

1,2,4-OXADIAZOLAS: UMA BREVE REVISÃO DA LITERATURA SOBRE A SÍNTESE E APLICAÇÕES FARMACOLÓGICAS

1,2,4-OXADIAZOLE: A BRIEF REVIEW FROM THE LITERATURE ABOUT THE SYNTHESIS AND PHARMACOLOGICAL APPLICATIONS

ROSA¹, M. F. ; MORCELLI², A. C. T.; LOBO³, V. S.

1 - Docente do Centro de Engenharias e Ciências Exatas da UNIOESTE, campus Toledo - PR, Brasil

2 - Bacharel em Química pela UNIOESTE, Toledo - PR, Brasil

3 - Docente da Universidade Tecnológica Federal do Paraná, Toledo - PR, Brasil

Email: mauricio_rosa@ymail.com

RESUMO:

Este trabalho contempla uma breve revisão da literatura, empregando os periódicos das bases de dados Scielo, Sciencedirect e ACS, sobre os métodos mais utilizados para síntese do anel 1,2,4-oxadiazólico, destacando suas vantagens e desvantagens. Foi realizada também uma pesquisa sobre as principais funções deste grupamento, sua ação no tratamento de doenças, os testes realizados para a confirmação das ações farmacológicas e os resultados obtidos.

Palavras-chave: oxadiazolas; síntese; farmacologia.

ABSTRACT:

This work includes a brief literature review, using the periodicals of the Scielo, Sciencedirect and ACS databases, about the most used methods for the synthesis of 1,2,4-oxadiazole ring, highlighting their advantages and disadvantages. It was also done a search in the literature about the main functions of this group, its action in the treatment of diseases, the tests made for the confirmation of the pharmacological actions and the results obtained.

Keywords: oxadiazole; synthesis; pharmacology.

1. INTRODUCTION

Organic chemistry is very important for drugs synthesis, because it allows us to build molecules from the simplest to the most complex. This area of organic chemistry presents some essential features, such as the development of a sequence of synthetic steps, the concern about good yields and the rate of purity of the product. At this point, we can differentiate the drugs of other organic products such as insecticides, pesticides and dyes, for example, as drugs show a high degree of purity directly linked to the synthetic methodology and to the quality of raw materials and of intermediates involved in the synthesis, mainly because many drugs may not be administered in racemic form.

According to Menegatti *et al.* (2001), drugs of synthetic origin represent a significant quota of the pharmaceutical market and when we analyze the structure of these drugs, it is observed that 62% of them are heterocyclic, of these, 95% have nitrogen and 18% have the oxygen atoms in their structure.

There are many heterocyclic compounds with pharmacological activities found in the literature, such as acridines, pyrazolones, pyrazoles, imidazoles, oxazolidines, pyridines and thiazolines. Among these the oxadiazoles are among the most cited in the literature.

This family of compounds is structurally characterized by a heterocyclic ring of 5 members containing two nitrogen atoms and one oxygen atom. Depending on the positions of these atoms in the heterocyclic nucleus it can be described four isomeric structures represented in Figure 1 (ROSA, 1992).

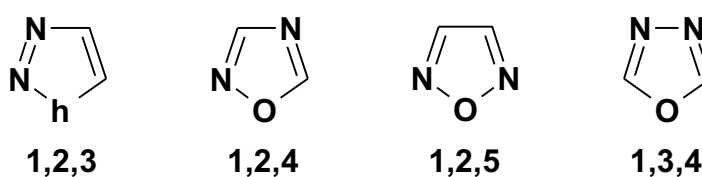


Figure 1: oxadiazole heterocycle isomers.

The isomers 1,3,4- and 1,2,4-oxadiazole are the most studied, because they give the best pharmacological results. Its metabolic profile and the ability to engage in hydrogen bonds give the oxadiazole a bioisosteric relationship with amides and esters (SANTOS FILHO, 2002). Because of the importance of their biological activities, significant progress has been observed in the synthesis of new oxadiazoles aiming to produce analgesics, antispasmodics and anti-inflammatories (SRIVASTAVA *et al.*, 2003).

The 1,2,4-oxadiazole nucleus is also used as esters and amides bioisosters in biological studies. This unit is present in muscarinic agonists drugs (MACOR *et al.*, 1996), in serotonergic (antidepressant) and in drugs antagonists (SWAIN *et al.*, 1991; WIEDER-WELLS *et al.*, 2004).

The synthesis and the evaluation of several derivatives of the group in question, where the affinity by muscarinic receptors is strong, puts them among the possible drugs for the treatment of Alzheimer's disease (ORLEK *et al.*, 1991).

This way, it came the interest in conducting a bibliography review on the group 1,2,4-oxadiazole in order to collect information about its use in pharmacology and about the methods employed in its synthesis.

2. METHODOLOGY

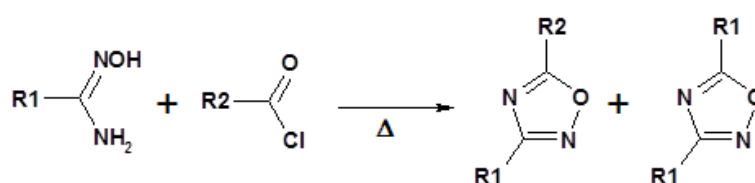
This research was done employing literature databases, such as Scielo, Sciencedirect and ACS, using as keywords 1,2,4-oxadiazole, synthesis and pharmacology. The papers, written in Portuguese or English languages, were selected from the last twenty years, except those of historical importance.

3. MATERIAL AND METHODS

3.1 - Methods of synthesis

The 1,2,4-oxadiazole are heterocyclic substances very important and comprise a large class of compounds that have vast amount of available information in the literature, not only about its synthesis as well as about its pharmacological activity.

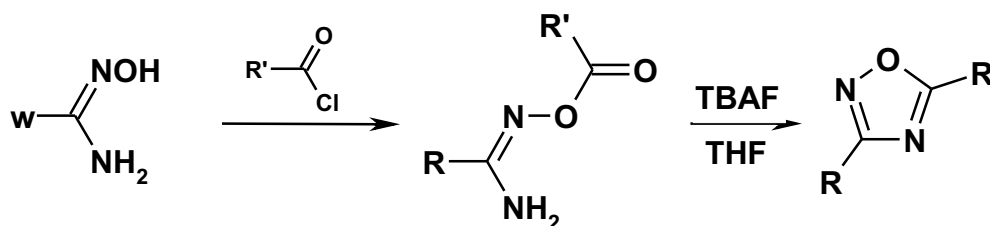
The first method of preparing this compound was described by Tiemann and Kruger in 1884 and consisted of reacting an amidoxime with an acyl chloride, warming the reaction beyond the amidoxime melting point to promote the coupling of the two substrates and subsequent cyclization (Scheme 1).



Scheme 1: Oxadiazole synthetic route done by Tiemann and Krüger in 1884.

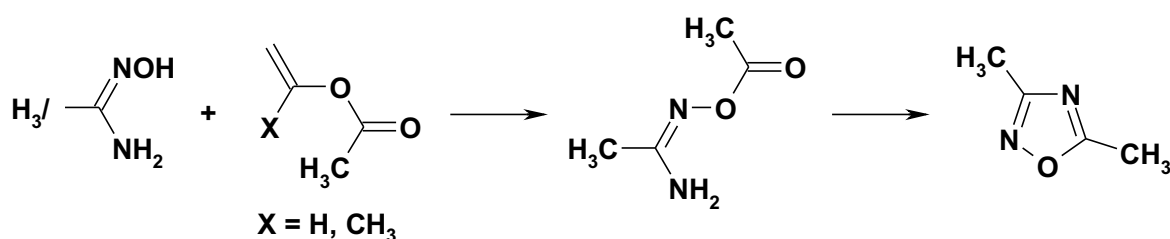
This method, although very used, has some disadvantages. Among these stand out: low income, long reaction time (6 -12h), difficult purification and formation of byproducts, such as oxadiazole resulting from amidoxime cyclization.

Gangloff *et al.* (2001) reported the use of tetrabutylammonium fluoride (TBAF) as a very efficient catalyst in the cyclization step of the intermediate *O*-acylated (Scheme 2). According to the authors the reaction occurs under mild conditions of temperature, especially when using one equivalent of TBAF and THF or acetonitrile as solvent. The use of less polar solvents like dichloromethane did not result in the product formation, what helps previous studies about the strongly basic behavior of fluoride ions in polar aprotic solvents (BARTSCH, 1970). The use of weaker bases such as pyridine, require heating so that the reaction can occur. The authors also report that the presence of substituents at the *ortho* positions of aromatic groups present in the 5 position of the heterocyclic ring tend to increase the reaction time.



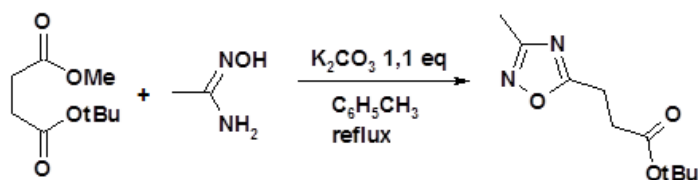
Scheme 2 - Reaction scheme proposed by GANGLOFF *et al.*

Alternative methods suggest the use of esters in the place of the acyl chlorides can be found in the literature. These methods require the presence of strong bases such as NaH or NaOEt, heating at reflux temperature in THF or EtOH and typically provide low yields. According to Durden and Heywood (1971) the reaction of esters with amidoximes can be governed by the same factors that governs the basic hydrolysis of the esters, or the electrophilicity of the carbonyl group and the basicity of the group that is being displaced. Simple esters of dichloroacetic and trichloroacetic acids react like amidoximes in a direct way to form 1,2,4-oxadiazole, while esters of aliphatic acids do not generate product in an appreciable form. Still according to the authors the use of vinyl or allyl acetates with acetamidoxime is a particularly useful method for obtaining a direct form 3,5-dimethyl-1,2,4-oxadiazole (Scheme 3).



