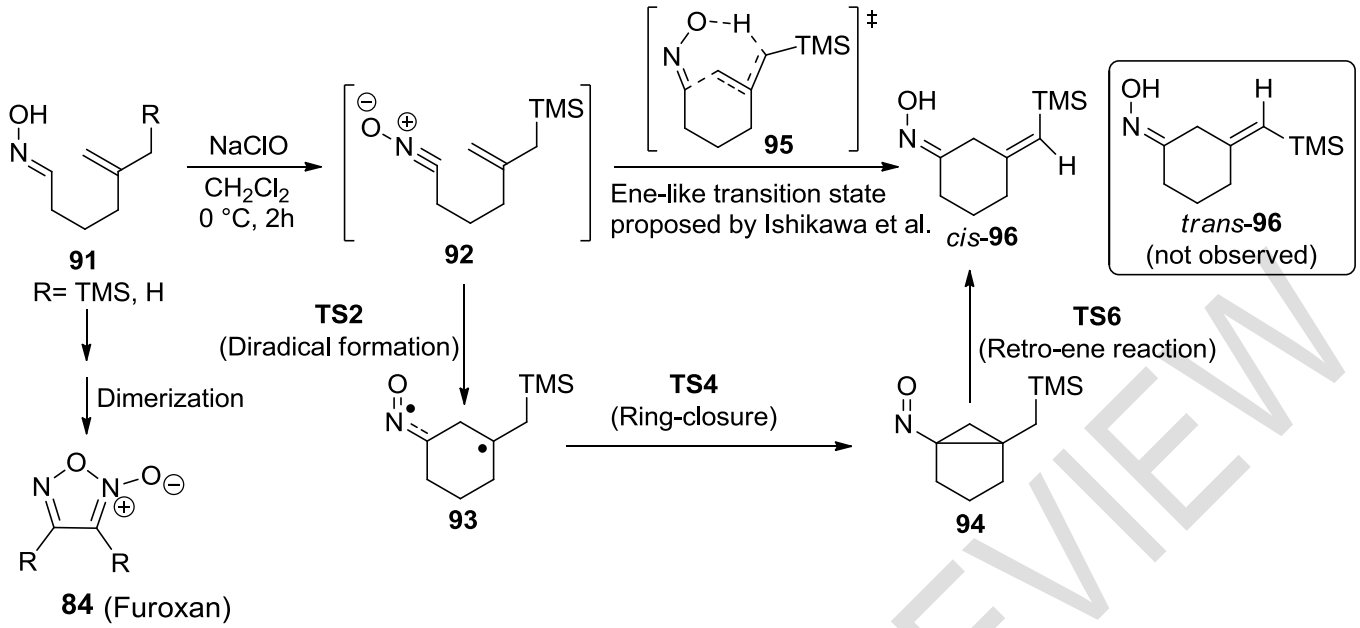
Scheme 14. The route by synthesis of 1,2,5-oxadiazole derivatives”..

According to the same authors, two paths have been proposed for the dimerization of nitrile oxide **83** to furoxans **84** (obtained from intermediaries **87, 88, 89**, and **90**). The accepted mechanism for the reaction consists in a 1,3-dipolar cycloaddition, where a nitrile oxide acts as a dipole while the C-N multiple bonds in the other nitrile oxide act as a dipolarophile (Scheme 15).



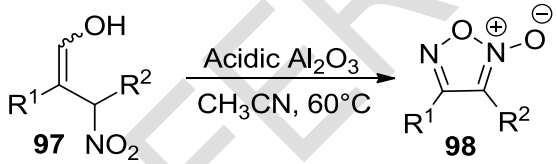
Scheme 15. Proposed mechanism to obtain 1,2,5-oxadiazoles and derivatives.

According Yu and Houk [54], “the density functional theory studies of intramolecular ene-like reactions between nitrile oxides and alkenes show that this reaction is a three-step process that involves a stepwise carbenoid addition of nitrile oxide to form a bicyclic nitroso compound, followed by a retro-ene reaction of the nitroso cyclopropane intermediate **94**. The competitive reactions, either the intramolecular (3+2) reactions between nitrile oxides and alkenes or the intermolecular dimerization of nitrile oxides to form furoxans **84**, can overwhelm the intramolecular 1,3-dipolar ene reactions when the tether bond the nitrile oxide and alkene is elongated or some substituents such as TMS group are absent”. This data is corroborated by those described by Ishikawa *et al* [55].



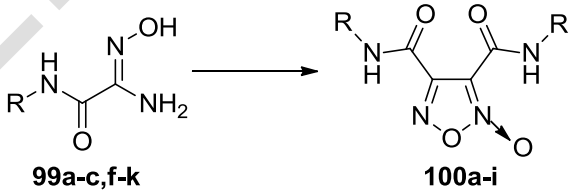
Scheme 16. 1,1-Cycloaddition mechanism to form bicyclic intermediate **94**, followed by a retro-ene reaction to furnish cyclic oxime cis-7.