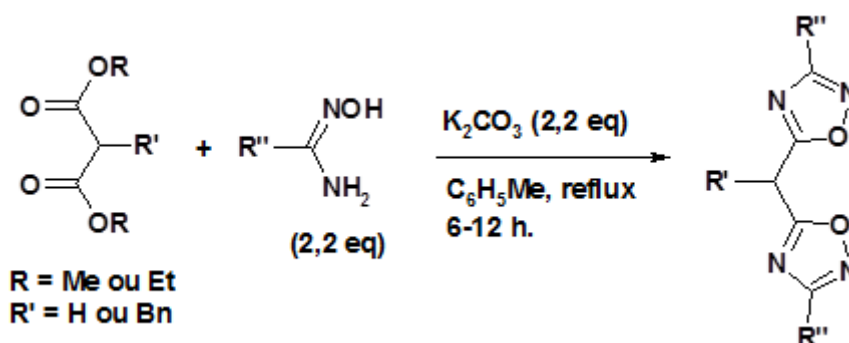
Scheme 3: General scheme of synthesis to obtain 1,2,4-oxadiazole from esters.

Recent studies (AMARASINGHE *et al.*, 2006) show that the use of methyl and ethyl esters and salts, such as K_2CO_3 or Ce_2CO_3 under reflux conditions in toluene, provide oxadiazole in good yield (Scheme 4) since these salts after its dissolution in the medium, act as very efficient bases in the step of cyclodehydration. The authors also reported the selective regarding to the alcohol structure used to obtain the ester. In the reaction of methyl succinate and *t*-butyl with acetamidoxime in the reaction conditions, only the methyl moiety reacts, remaining the *t*-butyl group intact.



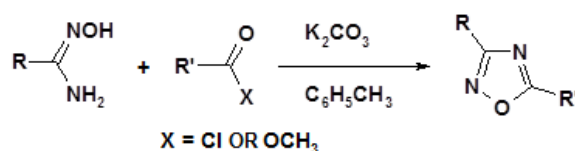
Scheme 4: General scheme for the synthesis of 1,2,4-oxadiazole proposed by AMARASINGHE *et al.*

This method also showed to be very effective for the synthesis of the bis-oxadiazole structures from esters of malonic acid with yields ranging from good to reasonable (Scheme 5).



Scheme 5 - General scheme of synthesis of bis-oxadiazole catalyzed by K_2CO_3 .

Sharma *et al.* (2009) synthesized 20 oxadiazole derivatives from long chain carboxylic acids in the form of esters or acyl chlorides in the presence of K_2CO_3 as a catalyst (Scheme 6). In the used methodology the authors mixed the solubilized amidoxime in toluene with the carboxylic derivative (ester or acyl chloride), and then adding K_2CO_3 and the mixture remained under reflux for 6 to 12 hours with stirring. The acyl chlorides used were prepared *in situ*, since they are not commercially available, and the excess of thionyl chloride was removed by distillation before the adding of amidoxime. The authors compared the yields obtained when using esters or acyl chlorides, with the use of these last ones, in general, have provided the best yields (70-79%) and shorter reaction times (1,2-2,5 h).

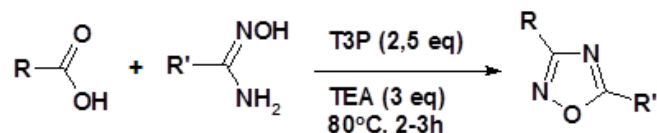


Scheme 6 - General scheme for the synthesis of 1,2,4-oxadiazole proposed by SHARMA et al.

Methods that employ reagents that act as activators of the carboxylic group (SURESHBABU *et al.*, 2008) such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC), dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI), *O*-(benzotriazole-1-yl), *N,N,N',N'*-tetramethyluronium-tetrafluoroborate (TBTU) and the Burgess reagent has been widely used in exhaustive reflux conditions with DMF or pyridine, to facilitate obtaining the 1,2,4-oxadiazole by *O*-acylation, in a one step process. These agents aims to facilitate the purification of the oxadiazole products by simple liquid-liquid extraction or filtration.

Recent studies (AUGUSTINE *et al.*, 2009) show the use of propylphosphonic anhydride (T3P[®]) as a new route of direct conversion of carboxylic acids into 1,2,4-oxadiazole (Scheme 7). This method consists on the reaction of a carboxylic acid with an amidoxime in the presence of T3P[®] as an activating agent of the carboxylic group, triethanolamine (TEA) and ethyl acetate (EtOAc) as the solvent. The authors employed a variety of aliphatic and aromatic carboxylic acids, and the obtained yields range from

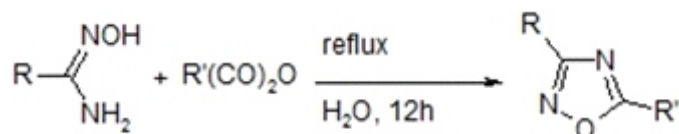
87 to 97%, independent on the functional present group in the alkyl/aryl structures. Methods using mixtures of solvents, such as EtOAc-DMF, allowed that the reactions would be realized at higher temperatures (110°C) decreasing the reaction time without affecting the yield of the reaction.



Scheme 7: Schematic of reaction using T3P[®] to obtain 1,2,4-oxadiazole.

T3P[®] makes only water soluble byproducts, is less toxic and the method is very simple. Furthermore, this method does not require the initial conversion of carboxylic acids in their corresponding acid chlorides or esters.

Kaboudin and Malekzadeh (2011) recently reported the synthesis of 14 oxadiazole derivatives reacting with amidoxime with an acid anhydride in an aqueous medium under reflux of 12h in the absence of catalysts (Scheme 8), with yields ranging from poor to excellent (35-93%) (Table 1).



Scheme 8 – Reactional scheme proposed by Kaboudin and Malekzadeh (2011)

TABLE 1 – Substituents and yields obtained by Kaboudin and Malekzadeh (2011)

w	R'	Yield (%)
/ ₆ H ₅	/ ₆ H ₅	7
o-C ₆ H ₄	C ₆ H ₅	60
p-BrC ₆ H ₄	C ₆ H ₅	81
2,4-Cl ₂ C ₆ H ₃	C ₆ H ₅	52
m-ClC ₆ H ₄	C ₆ H ₅	85
p-MeOC ₆ H ₄	C ₆ H ₅	69
Cyclohexyl	C ₆ H ₅	86
C ₆ H ₅	p-CH ₃ C ₆ H ₄	81
2,4-Cl ₂ C ₆ H ₃	p-CH ₃ C ₆ H ₄	72
p-BrC ₆ H ₄	p-CH ₃ C ₆ H ₄	76
C ₆ H ₅	n-C ₅ H ₁₁	53
2,4-Cl ₂ C ₆ H ₃	n-C ₅ H ₁₁	40
m-ClC ₆ H ₄	n-C ₅ H ₁₁	35
p-BrC ₆ H ₄	n-C ₅ H ₁₁	48

Another synthetic approach to obtain the oxadiazole ring is the 1,3-dipolar cycloaddition of nitrile oxides to nitriles (RAJAGOPALAN, 1969; QUADRELLI *et al.*, 1997). This is an advantageous way due to the easy synthetic access to the raw materials by its commercial availability, but the low reactivity of triple bond of the nitrile becomes the reaction less favorable. This way, the cycloaddition 1,3-dipolar of nitrile to nitrile oxides non-activated occurs only under conditions of vigorous reaction when the formation of 1,2,4-oxadiazole competes with dimerization of nitrile oxides unstable to provide 1,2,5-oxadiazole-2-oxide (furoxan) or 1,2,4-oxadiazole-4-oxide (Figure 2). The activation of the nitrile group (CN) can be obtained by the introducing of electron acceptor groups linked to the nitrile carbon (BOKACH *et al.*, 2003).

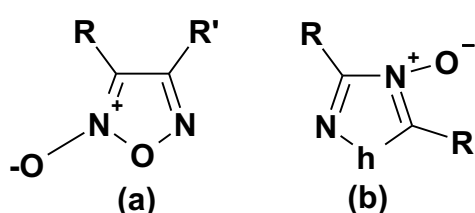


FIGURE 2: Structural formulas of (a) 1,2,5-oxadiazole-2-oxide and (b) 1,2,4-oxadiazole-4-oxide.

An emerging method for obtaining the 1,2,4-oxadiazole derivatives is the application of microwave irradiation (MW). This technology became popular among synthetic organic chemists to improve classical organic reactions by obtaining better yields in shorter reaction times (BOUGRIN *et al.*, 2003).