Curini *et al* [56] described "the synthesis of 1,2,5-oxadiazole *N*-oxides **98** from α-nitro-ketoximes **97** using acidic alumina as a catalyst. According to the authors, acidic alumina is an excellent heterogeneous catalyst for the conversion of α-nitro-oximes into their corresponding 1,2,5-oxadiazoles *N*-oxides (Scheme 17). The reaction was carried out by adding a solution of the α-nitro-oxime in acetonitrile to the suspension of acidic alumina in acetonitrile at 60°C". The reaction takes from 1 to 5 hours and after purification provided the 1,2,5-oxadiazole *N*-oxides derivatives **98** in good yield.



Scheme 17. Synthesis of 1,2,5-oxadiazole N-oxides derivatives.

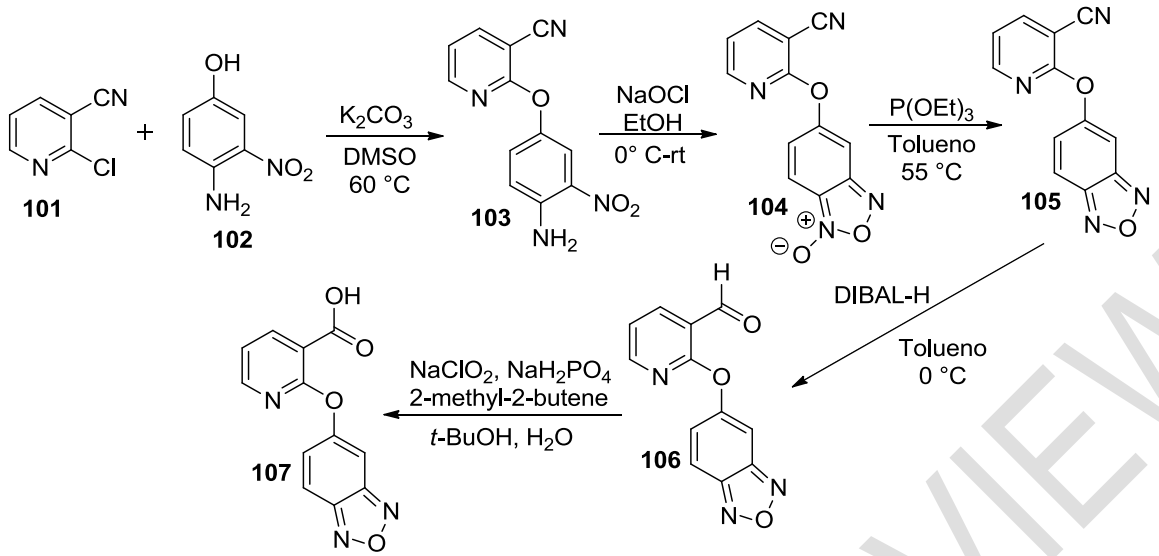
According to Yarovenko *et al* [57], the 1,2,5-oxadiazole *N*-oxides **100a-i** was synthesized from amide oximes **99** in one step through nitrosation in the presence of H_2SO_4 (Scheme 18). Hence, the authors demonstrated for the first time that 1,2,5-oxadiazole *N*-oxides can be prepared by nitrosation of amide oximes. This procedure allows one to synthesize bis-carbamoyl-furoxanes **100a-i** in good yields (60-91%) starting from available compounds..



R = Ph (**99a**, **100a**), 4- $MeOC_6H_4$ (**99g**, **100b**), 3,4-$Cl_2C_6H_3$ (**99c**, **100c**),
4-$NO_2C_6H_4$ (**99h**, **100d**), 2,3-$Me_2C_6H_3$ (**99i**, **100e**), 3-$MeOC_6H_4$ (**99j**, **100f**),
4-ClC_6H_4 (**99f**, **100g**), 4-MeC_6H_4 (**99k**, **100h**), 2,6-$Me_2C_6H_3$ (**99b**, **100i**),

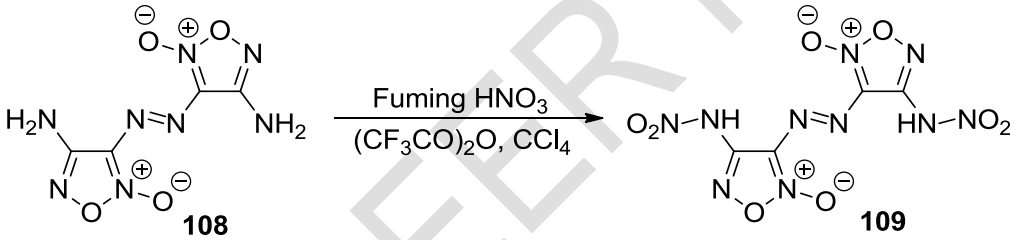
Scheme 18. 1,2,5-oxadiazole-*N*-oxides synthesis by one pot reaction.

According to Ruggeri *et al* [58], 4-amino-3-nitrophenol **102** reacts with 2-chloronicotinonitrile **101** under mild conditions (K_2CO_3, DMSO, 60 ºC to provide the compound **103** in 77% yield (Scheme 19). 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 benzofuran **105** was realized. Compound **105** was isolated in 99% yield. The nitrile **105** and has been reduced with DIBALH to provide intermediate aldehyde 106 in 97% yield. In sequence compound **106** was oxidized with sodium chlorite to obtain acid **107** in a 94% yield.



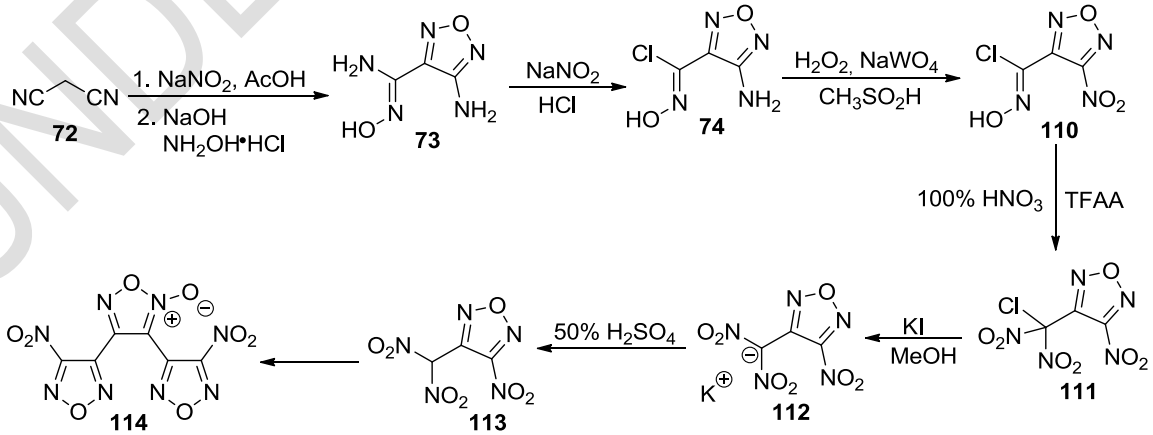
Scheme 19. Synthesis de 1,2,5-oxadiazoles from 4-amino3-nitrophenol **102**.

The nitramine derivatives of 1,2,5-oxadiazole *N*-oxide are precursors for the synthesis of 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] **109**, via nitration of compound **108** using $HNO_3/(CF_3CO)_2O$ in molar ratio 15:3 in CCl_4 at -5 ^{0}C for 0.5 h (Scheme 20). The structure of 3,3´-(diazene-1,2-diyl)-bis[4-(nitroamino)-1,2,5-oxadiazole 2-oxide] 109 was confirmed by means of ^{1}H, ^{13}C, ^{14}N-NMR, IR spectroscopy and high-resolution mass spectra (HRMS).



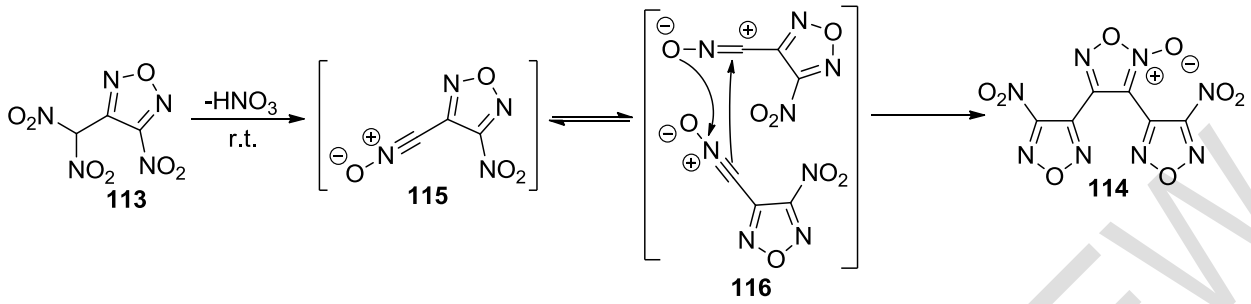
Scheme 20. Synthesis of compound 3,3′-(diazene-1,2-diyl)bis[4-(nitroamino)-1,2,5-oxadiazole 2-oxide] 109.

In 2020, Shreeve *et al* [60] "synthesized compounds **110** and **111** using the methodology described in the literature.[60,61] In sequence. the reaction mixture was stirred at 25 ºC, and heated at 50 ºC for 2 h then was purified to obtain compound **110** in a yield of 70%. Compound **110** was nitrated with 100% nitric acid in trifluoroacetic anhydride (TFAA) at 0 ºC to provide **111** in yield of 60%. Then compound **111** was treated with potassium iodide in methanol to provide **112** in a yield of 70%. Compound **113** was obtained by acidification of **112** with 50% sulfuric acid. Recrystallization of **113** from dichloromethane at room temperature provides compound **114** with a yield of 86.5% (Scheme 20). All compounds were characterized by infrared (IR), ^{1}H, and ^{13}C NMR spectroscopy, and elemental analysis. Crystals compound **113**, was subjected to diffraction single-crystal X-ray diffraction".