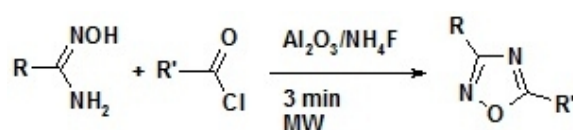
Since the last two decades of the 20th century, there is an increasing demand for the development of sustainable chemistry in order to minimize the large amount of waste and the consecutive treatment. One of the major contributions to this volume of waste are the components used as the volatile solvent in the synthesis steps of sequential purification of the desired compound. The use of solvents in organic synthesis reactions have been classified as essential due to its role in facilitating the transfer of heat from the reaction mixture with the neighborhood, promoting the diffusion of molecules along to the reaction bottle, and reduced of the difficulty of transfers between reactant and product. However, it is known that the reactions can occur in the solid phase, being in the most of the cases more selective (due to organized crystalline structure), and more efficient than in the liquid phase reactions (CANDEIAS *et al.*, 2009).

The use of these reactions has several advantages in comparison with classical conditions (BOUGRIN *et al.*, 2003):

- reducing the inherent risks to the use of large amounts of volatile organic solvents;
- it's not needed to recover, purify and reuse the solvent, reducing this way the arising pollution from these operations;

- in the most of the cases, the desired products are in sufficient purity to avoid the chromatography or even recrystallization, simplifying synthetic steps.
- faster reaction can be completed within 1 to 10 minutes;
- procedure economically attractive to the industry due to the non-used of solvent and less trappings necessary.

The conventional method for *O*-acylation of an amidoxime using an acid chloride in the presence of a coupling reagent generally do not provide appreciable yields under MW conditions. However, the same reaction in the presence of ammonium fluoride supported on alumina, is obtained 1,2,4-oxadiazole with good yields in only 3 minutes under MW irradiation (KABOUDIN; SAADATI, 2005).

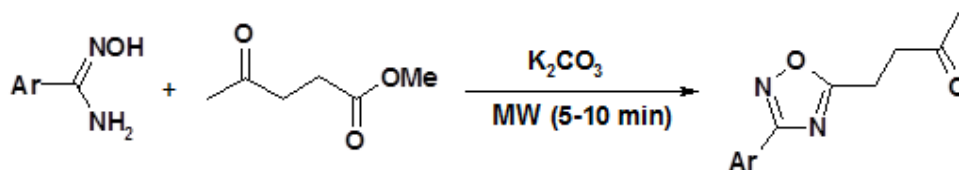


Scheme 9 – Reaction conditions used by KABOUDIN and SAADATI (2005)

TABLE 2 – Substituents and yields obtained by KABOUDIN and SAADATI (2005)

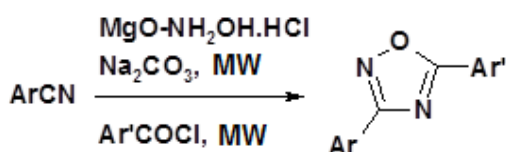
R	R'	Yield (%)	R	R'	Yield (%)
C ₆ H ₅	C ₆ H ₅	90	C ₆ H ₅	p-MeOC ₆ H ₄	78
p-ClC ₆ H ₄ CH ₂	C ₆ H ₅	£\$	2,4-Cl ₂ C ₆ H ₃	p-MeOC ₆ H ₄	71
p-ClC ₆ H ₄	C ₆ H ₅	87	p-ClC ₆ H ₄ CH ₂	p-NO ₂ C ₆ H ₄	80
2,4-Cl ₂ C ₆ H ₃	C ₆ H ₅	75	p-ClC ₆ H ₄	p-NO ₂ C ₆ H ₄	86
C ₆ H ₁₁	C ₆ H ₅	85	C ₆ H ₁₁	p-NO ₂ C ₆ H ₄	82

FREITAS *et al.* (2007) related the reaction of methyl levulinate with amidoxime in the presence of potassium carbonate in MW conditions for the synthesis of 1,2,4-oxadiazole (Scheme 10). The obtained yields were higher than those obtained by the conventional method and the reaction times were approximately 5-10 min, against a reaction time of 18 h by the classical method. The synthetic methodology employed consisted not only in the solely in a mortar milling of methyl levulinate, the appropriated amidoxime and K₂CO₃. Then the mixture was transferred to a test tube and was irradiated in a home microwave oven for 10 minutes using 100% of the equipment power (650 W). After cooling, the content was chromatographed on silica gel using AcOEt-hexane as eluent.



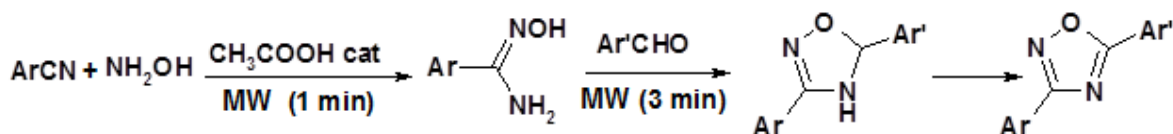
Scheme 10: Reaction scheme to the synthesis of 1,2,4-oxadiazole proposed by FREITAS *et al.* (2007)

KABOUDIN and SAADATI (2007) proposed a method in a single step based on the reaction of nitrile with hydroxylamine hydrochloride in the presence of sodium carbonate supported on magnesium oxide, followed by the reaction with acyl halides (Scheme 11). In this method, initially hydroxylamine hydrochloride, sodium carbonate and the magnesium oxide are intimately mixed in a mortar until to obtain finely and homogeneous dust. In sequence is added the nitrile, and the mixture is stirred for 5 minutes and then irradiated for 5 minutes (180 W). To the formed product is added to the acyl chloride and the reaction mixture is irradiated for 2-5 minutes at 600 W. By this method 12 derivatives were synthesized 1,2,4-oxadiazoles with reasonable yields (40 to 70%).



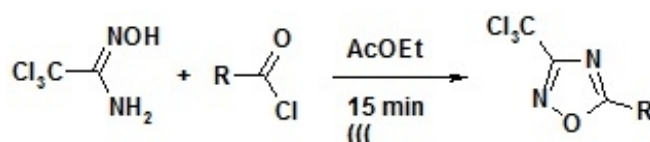
Scheme 11 - Reaction scheme to obtain 1,2,4-oxadiazole proposed by KABOUDIN and SAADATI (2005)

ADIB *et al.* (2006) obtained 12 oxadiazole derivatives in only one step without the use of activated derivatives of carboxylic acids. The synthesis of the intermediate amidoxime is done by MW, having acetic acid as catalyst, in a fast process (1 minute). The aldehyde is added in sequence and the mixture is irradiated by microwave during 3 minutes to obtain the oxadiazole with excellent yields (92-97%) (Scheme 12). Mechanistically the process passes by the formation of an intermediate 4,5-dihydro-1,2,4-oxadiazole (oxadiazoline) that undergoes the oxidation in the reaction conditions.



Scheme 12 - Reaction scheme for the synthesis of 1,2,4-oxadiazole proposed by ADIB *et al.* (2006)

Recently it was published in the literature a synthetic procedure using irradiation by ultrasound (USI) in the synthesis of oxadiazole (BRETANHA *et al.*, 2011). In this work the authors report the synthesis of 12 oxadiazole derivatives containing the trichloromethyl group in the position 3 and different alkyl and aryl groups in the position 5 obtained by the reaction of trichloroacetamidoxime with the appropriated acyl chloride (Scheme 13). It was done the comparison in terms of time and performance of the conventional process (in reflux with different solvents) against the USI process, having ethyl acetate as solvent. In all experiments using the conventional process were spent 20 hours and the yields ranged from 60 to 90%, while for the USI process were spent 15 minutes and the yields ranged from 84 to 98 %, showing the potential use of this technique in the synthesis of these heterocycles.



Scheme 13 – Reaction scheme propose by BRETANHA *et al.* (2011).

TABLE 3 – Substituents and yields obtained by BRETANHA *et al.* (2011) [27]

R	Yield (%)	R	Yield (%)
C ₆ H ₅	92	o-IC ₆ H ₄	98
p-MeC ₆ H ₄	93	Me	86
p-NO ₂ C ₆ H ₄	94	Et	90
o-FC ₆ H ₄	95	CH ₂ Cl	89
o-MeOC ₆ H ₄	84	CHCl ₂	88
m-BrC ₆ H ₄	96	CCl ₃	90

The chemistry of the 1,2,4-oxadiazole has been re-examined many times along the years. Derivatives heterocyclic of nitrogen and oxygen in positions 1,2,4 are important from synthetic interest viewpoint because they represent an important class of natural and unnatural products, many of which present biological activities. The basic concept behind these developments is that the 1,2,4-oxadiazole ring is a bioisosteric alternative of hydrolysis resistant to one molecule of ester or amide [20], and one better performance *in vivo* is often observed due to the metabolic stability of the oxadiazole ring in the aqueous medium within the complete range of pH to the climate temperature (ISPIKOUDI *et al.*, 2010).

The bioisosteric replacement of an amide portion represents a center focus because of its implications in peptide chemistry and development of peptidomimetics, which are being explored in large part to contour some of the disadvantages of native peptides and to increase the bioavailability and potency of drugs based on peptide, furthermore, the core 1,2,4-oxadiazole is the structural core unit of the muscarinic agonist (DUCHET *et al.*, 2010).

4. PHARMACOLOGICAL ACTIVITIES

Some derivatives of 1,2,4-oxadiazole have analgesic effects, anti-inflammatory and anti-cancer and show high efficacy as agonists and antagonists for different receptors.