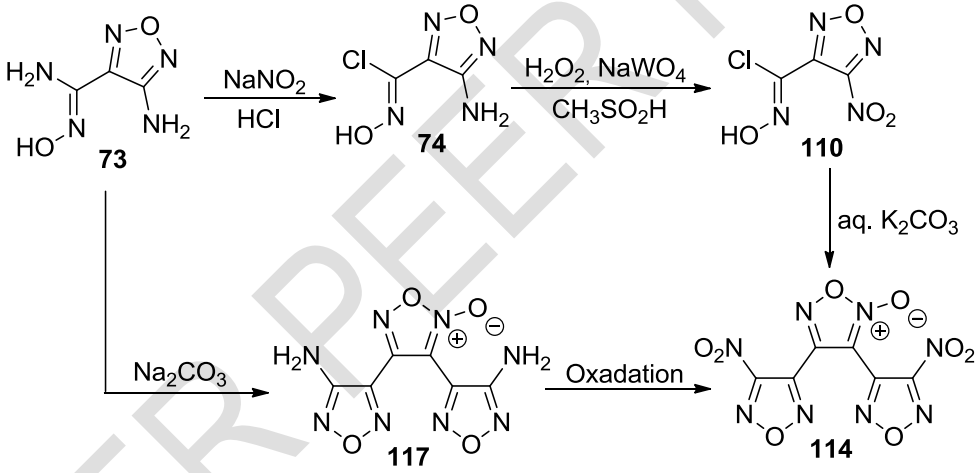
Scheme 21. Synthesis of 3,4-*Bis*(4-nitro-1,2,5-oxadizaol-3-yl)-1,2,5-oxadiazole-*N*-oxide **114**.

Also, according to the same authors [60], “a proposal for a mechanism for the synthesis of **114** is illustrated in Scheme 22. In this, a 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**. In sequence, the two isomers undergo rapid cyclization to form stable 1,2,5-oxadiazole *N*-oxide **114** at 25 ºC”.



Scheme 22. Mechanistic proposal for formation of compound 114.

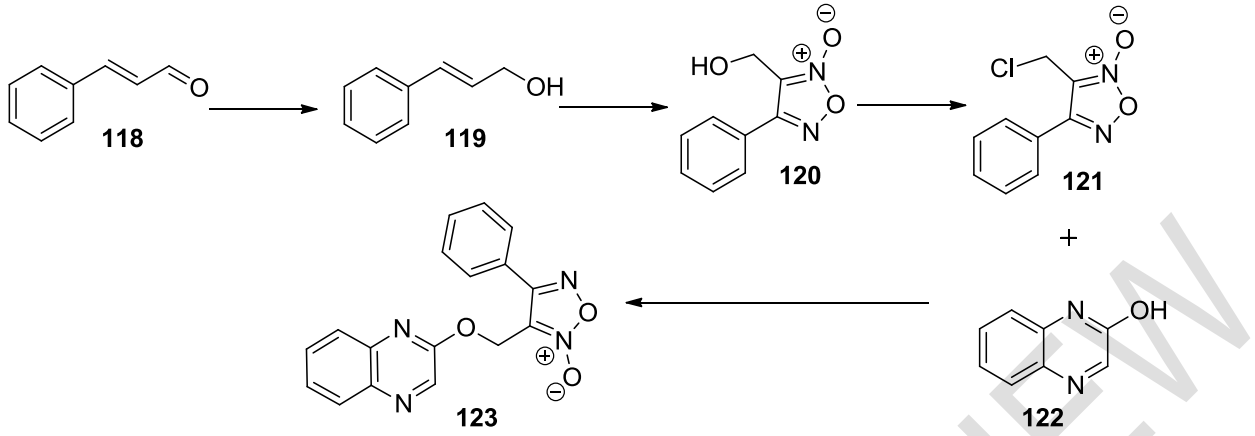
“The synthesis and characterization of 3-chlorocarbohydroxymoyl-4-nitro-1,2,5-oxadiazole and its transformation to dinitro trifurazanoxide were described for the first time” by Duddu *et al* [61]. A synthetic route consisted of the oxidation of compound **74** using aq. 70% H_2O_2 in presence of tungsten-based catalyst $(Bmim)_4W_{10}O_{23}$, initially by stirring the reaction mixture at room temperature, and then heating it at 52°C for 4 h. After purification afforded compound **110** as a pale yellow liquid. Carbon NMR analysis of this liquid showed a resonance at δ 158.71 ppm as a triplet due to the coupling of the nitro group nitrogen with aromatic ring carbon, suggesting the formation of the desired nitro compound **110**. Then compound **110** was reacted with an aq. potassium carbonate solution stirring the reaction mixture at room temperature for 2 h followed by purification to provide the compound **114**. Another synthesis proposal consisted of reacting compound **73** with sodium carbonate to produce compound **117**, which was subjected to an oxidation reaction to provide compound **114**. Compound **114** was characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.



Scheme 23. Synthesis of dinitro trifurazanoxide **114**.

El-Hamouly *et al* [62] reported that cinnamaldehyde **118** was treated with sodium borohydride in methanol at 0°C to provide the cinnamyl alcohol **119** after 2 h of reaction. According to Kumar *et al* [63] “a 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”**. In sequence, the compound **120** com thionyl chloride in presence of pyridine and anhydrous dichloromethane to provides compound 3-(chloromethyl)-4-phenyl-1,2,5-oxadiazole 2-oxide **121** already reported by Wang *et al* [64]. Then, to a solution of **121** and quinoxaline-2-ol **122** in acetone was added anhydrous K_2CO_3 and maintained for 5 h to provide 4-phenyl-3-(quinoxalin-2-yloxy)-1,2,5-oxadiazole 2-oxide **123**

(Scheme 23). Compounds **123** were fully characterized by infrared, ^{1}H and ^{13}C NMR spectroscopy, and LC-MS m/z.