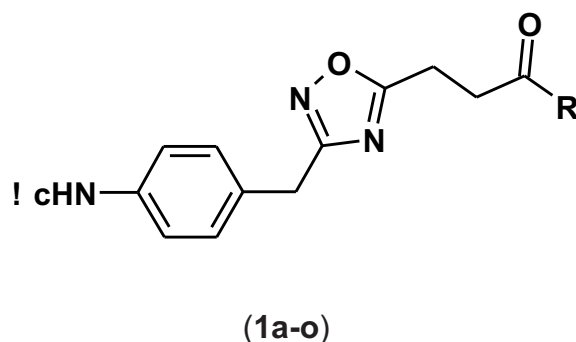
4.1 Anti-inflammatory activity

Inflammation is a complex phenomenon involving relation of humoral and cellular responses through a series of inflammatory mediators. It is an usual symptom covering different pathologies (KONTOGIORGIS; HADJIPAVLOU-LITINA, 2005). The acute inflammatory reaction is characterized by arteriolar dilation, increasing of vascular permeability, leukocyte accumulation and pain. The inflammation can be caused by physical, chemical or biological, agents causing disturbances in the cell membrane, causing the activation of phospholipase A2 and liberation of arachidonic acid and its metabolites, PAF-acether (Platelet Activating Factor) and lysosomal enzymes (SAKAE *et al.*, 2005).

An anti-inflammatory agent is that one which reduces or prevents one or more components of the inflammatory reaction. The pharmacological control of the inflammation can be exercised in two ways: by antagonizing or inhibiting the liberation of inflammatory mediators responsible for the triggering or amplification of the inflammatory reaction, or acting directly on the inflammatory cells (KOROLKOVAS; BURCKHALTER, 2005).

The most widely used method to evaluate the anti-inflammatory is to test the ability of compounds in study in the reduction of edema in the rat's hind paw caused by injection of an inflammatory agent such as carrageenan.

FAROOQUI *et al.* (2009) tested the anti-inflammatory activity of 15 different 1,2,4-oxadiazole-3,5-disubstituted derivatives (Table 4) in mice with inflammation induced carrageenan.

TABLE 4: Anti-inflammatory activity of 1,2,4-oxadiazole-3,5-disubstituted.

Compounds	R	% Inflammation inhibition
1a	OH	75,34 ±3,4
1b	Aniline	34,24 ±4,7
1c	<i>m</i> -anisidine	35,61 ±4,5
1d	<i>o</i> -anisidine	87,67 ±1,6
1e	<i>p</i> -anisidine	49,31 ±4,2
1f	<i>o</i> -fluoroaniline	67,12 ±7,3
1g	<i>p</i> -fluoroaniline	64,38 ±5
1h	2,4-fluoroaniline	52,05 ±6,7
1i	3-fluoro-4-methoxyaniline	60,27 ±7,3
1j	3,4-dimethoxyaniline	95,89 ±1,9
1k	<i>m</i> -toludine	16,43 ±5,7
1l	4-trifluoromethylaniline	36,98 ±5,7
1m	3-ethynylaniline	84,93 ±1,6
1n	Pyridine	87,67 ±1,9
1o	Benzylamine	76,71 ±6,2
Control	Control	0
Reference	Diclofenac	50,68 ±9

The anti-inflammatory activity of the synthesized compounds is connected to the molecular basic structure skeleton. The compound **1a** exhibited great power but probably the presence of one or more lipophilic substituents on the aromatic ring further increase the activity. The compound **1j** is the most powerful and has two methoxy groups

at positions *ortho* and *para* comparing with just one methoxy substituent present in the compound 1d, revealing the importance of electron donating groups in the *ortho* and *para* positions on the aromatic ring.

Derivatives 3-aryl-5-decapentil-1,2,4-oxadiazole (2a-f) (Figure 3) also showed anti-inflammatory activity (BEZERRA *et al.*, 2000)

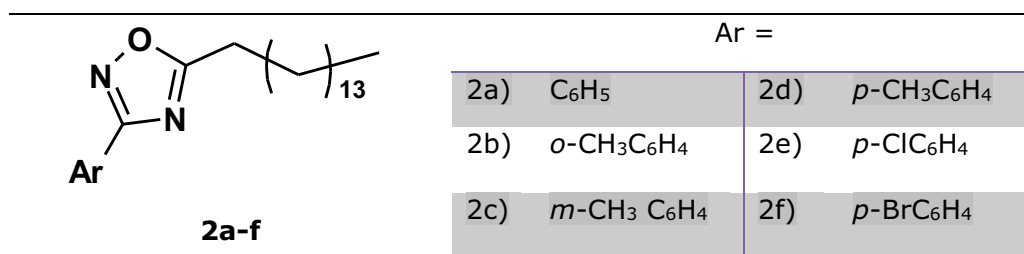


FIGURE 3: Derivatives of 3-aryl-5-decapentil-1,2,4-oxadiazole.

The oxadiazole **2a**, **2e** and **2f** reduced the induced edema by carrageenan in mice in 29, 33 and 34%, respectively. The compounds **2b**, **2c** and **2d**, which have substituents on the aromatic ring respectively in *ortho*, *meta* and *para* positions showed a reduction of the edema from 55, 67 and 67%, respectively. In addition, the anti-inflammatory effect of the compounds **2c** and **2d** was comparable with aspirin (68%) and ibuprofen (73 %). The compounds with decapentil group in C5 of 1,2,4-oxadiazole have higher anti-inflammatory activity, because the compounds with longer hydrocarbon chains are able to enter in cells more quickly, and leave more slowly than those with shorter chains, due to its increased hydrophobicity, or perhaps, the smaller molecules, such as isopropyl group at C5, for example, are excreted more rapidly.

Some 1,2,4-oxadiazole peptidomimetic (Figure 4) were also tested for their anti-inflammatory activity by Leite *et al.* (2000).

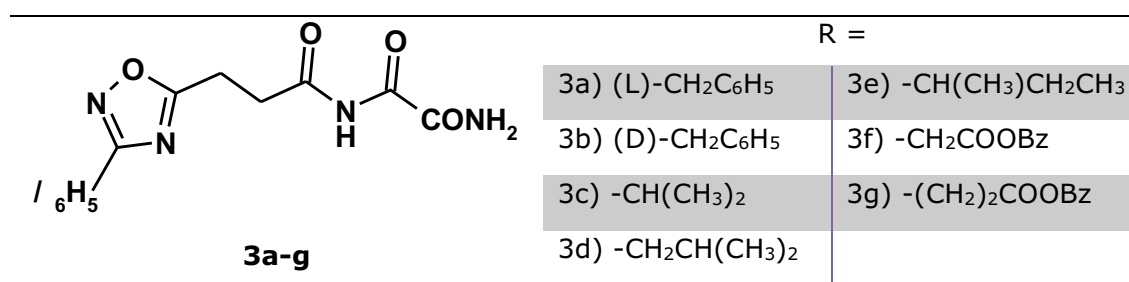


FIGURE 4: Derivatives of 1,2,4-oxadiazole tested by LEITE *et al.* (2000)

The compounds **3a**, **3b**, **3c**, **3d**, **3f** and **3g** significantly inhibited the induced edema by carrageenan in rat's paw, depending on the dose employed. The compound **3e**, at a dosage of 3mg/kg, did not showed any noticeable inhibitory effect on the edema induced by carrageenan. Higher doses of this derivative have not been studied since they cause toxic effects in animals with death in about 1 minute after administration. Oral administration of the compounds **3a**, **3c** and **3g** was completely ineffective in inhibiting the edema at all observed periods.

The pharmacological results demonstrate that compounds **3a**, **3c** and **3g**, when administered intravenously, are anti-edematous. However, when administered orally do not modify the edema induced by carrageenan, what suggests its inability to be absorbed or possible destruction by digestive enzymes.

4.2 - Anti-cancer activity

Many classes of anticancer drugs were developed, however, most of the drugs cause side effects due to lack of specificity of tumor and its multidrug.

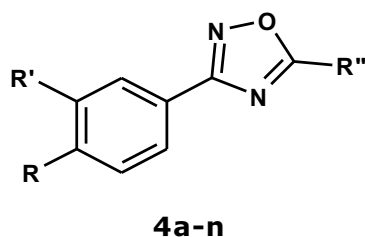
The main factors that contribute to cancer cell survival are: the variation in the metabolism because make them able to survive in conditions of very low oxygen and this what they take an important selective advantage over normal cells, the difficulty of drug absorption in the target tissues and tumor location.

Some chemotherapeutic agents lose their effectiveness after prolonged exposure, because the cells become resistant to the drugs. Therefore, the synthesis of new and effective anti-cancer agents becomes necessary.

The 1,2,4-oxadiazole were also tested on their anti-cancer activity. In 2009, Kumar *et al.* (2009) have synthesized and tested the activity of 14 derivatives of 1,2,4-oxadiazole-3,5-disubstituted (Table 5) against cell lines of prostate cancer (PC3, DU145 and LNCaP), breast (MCF7 and MDA231), colon (HCT116) and pancreas (PaCa2).

TABLE 5: 1,2,4-oxadiazole tested for anti-cancer activity.

Compounds	R	R'	R''
4a	H	H	<i>p</i> -FC ₆ H ₄
4b	H	H	Pyridine-4-il
4c	OCH ₃	OBn	Pyridine-4-il
4d	OC ₅ H ₉	OCH ₃	C ₆ H ₅
4e	OC ₅ H ₉	OCH ₃	<i>p</i> -FC ₆ H ₄
4f	OC ₅ H ₉	OCH ₃	<i>p</i> -ClC ₆ H ₄
4g	OC ₅ H ₉	OCH ₃	<i>p</i> -HOC ₆ H ₄
4h	OC ₅ H ₉	OCH ₃	Pyridine-4-il
4i	OC ₅ H ₉	OCH ₃	Pyridine-3-il
4j	OC ₅ H ₉	OCH ₃	(Indol-3-il) methyl
4k	OC ₅ H ₉	OCH ₃	CH ₂ COCH ₃
4l	OH	OCH ₃	<i>p</i> -FC ₆ H ₄
4m	OC ₅ H ₉	OCH ₃	Pyrrolidine-2-il
4n	OC ₅ H ₉	OCH ₃	Pyrrolidine-4-il



The positions of substitution at C3 and C5 of the nucleus 1,2,4-oxadiazole played an important role in anti-cancer function. The radical R", at the C5 position is responsible for providing the to the potency and specificity compound. When R = H or OH or when R'= H or OBn is observed the decrease in the potency of the compound. Some compounds were highly effective and exhibit specificity for certain cell type in relation to the other.

The compounds **4a** and **4b** showed weak inhibitory activity against cancer lines tested. The substitution by the groups 3'-cyclopentyloxy and 4'-methoxy in the aryl ring of the position C3, respectively (**4e** and **4h**), increase the activity in relation to **4a** and **4b**. However, a larger group such as OBz (**4c**) at the position R 'is detrimental to the activity. The compound **4g** showed to be a potent cytotoxic agent against the various cancer cell lines tested. The compounds **4f**, **4h**, **4j**, **4k**, **4n** show selectivity against cell lines of pancreatic cancer. The compound **4m** exhibited high selectivity and high effectiveness against cell lines of prostate cancer. The substituents at the C3 and C5 positions of the ring 1,2,4-oxadiazole showed to be vital for the potency, suggesting specific interactions with biological targets of these groups .

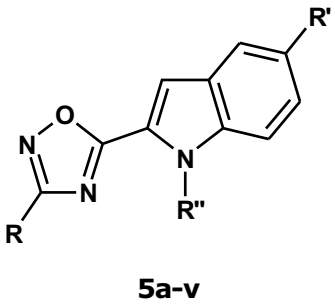
Khatik *et al.* (2012) synthesized and tested against prostate cancer cells (DU-145) some sulfide and sulfonyl derivatives of 1,2,4-oxadiazole nucleus. Six of them showed good activity, with IC₅₀ values ranging from 0.5 to 5.1 μ M, against androgen independent cells (PC-3), and low cytotoxicity on non-cancerous cells (MCF-10A).

4.2.1 Activity proapoptotic

The apoptosis is the programmed cell destruction. It occurs in an organized form and, different from the necrosis, requires energy for its execution. It can be caused by a pathological stimulus, such as a DNA damage, for example. When the damage caused to DNA is greater than the cell's ability to reverse it, it is safer for the organism that the cell death program is activated by radioactive stimuli, chemical or viral, because the failure of apoptosis can benefit the multiplication of a mutant cell originating tumors. The discovery of small molecules able to selectively induce apoptosis in cancer cells through a variety of mechanisms represents an attractive prospect for the future treatment of cancer.

Recent researches show the proapoptotic action of 1,2,4-oxadiazole based in the indole ring (ZIEDAN *et al.*, 2010). The table 6 shows the oxadiazole compounds (**5a-v**) tested for proapoptotic action.

TABLE 6: 3,5-disubstituted oxadiazole based on the indole ring structure.

	R	R'	R''	R	R'	R''	
	5a	CH ₃	H	H	5l	<i>p</i> -ClC ₆ H ₅	OCH ₃
5b	CH ₃	OCH ₃	H	5m	<i>p</i> -ClC ₆ H ₅	F	H
5c	CH ₃	F	H	5n	<i>p</i> -ClC ₆ H ₅	NO ₂	H
5d	CH ₃	Cl	H	5o	<i>p</i> -ClC ₆ H ₅	Cl	H
5e	C ₆ H ₅	H	H	5p	<i>p</i> -ClC ₆ H ₅	Cl	CH ₃
5f	C ₆ H ₅	OCH ₃	H	5q	<i>p</i> -OCH ₃ C ₆ H ₅	H	H
5g	C ₆ H ₅	OH	H	5r	<i>p</i> -OCH ₃ C ₆ H ₅	H	CH ₃
5h	C ₆ H ₅	F	H	5s	<i>p</i> -OCH ₃ C ₆ H ₅	OCH ₃	H
5i	C ₆ H ₅	NO ₂	H	5t	<i>p</i> -OCH ₃ C ₆ H ₅	F	H
5j	C ₆ H ₅	Cl	H	5u	<i>p</i> -OCH ₃ C ₆ H ₅	Cl	H
5k	<i>p</i> -ClC ₆ H ₅	H	H	5v	NH ₂	H	H

The anti-tumor effect *in vitro* of the compounds **5a-v** was evaluated against a panel of cancer cell lines of different human tissues, including colon (COLO 320), pancreatic (MiaPaCa -2), breast (MCF -7) and peripheral blood of a patient with leukemia of T-cell. In general, the cell lines of colon and pancreas were the most sensitive to the indol-oxadiazole and the exposure of the cells to the compounds resulted in a decrease (dependent on the dose) of the cell viability with about 50% of inhibition in the micromolar concentration range. The most active compounds in the colon (**5n** and **5u**) were less active compared with diaryl-oxadiazole. However, the other compounds of the present series showed a low inhibition index in micromolar concentration, on strains of pancreatic cancer, breast cancer and leukemia T cells, where the diaryl-oxadiazole was taken as inactive.

Tests with strain H9c2 of the heart of muscle cells (characterized by a high abundance of mitochondria) showed selectivity in the most of the cases. Through studies of relation between the structure and indol-oxadiazole activity, it is noted that in certain compounds that have one nitrogen in the indole ring is substituted (R' = H) and a phenyl substituent in R (**5g** and **5h**) were able to induce the cell death by apoptosis in the cell strains of colon and pancreas, while the compounds **5e** and **5k**, structurally related, induced the apoptosis only in colon cells.

Still analyzing the relation between structure and activity of the compounds, the data clearly demonstrated that the both electron withdrawing groups (eg, R' = NO₂, **5n**) and electron donating groups (R' = OMe, compounds **5l** and **5s**) are tolerated in the position 5 of the indole ring with respect to the power cell lines of colon and pancreas. The effect of specific R' in relation to different substituents is difficult to determine, because compounds related to the same group R' give quite different results. For example, the compound **5u** is the most active of the series on colon and pancreas lineages, while the **5o**, its closer analogue, is among the least actives.

For most of the compounds in the series, the nitrogen of the indole ring is without

substituent, except **5p** and **5r** (where R' = Me), which were among the least active in the series. This suggests that the substitution radical Me in the indole nitrogen decreases the activity of the compound.

Some of the tested compounds, especially **5l**, **5n** and **5t**, were active in apoptosis promoting through the activation of the caspase -3 and 7 (responsible for cleaving protein substrates of the cell), or by a caspase independent pathway, depending on the type of the cell and the compound studied. The cell necrosis was induced by the compound **5u** and this type of cell death may also be interpreted by the toxic effects which other compounds may cause to the cells. These results are relevant considering that the development of mechanisms resistant to apoptosis confer high survival capacity and low drug sensitivity of tumor cells.

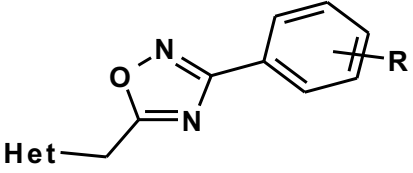
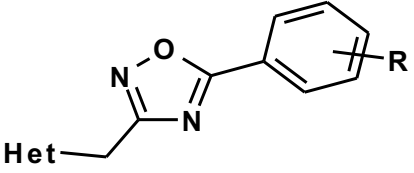
4.3 Anticonvulsant activity

Studies to obtain more information about the anticonvulsant action of this class of compounds have also been carried out because, in spite of the development of several anticonvulsants, the epilepsy treatment still remains insufficient. About a third of the patients do not answer well to the treatments currently available (GUILHOTO *et al.*, 2007).

The best known mechanisms that result in anticonvulsant activity are the potentiation of GABA (γ -aminobutyric acid) and the lock of the sodium channel (Lankau *et al.*, 2007).

Three trial models, the MES test, PTZ test and the rotarod were used in rats by Lankau *et al.* (2007) to obtain the characterization of primary compounds and a first clue to the effectiveness and safety of 1,2,4-oxadiazole synthesized (Table 7).

TABLE 7: 3-aryl and 5-aryl-1,2,4-oxadiazole.

 6a-i			 7a-f		
Compounds	Heterocycle	R	Compounds	Heterocycle	R
6a	1-Imidazolyl	H	7a	1-[1,2,4]Triazol	H
6b	1-Imidazolyl	4-Cl	7b	1-[1,2,4]Triazol	2-F
6c	1-[1,2,4]Triazol	H	7c	1-[1,2,4]Triazol	3-F
6d	1-[1,2,4]Triazol	4-Cl	7d	1-[1,2,4]Triazol	4-F
6e	1-[1,2,4]Triazol	2-F	7e	1-[1,2,4]Triazol	3-CH ₃
6f	1-[1,2,4]Triazol	3-F	7f	1-[1,2,4]Triazol	4-Cl
6g	1-[1,2,4]Triazol	3-CH ₃			
6h	1-[1,2,4]Triazol	4-CH ₃			
6i	5-Methyl-1-[1,2,4]triazol	3-F			

All synthesized compounds with *in vivo* activity, potentiated the induced GABA currents in rat cortical neurons, however, without interaction with the benzodiazepine site, which is usually expected for this positive modulation. This indicates that the compounds modulate GABA reception by a different link site.