Scheme 24. Synthesis of 4-phenyl-3-(quinoxalin-2-yloxy)-1,2,5-oxadiazole 2-oxide **123.**

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

Derivatives of 1,2,5-ozadiazole and derivatives have a wide spectrum of applications. First, they are used as starting materials in organic synthesis and medicinal chemistry. Attention has been given to 1,2,5-oxadiazole 2-oxide as the source of NO in biological studies, biological markers, and fluorescent and energetic materials. On the other hand, the applications of 1,2,5-oxadiazole *N*-oxide have agricultural activities are known.

3.1. Medicinal chemistry

1,2,5-Oxadiazole and derivatives are tested as potential pharmaceuticals. For example, 1,2,5-Oxadiazole *N*-oxide 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 an antimalarial compound on the chloroquine-sensitive D10 and the chloroquine-resistant W2 strains of Plasmodium falciparum (compound **127**) [68] (Figure 7).

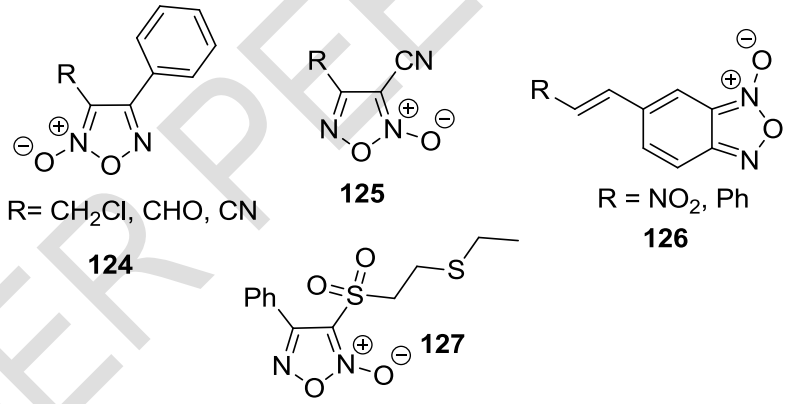


Fig. 7. Examples 1,2,5-oxadiazole *N*-oxide as potential pharmaceuticals.

According to Di Paolo *et al* [69] compound, "**128a** and analog **128b** have been found to be potent inhibitors of tumor cell growth *in vitro* (Figure 8). To enhance the aqueous solubility of these compounds, the hemisuccinate **128a** was transformed compound into **129a**. In sequence, phosphate monoesters of **128a** and **128b** was converted to compound **130a** and **130b**, respectively. These novel 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"**.

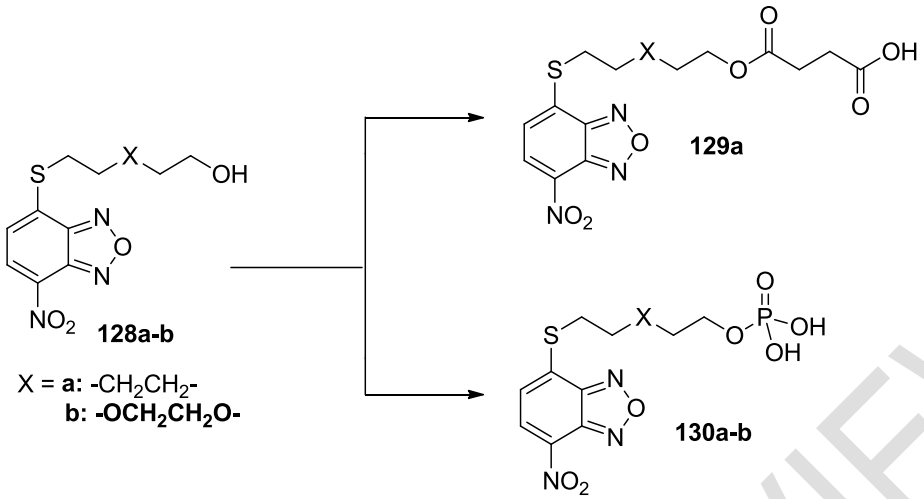


Fig. 8. Examples of 1,2,5-oxadiazole as potent inhibitors of tumor cell growth *in vitro*.

Kenwood *et al* [70] reported that BAM15 (Figure 9) is bioactive in vivo and protects from acute renal ischemic reperfusion injury in mice. However, Childress *et al* [71]. proposed "a study to make profiling 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 fibrosi".

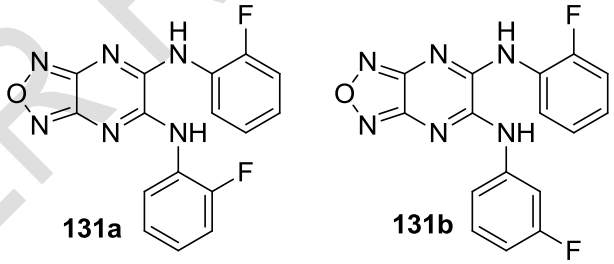


Fig. 9. Potential 1,2,4-oxadiazoles decoupling mitochondrial functions.