The compounds **6b**, **6d** and **6g** also acted as potent blockers of the sodium channels. A combination of both mechanisms in a molecule may be a new approach to develop a potent anticonvulsant.

In summary, the results indicate that both oxadiazole acting as sodium channel blockers or selective enhancers to GABA have efficacy in the anticonvulsant activity. The tested substances are better tolerated than the benzodiazepines.

4.4 - Anti-HIV Activity

The epidemic of the Acquired Immunodeficiency Syndrome (AIDS) is a worldwide public health problem. Currently there are millions of infected people with HIV virus, its causative agent.

The effective therapeutic agents developed to combat the progression of AIDS are based on four groups of drugs: (1) nucleoside transcriptase reverse (NRTIs), (2) inhibitors not nucleoside of reverse transcriptase (NNRTIs), (3) protease inhibitors (PI) and (4) fusion inhibitors. Efforts are concentrated on the search for new molecules with anti-HIV activity, focus on the development of NNRTIs, because this class has advantage to be minimally toxic and inhibit HIV through an allosteric mechanism, which changes the three-dimensional structure of the enzyme active site, not allowing their reaction, anymore in spite of having significant problems with the resistance development (DOLBIER *et al.*, 1999).

The alkenyldiarilmethanes (ADAMs) are a class of non-nucleoside inhibitors. However, the potential utility of ADAMs is limited for the presence of labile metabolically methyl esters which are hydrolyzed by unspecific esterases present in the blood plasma, resulting in the formation of inactive metabolites of carboxylic acid. In order to discover an ADAM metabolically stable, Sakamoto *et al.* (2007) synthesized and tested ADAM shown in Figure 5, in which the system was incorporating 1,2,4-oxadiazole.

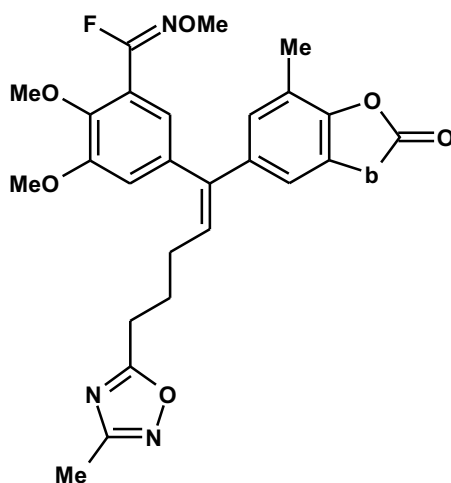


Figure 5: ADAM incorporating the system 1,2,4-oxadiazole.

The compound exhibited enhanced metabolic stability in rat plasma, along with the ability to inhibit the reverse transcriptase of HIV-1, and the cytopathic effect of HIV-1RF, and HIV-1IIIB (Different types of HIV have been identified: HIV-1 and HIV-2, and yet these two types are divided into groups and subgroups, which shows the great variety viral gene.) in submicromolar concentrations.

4.5 -Antifungal activity

A set of molecules containing the nucleus 1,2,4-oxadiazole, substituted 1,2,3-triazole, which also has occupied a central position in medicinal chemistry, and the piperidine, present in many bioactive substances have been tested for its ability antifungals by Sangshetti *et al.* (2009).

The synthesized compounds illustrated in Figure 6, were tested for *in vitro* antifungal activity. This activity was evaluated against different fungal strains, such as *C. albicans*, *F. oxysporum*, *A. flavus*, *A. niger* and *C. Neoformans*, and the values of minimum inhibitory concentration (MIC) were determined using the standard method on agar plates. The miconazole and fluconazole were used as standard of comparison of antifungal activity.

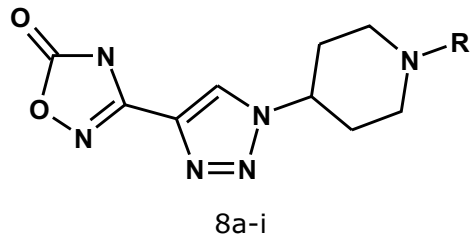
 8a-i	R=	
	8a) CH ₃	8f) COC ₆ H ₅
8b) CH ₂ CH ₃	8g) CO(<i>p</i> -ClC ₆ H ₄)	
8c) COCH ₃	8h) SO ₂ CH ₃	
8d) COCH ₂ CH ₃	8i) SO ₂ (<i>p</i> -CH ₃ C ₆ H ₄)	
8e) COC ₃ H ₇	8j) H	

Figure 6: 3-(1-(1-substitutedpiperidine-4-yl)-1H-1,2,3-triazole-4-yl)-1,2,4-oxadiazole-5(4H)-one.

Many of the new synthesized compounds showed good antifungal activity. From the data of Table 8, it is found that the compounds **8a** and **8h** are the most active between all the compounds tested against all microorganisms, except for *C. neoformans*. In relation to *A. niger*, **8h** is more potent than miconazole and has its value comparable to fluconazole, as shown by the lower MIC. The compound **8a** was more potent than miconazole against *C. albicans* (MIC-20) and *A. flavus* (MIC-10) and equipotent with miconazole against *F. oxysporum* (MIC-25) and *A. niger* (MIC-12.5).

TABLE 8: Antifungal activity of the synthesized compounds (MIC ($\mu\text{g/mL}$)).

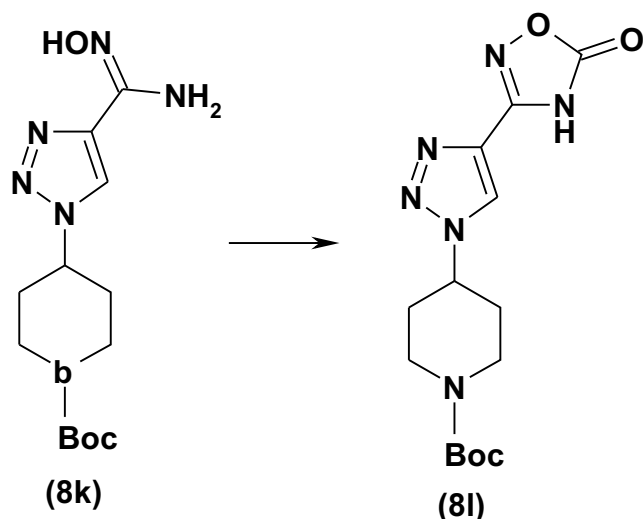
Compounds	<i>C. albicans</i>	<i>F. oxysporum</i>	<i>A. flavus</i>	<i>A. niger</i>	<i>C. neoformans</i>
8a	20	25	10	12,5	60
8b	37	39	19	19	39
8c	60	61	31	31	65
8d	85	90	42	42	85
8e	90	95	–	–	85
8f	85	88	42	42	85
8g	40	55	20	25	40
8h	20	25	15	10	27,5
8i	30	33	25	20	40
Miconazole	25	25	12,5	12,5	25
Fluconazole	5	5	5	10	5

The substitutions on piperidine nitrogen caused different results in relation to the activity of the molecule. It is observed that the methyl substituent (**8a**) increases the molecule activity when compared to the structure without substituent (**8j**). However the increase of the alkyl chain (**8b**) or the introduction of the acetyl group (**8c**) causes the decrease of the antifungal activity. The substitution for acyl groups with longer alkyl chains (propionyl -**8d** and butyryl-**8e**) cause greater loss of activity, and the replacement for the benzoyl group either takes to an increase of the activity when compared to **8c** and **8d**.

However, the introduction of the mesyl group in the same piperidine nitrogen provided the most active compound of the series (**8h**). This compound is more potent than miconazole against *C. albicans* (MIC-20) and *A. niger* (MIC-10) equipotent to miconazole against *F. oxysporum* and equipotent with fluconazole against and *A. niger* (MIC-10).

The authors also found the antifungal activity of the synthetic intermediates (**8k**) and (**8l**). They observed that the introduction of the nucleus 1,2,4-oxadiazole to triazole ring (**8l**) enhanced the antifungal activity when compared to the activity of the intermediates amidoximes (**8k**) (Scheme 14), indicating the importance of this heterocyclic nucleus for the molecule activity.

The results suggest that the series containing 1,2,3-triazoles with nucleus 1,2,4-oxadiazole and the piperidine ring substituted by the methyl or methylsulfone groups in the piperidine nitrogen may serve as important pharmacophores for the conception of new anti-fungal agents with potent activity and minimal toxicity.



Scheme 14 – Structures of the compounds evaluated proposed by SANGSHETTI *et al.* (2009)

4.6 Other activities

Another application for this heterocycle is the prevention of the pro-depressant effect of L-arginine. Studies have demonstrated that L-arginine, an amino acid precursor of nitric oxide, has a dual effect (antidepressant and pro-depressant) in the forced swimming test.

In 2007, Ergun *et al.* tested [1H-[1,2,4]oxadiazole[4,3-a]quinoxalin-1-ona] (ODQ - Figure 7) for this purpose realizing Porsolt's test (forced swimming test). The results showed that doses of ODQ (3 and 10mg/kg) canceled the pro-depressant effect of L-arginine (300 and 1000mg/kg), while anti-depressant component produced by 100 mg/kg L-arginine was not affected.