Recently Steeneck *et al* [72] reported "the pharmacokinetics of compound **132** was investigated in more detail and with emphasis on human glucuronidation (Figure 10). For this, the PK in a humanized mouse liver model was studied using PXB mice (PhoenixBio)". According to Katoh *et al* [73] "these are chimeric mice with a humanized liver that is repopulated by human hepatocytes so that the major human drug-metabolizing enzymes and transporters are present in the liver". "The use of this kind of mice as animal models for predicting human drug metabolism and pharmacokinetics has been reported in the literature" [74]. The authors [72] realized "the optimization of analogue **132** showed cellular and biochemical IDO1 IC_{50} values in the low nanomolar range, a suitable in vitro ADME/PK profile, and efficient in an animal model of cancer. In a humanized liver mouse model the lead compound exhibited significantly reduced glucuronidation compared to epacadostat **133"**.

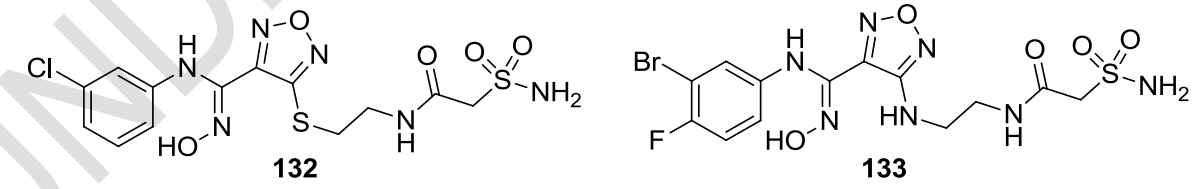


Fig. 10. Examples of IDO1 Inhibitors of compounds **132** and **133**.

According to Song *et al* [75] "although epacadostat shows strong inhibitory activity against IDO1 and is further studied in clinical trails, 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 activities against hIDO1 and IDO1-expressing HEK 293T cells. On the other hand, compound **135** showed improved PK properties with a 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".

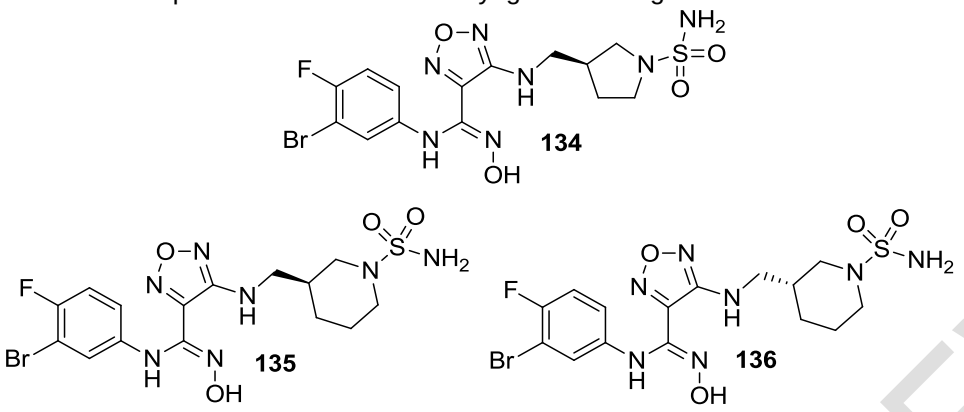


Fig. 11. 1,2,5-oxadiazoles com inhibitory activity against Indoleamine-2,3-dioxygenase-1 (IDO1).

A series of nonsteroidal drugs (NSAIDs) obtained by linking ibuprofen to selected 1,2,5-oxadiazole N-oxide moieties and to 1,2,5-oxadiazole derivatives 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 derivatives has been described by Wan *et al* [76] and compound **138** exhibited the best activity with IC_{50} values of 3.58–0.0008 μM. Preliminary pharmacological studies showed that **138** induced apoptosis and hardly affected the cell cycle of the MDA-MB-231 cell line. Finally, compounds **139a-b** exhibit potent anti-HIV-1 activity.

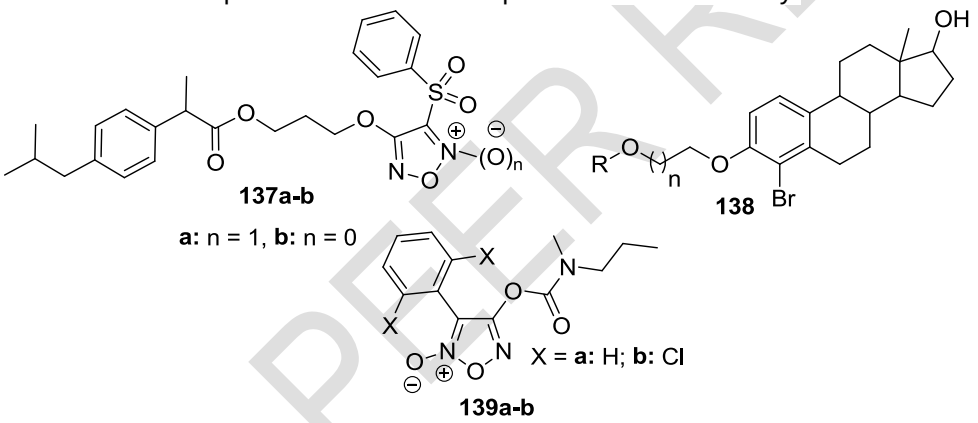


Fig. 12. 1,2,5-oxadiazoles with potential anti-inflammatory activity.