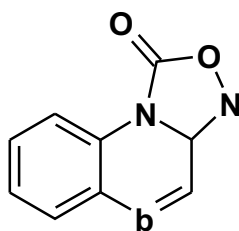


Figure 7 – Structural formula of ODQ

According to Bignami (2015), the orphan drugs' are medical products intended for the prevention diagnosis, or treatment of serious diseases or that constitute a risk to life and are rare. These medications are designated as "orphans" because in normal market conditions, the pharmaceutical industry has little interest in the development and commercialization of products targeted for the small number of patients affected by rare diseases, such as Duchenne muscular dystrophy, because the

On May 27, 2005, the Committee for Orphan Drugs published its favorable opinion for orphan designation of the acid 3-[5-(2-fluoro-phenyl)-(1,2,4-oxadiazole-3-yl)]- benzoic for the treatment of Duchenne muscular dystrophy (EUROPEAN MEDICINES AGENCY, 2015) [46]. This is a genetic neuromuscular disease characterized by a progressive and irreversible weakness of the skeletal muscles, leading the patient to severe respiratory difficulty and death (FONSECA *et al.*, 2007). The 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid, produced by PTC Therapeutics (2015) and known commercially in Europe as Translarna (Figure 8), is a drug which may surpass a specific type of abnormality present in the dystrophin gene of some Duchenne patients. Therefore, it could allow the production of functional dystrophin protein in muscle cells of this group of patients.

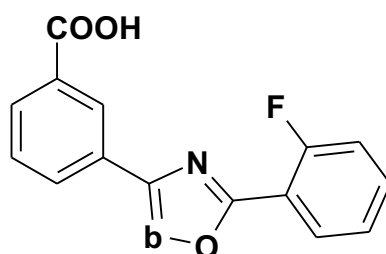


Figure 8 - Structural formula of Ataluren[®]

There are still other useful applications of this group that were not cited in this work, including plant protection (ROHR, 1989; JESCHKE *et al.*, 1995), use as crystalline liquid mesophases (GALLARDO *et al.*, 2011; SHANKER; TSCHIERKE, 2011), OLED's (WU *et al.*, 2005), tracers for Positron Emission Tomography (PET) (BARROW *et al.*, 2011), polymers (ROSSER *et al.*, 1981) and optical brighteners, among others (PROSSEL *et al.*, 1978), which demonstrates the great versatility of this family of compounds.

5. FINAL CONSIDERATIONS

As can be observed, there are many efficient ways to obtain 1,2,4-oxadiazole. Besides the methods mentioned here, with more research is still possible to find in the literature different ways to achieve the heterocycle in question. Searches of other synthetic routes are important, because they aim the search of reagents and reaction conditions more efficient.

The fact of the oxadiazole ring is a part of the structural nucleus of the muscarinic agonist is an important factor for its efficiency in the use of drugs. The pharmacological activity of the groups 1,2,4-oxadiazole depends on the structure of the compound. There are still many drugs, whose the activities need to be potentiated and untreated diseases that need effective medications for its cure. Therefore, this line of research is of paramount importance to the organic medicinal chemistry.

6. REFERENCES

ADIB, M.; JAHROMI, A. H.; TAVOOSI, N.; MAHDAVI, M.; BIJANZADEH, H. R. Microwave-assisted efficient, one-pot, three-component synthesis of 3,5-disubstituted 1,2,4-oxadiazoles under solvent-free conditions. *Tetrahedron Lett* **2006**, *47*, 2965.

AMARASINGHE, K. K. D.; MAIER, M. B., SRIVASTAVA, A.; GRAY, J. L. One-pot synthesis of 1,2,4-oxadiazoles from carboxylic acid esters and amidoximes using potassium carbonate. *Tetrahedron Letters* **2006**, *47*, 3629.

AUGUSTINE, J. K.;VAIRAPERUMAL, V.; NARASIMHAN, S.; ALAGARSAMY, P.; RADHAKRISHNAN, A. Propylphosphonic anhydride (T3P[®]): an efficient reagent for the one-pot synthesis of 1,2,4-oxadiazoles, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *Tetrahedron* **2009**, *65*, 9989.

BARROW, J. C.; HARRISON, S.; MULHEARN, J.; SUR, C.; WILLIAMS, D. L.; WOLKENBERG, S. US Patent 0081297 **2011**.

BARTSCH, R. A. Eliminations from 2-butyl halides induced by halide ions in dimethylformamide and dimethyl sulfoxide. *J. Org. Chem.* **1970**, *35*, 1023.

BEZERRA, N. M. M.; OLIVEIRA, S. P.; SRIVASTAVA, R. M.; SILVA, J. R. Synthesis of 3-aryl-5-decapentyl-1,2,4-oxadiazoles possessing antiinflammatory and antitumor properties. *Il Farmaco* **2005**, *60*, 955.

BIGNAMI, F. EURORDISES. Disponível em: <<http://www.eurordis.org/pt-pt/content/oque-e-um-medicamento-orfao>>. Acess in 19/11/2015.

BOKACH, N. A.; ANATOLII V. KHRIPOUN, A. V.; KUKUSHKIN, V. Y.; HAUKKA, M.; POMBEIRO, A. J. L. A route to 1,2,4-oxadiazoles and their complexes via platinum-mediated 1,3-dipolar cycloaddition of nitrile oxides to organonitriles. *Inorg. Chem.* **2003**, *42*, 896.

BOUGRIN, K.; LOUPY, A.; SOUFIAOUI, M. Microwave-assisted solvent-free heterocyclic synthesis. *J. Photochem. Photobiol. C* **2005**, *6*, 139.

BOKACH, N. A.; ANATOLII V. KHRIPOUN, A. V.; KUKUSHKIN, V. Y.; HAUKKA, M.; POMBEIRO, A. J. L. A route to 1,2,4-oxadiazoles and their complexes via platinum-mediated 1,3-dipolar cycloaddition of nitrile oxides to organonitriles. *Inorg. Chem.* **2003**, *42*, 896.

BOUGRIN, K.; LOUPY, A.; SOUFIAOUI, M. Microwave-assisted solvent-free heterocyclic synthesis. *J. Photochem. Photobiol. C* **2005**, *6*, 139.

BRETANHA, L. C.; TEIXEIRA, V. E.; RITTER, M.; SIQUEIRA, G. M.; CUNICO, W.; PEREIRA, C. M.P.; FREITAG, R. A. Ultrasound-promoted synthesis of 3-trichloromethyl-5-alkyl(aryl)-1,2,4-oxadiazoles. *Ultrasonics Sonochem.* **2011**, *18*, 704.

CANDEIAS, N. R.; BRANCO, L. C.; GOIS, P. M.; AFONSO, C. A. M.; TRINDADE, A. F. MORE sustainable approaches for the synthesis of N-based heterocycles. *Chem. Rev.* **2009**, *109*, 2703.

DOLBIER JR., W. R.; BURKHOLDER, C. R.; MÉDEBIELLE, M. J. *FLUORINE CHEM.* **1999**, *95*, 127-130.

DUCHET, L.; LEGEAY, J. C.; CARRIÈ, D.; PAQUIN, L.; EYNDE, J. J. V.; BAZUREAU, J. P. Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles using ionic liquid-phase organic synthesis (IoLIPOS) methodology. *Tetrahedron* **2010**, *66*, 986.

DURDEN JR, J. A.; HEYWOO, D. L. The reaction of "activated" esters with amidoximes. A convenient synthesis of 1,2,4-oxadiazoles. *J. Org. Chem.* **1971**, *36*, 1306.

ERGÜN, Y.; ERGÜN, U. G. Ö. *Eur. J. Pharmacol.* **2007**, *554*, 150.

European Medicines Agency. Disponível em: <http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005403.pdf>. Acess in 19/11/2015.

FAROOQUI, M.; BORA, R.; PATIL, C. R. Synthesis, analgesic and anti-inflammatory activities of novel 3-(4-acetamido-benzyl)-5-substituted-1,2,4-oxadiazoles. *Eur. J. Med. Chem.* **2009**, *44*, 794.

FONSECA, J. G.; MACHADO, M. J. F.; FERRAZ, C. L. M. S. Distrofia muscular de Duchenne: complicações respiratórias e seus tratamentos. *Rev. Cienc. Med.* **2007**, *16*, 109.

FREITAS, J. J. R.; FREITAS, J. C. R.; DA SILVA, L. P.; DE FREITAS, J. R.; KIMURA, G. Y. V.; SRIVASTAVA, R. M. Microwave-induced one-pot synthesis of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butan-2-ones under solvent free conditions. *Tetrahedron Letters* **2007**, *48*, 6195.

GALLARDO, H.; FERREIRA, M.; VIEIRA, A. A.; WESTPHAL, E.; MOLIN, F.; ECCHER, J.; BECHTOLD, I. H. Columnar mesomorphism of bent-rod mesogens containing 1,2,4-oxadiazole rings. *Tetrahedron* **2011**, *67*, 9491.

GANGLOFF, A. R.; LITVAK, J.; SHELTON, E. J.; SPERANDIO, D.; WANG, V. R.; RICE, K. D. Synthesis of 3,5-disubstituted-1,2,4-oxadiazoles using tetrabutylammonium fluoride as a mild and efficient catalyst. *Tetrahedron Lett.* **2001**, *42*, 1441.

GUILHOTO, L. M. F. F.; NOBRE, C.; SILVA, A. R. C. O.; TAVARES, C. Educational activities for elementary school teachers on epilepsy in the periphery of São Paulo. *J. Epilepsy Clin. Neurophysiol.* **2007**, *13*, 143.

ISPIKOUDI, M.; AMVRAZIS, M.; KONTOGIORGIS, C.; KOUMBIS, A. E.; LITINAS, K. E.; LITINA, D. H.; FYLAKTAKIDOU, K. C. Convenient synthesis and biological profile of 5-amino-substituted 1,2,4-oxadiazole derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 5635.

JESCHKE, P.; LINDNER, W.; WACHENDORFF-NEUMANN, U.; ERDELEN, C. BAYER Aktiengesellschaft US Patent 5,428,049 **1995**.

KABOUDIN, B., MALEKZADEH, L. . Organic reactions in water: an efficient method for the synthesis of 1,2,4-oxadiazole in water. *Tetrahedron Lett.* **2011**, *52*, 6424.

KABOUDIN, B.; SAADATI, F. Magnesia-supported hydroxylamine hydrochloride in the presence of sodium carbonate as an efficient reagent for the synthesis of 1,2,4-oxadiazoles from nitriles. *Tetrahedron Letters* **2007**, *48*, 2829.

KABOUDIN, B.; SAADATI, F. Novel method for the synthesis of 1,2,4-oxadiazoles using alumina supported ammonium fluoride under solvent-free condition. *J. Heteroc. Chem.* **2005**, *42*, 699.

KHATIK, G. L.; KAUR, J.; KUMAR, V.; TIKOO, K.; NAIR, V. A. 1,2,4-oxadiazoles: a new class of anti-prostate cancer agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1912.

KONTOGIORGIS, C. A.; HADJIPAVLOU-LITINA, D. J. Synthesis and anti-inflammatory activity of coumarin derivatives. *J. Med. Chem.* **2005**, *48*, 6400.

KOROLKOVAS, A.; BURCKHALTER, J. H.; *Pharmaceutical Chemistry*, 1st edition, Guanabara-Koogan, Rio de Janeiro, 1988.

KUMAR, D.; GAUTAM PATEL, G.; JOHNSON, E. O.; SHAH, K. Synthesis and anticancer activities of novel 3,5-disubstituted-1,2,4-oxadiazoles. *Bioorg. Med. Chem. Letters* **2009**, *19*, 2739.

LANKAU, H. J.; UNVERFERTH, K.; GRUNWALD, C.; HARTENHAUER, H.; HEINECKE, K.; BERNÖSTER, K.; DOST, R.; EGERLAND, U.; RUNDDELDT, C. New GABA-modulating 1,2,4-oxadiazole. *Eur. J. Med. Chem.* **2007**, *42*, 873.

LEITE, A. C. L.; VIEIRA, R. F.; FARIA, A. R.; WANDERLEY, A. G.; AFITPOUR, P.; XIMENES, E. C. P. A.; SRIVASTAVA, R. M.; OLIVEIRA, C. F.; MEDEIROS, M.V.; ANTUNES, E.; BRONDANI, D. J. Synthesis, anti-inflammatory and antimicrobial activities of new 1,2,4-oxadiazoles peptideomimetics. *Il Farmaco* **2000**, *55*, 719.

MACOR, J. E.; ORDWAY, T.; SMITH, R. L., VERHOEST, P. R.; MACK, R. A. Synthesis and use of 5-vinyl-1,2,4-oxadiazoles as Michael acceptors. A rapid synthesis of the potent muscarinic agonist L-670,548. *J. Org. Chem.* **1996**, *61*, 3228.

MENEGATTI, R.; FRAGA, C. A. M.; BARREIRO, E. J. Quím. Nova Escola (Cadernos Temáticos), **2001**, n. 3, p. 16-22.

OrLEK, B. S., BLANEY, F. E., BROWN, F., CLARK, M. S. G., HADLEY, M. S., HATCHER, J., RILEY, G. J., ROSENBERG, H. E., WADSWORTH, H. J., WYMAN, P. Comparison of azabicyclic esters and oxadiazoles as ligands for the muscarinic receptor. *J. Med. Chem.* **1991**, *34*, 2726.

PROSSEL, G.; SCHINZEL, E.; RÖSCH, G. US Patent 4,122,257 **1978**.

PTCBio. Disponível em: <http://www.ptcbio.com/en/pipeline/ataluren-translarna/>. Acess in 19/11/2015.

QUADRELLI, P.; INVERNIZZI, A. G.; FALZONI, M.; CARAMELLA, P. Cycloadditions of nitrile oxides to amidoximes. A general synthesis of 3,5-disubstituted 1,2,4-oxadiazole-4-oxides. *Tetrahedron* **1997**, *53*, 1787.

RAJAGOPALAN, P. Dipolar addition reactions of nitrile oxides. VII. A new general method of synthesis of 3,5-disubstituted 1,2,4-oxadiazoles. *Tetrahedron Lett.* **1969**, *5*, 311.

ROHR, O. Ciba-Geigy Corp. US Patent 4,871,685 **1989**.

ROSA, M. F. *Dissertation in Organic Chemistry (MSc)*, Federal University of Rio de Janeiro, Brazil, 1992.

ROSSER, R. W.; SHALHOUB, I. M.; KWONG, H. US Patent 4,273,918 **1981**.

SAKAE, T. M.; BALDISSEROTO, C. M.; BIANCHINI, N. Comparison of *Casearia silvestris* with indometacine and placebo in reducing edema in the hind paw of rats, induced by the use of carrageenan. *Arq. Catarinenses Med.* **2005**, *34*, 33.

SAKAMOTO, T.; CULLEN, M. D.; HARTMAN, T. L.; WATSON, K. M.; BUCKHEIT, R. W.; PANNECOUQUE, C.; CLERCQ, E.; CUSHMAN, M. Synthesis and anti-HIV activity of new metabolically stable alkenyldiarylmethane non-nucleoside reverse transcriptase inhibitors incorporating N-methoxy imidoyl halide and 1,2,4-oxadiazole systems. *J. Med. Chem.* **2007**, *50*, 3314.

SANGSHETTI, J. N.; NAGAWADE, R. R.; SHINDE, D. B. Synthesis of novel 3-(1-(1-substituted piperidin-4-yl)-1H-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-5(4H)-one as antifungal agent. *Bioorg. Med. Chem. Letters* **2009**, *19*, 3564.

SANTOS FILHO, J. M. S. Bioisoterial planning, synthesis and pharmacological evaluation of new analogues of 1,2,4-oxadiazoles. *Dissertation in Biotechnology of Bioactive Products (MSc)*, Federal University of Pernambuco, Recife, Brazil, 2002.

SHANKER, G.; TSCHIERSKE, C. Synthesis of non-symmetrically substituted 1,2,4-oxadiazole derived liquid crystals. *Tetrahedron* **2011**, *67*, 8635.

SHARMA, S.; GANGAL, S.; RAUF, A. An efficient, one-pot synthesis of novel 3,5-disubstituted-1,2,4-oxadiazoles from long-chain carboxylic acid derivatives. *Acta Chim. Slov.* **2009**, *56*, 369.

SRIVASTAVA, R. M.; LIMA, A. A.; VIANA, O. S.; SILVA, M. J. C.; CATANHO, M. T. J. A.; MORAIS, J. O. F. Antiinflammatory property of 3-aryl-5-(n-propyl)-1,2,4-oxadiazoles and antimicrobial property of 3-aryl-5-(n-propyl)-4,5-dihydro-1,2,4-oxadiazoles: their synthesis and spectroscopic studies. *Bioorg. Med. Chem.* **2003**, *11*, 1821.

SURESHBABU, V. V.; HEMANTHA, H. P.; NAIK, S. A. Synthesis of 1,2,4-oxadiazole-linked orthogonally urethane-protected dipeptide mimetics. *Tetrahedron Letters*, **2008**, *49*, 5133.

SWAIN, R. B.; KNEEM, C.; MOSELEY, J.; SAUNDERS, J.; SEWARD, E. M.; STEVENSON, G.; BEER, M.; STANTON, J.; WATLING, K. Novel 5-HT₃ antagonists. Indole oxadiazoles. *J. Med. Chem.* **1991**, *34*, 140.

TIEMANN, F.; KRÜGER, P. Ueber amidoxime und azoxime. *Chem. Ber.* **1884**, *17*, 1685.

WIEDNER-WELLS, M. A.; HENNINGER, T. C.; FRAGA-SPANO, S. A.; BOGGS, C. M.; MATHEIS, M.; RITDHIE, D. M.; ARGENTIERI, D. C.; WATCHER, M. P.; HLASTA, D. J. Synthesis and structure-activity relationships of 3,5-diarylisoaxazoles and 3,5-diaryl-1,2,4-oxadiazoles, novel classes of small molecule interleukin 8 (IL-8) receptor antagonists. *Bioorg. Med. Chem. Letters* **2004**, *14*, 4307.

WU, F. I.; SHU, C. F.; CHIEN, C. H.; TAO, Y. T. Fluorene-based oxadiazoles: thermally stable electron-transporting materials for light-emitting devices *Synth. Metals* **2005**, *148*, 133.

ZIEDAN, N. I.; STEFANELLI, F.; FOGLI, S.; WESTWELL, A. D. Design, synthesis and pro-apoptotic antitumour properties of indole-based 3,5-disubstituted oxadiazoles. *Eur. J. Med. Chem.* **2010**, *45*, 4523.