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 determined based on spectroscopic UV, IR, and NMR analysis.

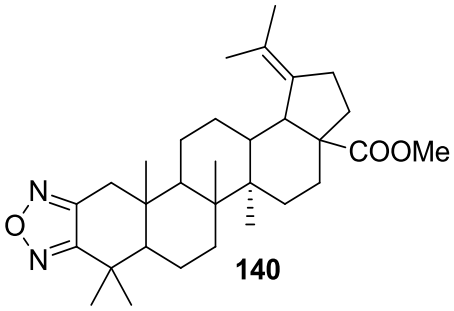
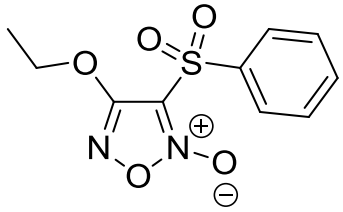


Fig. 13. 1,2,5-oxadiazoles with potential antibacterial and fungicidal activity.

Cena *et al* [78] reported "the synthesis and antioxidant activity of furoxan derivatives. According to the authors, CHF 2363 displays both a potent vasodilation activity and a 2-3 fold higher antioxidant action than *p*-cresol (Figure 14). This can be attributed to the product's ability to directly scavenge radicals and/or too 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



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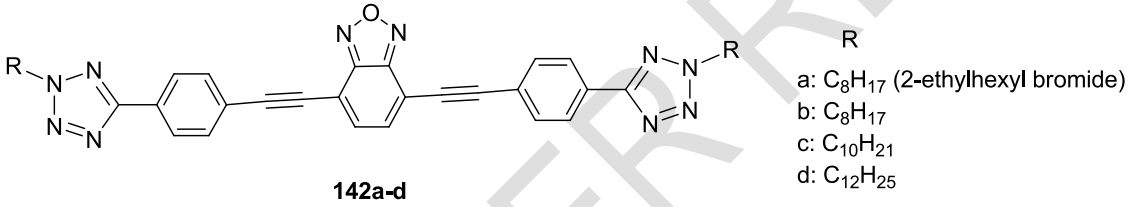
concentrations of NO display antioxidant actions".

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

3.2. Material chemistry

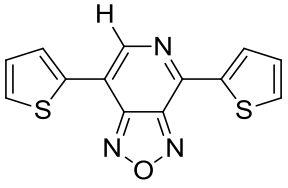
The application of compounds with 1,2,5-oxadiazole rings in materials chemistry is well known. Recently, Frizon *et al* [79] report "the synthesis and characterization of fluorophores containing a 2,1,3-benzoxadiazole unit associated with a p-conjugated system (D-p-A-p-D) (Figure 15). According to the authors, the fluorophores in solution exhibited an absorption maximum at around ∼419 nm (visible region), as expected for electronic transitions of the p-p∗ type (+ ∼2.7 × 107 L mol−1 cm−1), and strong solvent-dependent fluorescence emission (ΦFL ∼0.5) located in the bluish-green region. The Stokes' shift of these compounds is ca. 3,779 cm−1, which was attributed to an intramolecular charge transfer (ICT) state. In $CHCl_3$ 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 infrared, ^{1}H, and ^{13}C NMR spectroscopy, and mass spectrometry".



142a-d

Fig. 15. Examples of 1,2,5-oxadiazoles with luminescence properties.

According to Gorohmaru *et al* [80] "compound **143** (Figure 16) is a designed material with a basic skeleton suitable for a red-emitting dye. The compound possesses a widely conjugated π-electron system and therefore the excited singlet state emitting the fluorescence is expected to be shifted to a lower energy level. The spectroscopic parameters of compound **143** were determined which was designed as a red-emitting dye for the electroluminescence



143

(EL) device".

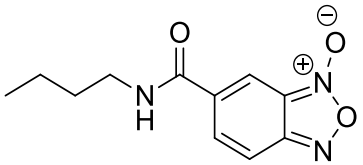
Fig. 16. 1,2,5-oxadiazole utilized at electroluminescence.

Šarlauskas and collaborator [81] "synthesized benzofuroxan (benzo[1,2-c]1,2,5-oxadiazole N-oxide) derivatives as potential energetic materials. Furthermore, also synthesized of other benzofuroxan derivatives, used 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, and CL-18, and thus could have potential applications as a HEDM".

3.3. Agricultural chemistry

According to Wilson co-workers [82], "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. For example, compounds 1,2,5-oxadiazole N-oxide and benzo [c [1,2,5] oxadiazole *N*-oxide 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 activity against *Triticum aestivum".*

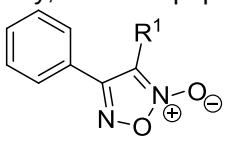
The most active compound, butylcarbamoylbenzo[1,2-c]1,2,5-oxadiazole N-oxide, **144** (Figure 17), displayed herbicidal activity at concentrations as low as 24 g/ha.



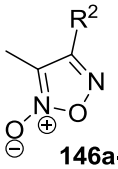
144

Fig. 17. Example of 1,2,5-oxadiazol with herbicidal activity.

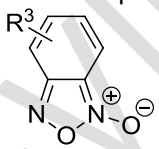
Fernandez *et al* [84] reported "the relationship between the herbicidal activity of a number of novel 1,2,5-oxadiazole *N*-oxides and some physicochemical properties related to this bioactivity, such as polarity, molecular volume, proton acceptor ability, lipophilicity, and reduction potential". According to the authors, the relationship between the phytotoxic activity of novel 1,2,5-oxadiazole *N*-oxide with different substituents (Figure 18) and some physicochemical properties related to such activity, such as lipophilicity descriptors, dipolar moment, hydrogen bond acceptor ability and reduction potential.



145a-e

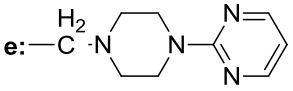


146a-d



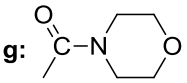
147a-i

R^1 = **a:** -CHO
b: -CH=NNHCO$_2$Me
c: -CH=NNHCSNH$_2$
d: -CH$_2$Cl

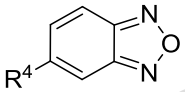


R^2 = **a:** -CHO
b: -CH=NNHCO$_2$Me
c: -CH=NNHCONH-hexyl
d: -CH=NNHCSNH$_2$

R^3 = **a:** -CH$_3$ **b:** -CHO
c: -CO$_2$H **d:** -CH=NNHCO$_2$Me
e: -CH=NNHCONH(CH$_2$)$_2$OMe
f: -CONH(CH$_2$)$_2$OMe



h: -CONH-butyl
i: -CONH-*p*-ClPh

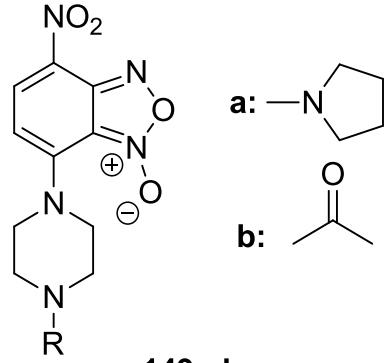


148a

R^4 = **a:** -CH=NNHCO$_2$Me

Fig. 18. 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 synthesized and used as antifungal agents. Their structures were determined by ^{1}H NMR, ^{13}C NMR, and HRMS. Their antifungal activities were tested in vitro with four important phytopathogenic fungi*, 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 pathogens, *Rhizoctonia solani, Sclerotinia sclerotiorum, Fusarium graminearum*, and *Phytophthora capsici in vitro*. However, the in vivo efficacies of compounds **149a** and **149b** (Figure 19) against *S. sclerotiorum* infected cole leave were evaluated". Compound **149b** displayed the maximum antifungal activity against F. graminearum (IC_{50} = 1.1 µg/mL, which is about 2-fold higher than that positive control carbendazim (IC_{50} = 0.5 µg/mL). On the other hand, compound **149a** exhibited antifungal effect against both *S. sclerotiorum* and *F. graminearum* Sehw., with IC_{50} values of 2.52 and 3.42 µg/mL, respectively.



149a-b

Fig. 19. 1,2,4-oxadiazoles *N*-oxide with potential fungicidal activity.

In 2008, Yusupova *et al* [86] described that the benzofuroxan derivatives presented fungicidal activity and that antifungal actions have not been investigated. Finally, other relevant applications of 1,2,5-oxadiazós are described in the literature [87-98].

4. CONCLUSION

This review, has summarized the synthetic methods and biological activities for 1,3,5-oxadiazole and derivatives reported in the literature during the past twenty-two years.
1,2,5-Oxadiazole and derivatives are not formed by direct oxidation of 1,2,5-oxadiazoles, but they can be synthesized by ring cyclization or cycloaddition pathways. The the routes used are the oxidative cyclization of 1,2-dione dioximes, the dehydration of α-nitro ketoximes, and, for symmetrically substituted 1,2,5-oxadiazole 2-oxides, dimerization of nitrile oxides. For nonsymmetrically substituted analogues, care must be taken in selecting the route and reaction conditions to avoid the formation of mixtures of 2- and 5-oxides.
The broad pharmacological activities of 1,2,5-oxadiazole and derivatives are evidenced by the numerous examples cited here. In each item biological activity topic, we have only provided selected examples of compounds with relevant activity being that these compounds may serve as prototypes for the development of more active oxadiazoles..
1,2,5-oxadiazole and derivatives were found to be very useful and easily modifying building blocks in drug design. Certainly, in later years, we will see an increasing number of works using 1,2,5-oxadiazolic nuclei as scaffolds in the design and synthesis of new anticancer drug candidates, in addition to other therapeutic applications.
Lastly, the chemistry and biological activity of the 1,2,5-oxadiazoles and derivatives will continue to be an object of study by chemists, biologists, physicists, pharmacists, etc.

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