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AN OVERVIEW OF 1, 3, 4-OXADIAZOLE

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Abstract-

A well-known reaction of amidoximes is the acylation reaction that was extensively studied in the 1920s and 1930s. Recent publications on amidoxime chemistry relate to the synthesis of O-acylated amidoximes and 1,2,4-oxadiazoles, one of the most accessible heterocycles. 1,2,4-Oxadiazoles have been extensively studied for use in pharmaceutical chemistry due to their bioisosteric properties with ester and amide groups that greatly enhance biological activity. A one-step synthesis of 1,2,4-oxadiazoles consists of an amidoxime and a carbonyl-containing reactant (ester, amide, acid, aldehyde), as well as a nitrile and an N-oxide. Five-membered 1,2,4-oxadiazole heterocycles have attracted considerable attention due to their unique biological isosteric properties and very broad range of biological activities. This makes it an ideal environment for new drug development. A century after his discovery of 1,2,4-oxadiazole, its extraordinary potential led the medicinal chemist and his 1,2,4-oxadiazole moieties to include several currently available Attracted the attention of pharmaceuticals. It is worth noting that interest in biological applications of 1,2,4-oxadiazoles has doubled over the past 15 years. After a brief historical introduction, here we provide a comprehensive overview of recent achievements in the synthesis of 1,2,4-oxadiazoles and key advances in their biological applications over the past five years. increase. and a brief comment on future prospects.

Keywords- Oxadiazoles, Biological activities, Synthesis, Mechanism of action**.**

Introduction-

The well-known amidoxime reactions involve their acylation, which has been the subject of extensive research between 1920 and 1930. The majority of recent publications on the chemistry of amidoximes discuss the synthesis of 1,2,4-oxadiazoles and O-acylated amidoximes, two of the most easily obtainable heterocycles. 1,2,4-oxadiazoles have undergone extensive research in preparation for use in pharmaceutical chemistry because they are bioisosteric with ester and amide groups and significantly increase biological activity. Along with the dehydration of O-acylated amidoximes, another route for the single-stage synthesis of 1,2,4-oxadiazoles involves

the interaction of amidoximes with carbonyl-containing reactants, such as esters, amides, acids, and aldehydes, as well as nitriles and N-oxides. The 1,3-cycloaddition of N-oxides is a different route to 1,2,4-oxadiazoles [1].

Among the various classes of heterocyclic compounds, 1,2,4-oxadiazoles are noted for their usefulness in several applications, including industrial materials, agricultural products (such as pesticides), and pharmaceuticals and medical products. , representing the greatest utility for these compounds. The 1,2,4-oxadiazole nucleus is found in a variety of synthetic drugs that exhibit a wide range of biological activities, including anti-inflammatory, antifungal, antibiotic, antioxidant, antispasmodic, and anticancer properties. Accordingly, several approaches for preparing this class of compounds have been described in the literature. In general, the synthesis of 1,2,4-oxadiazoles involves the coupling of an amidoxime with an activated carboxyl group to give an O-acylamidoxime, followed by its cyclodehydration. Cyclization of O-acylamidoxime is N,N'-dicyclohexylcarbodiimide (DCC), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide (EDC), N,N'-carbonyldiimidazole (CDI), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), and N,N'-diisopropylcarbodiimide (DIC)/HOBt [2,3].

Despite the wide range of methods available for producing the desired 1,2,4-oxadiazoles, some limitations exist, including the need for high temperatures, protracted reaction times, and the use of potentially dangerous solvents like DMF, diglyme, and 1,4-dioxane. In the field of organic synthesis, the use of water as a solvent has recently attracted more and more attention. Water is superior to traditional organic solvents in many ways, primarily because it is inexpensive and has nontoxic, nonpolluting, and flammable properties. [4]

On the other hand, because of the strict reaction control, high reaction rates, and energy savings, the use of microwaves to mediate organic transformations has emerged as a very useful and effective tool for synthetic protocols. There have been descriptions of microwave transformations using water as the solvent. According to several studies, water behaves as a pseudoorganic solvent at higher temperatures and pressures because the dielectric constant significantly decreases and an ionic product increases the solvating power toward organic molecules to a level comparable to that of acetone or ethanol, [4, 5]

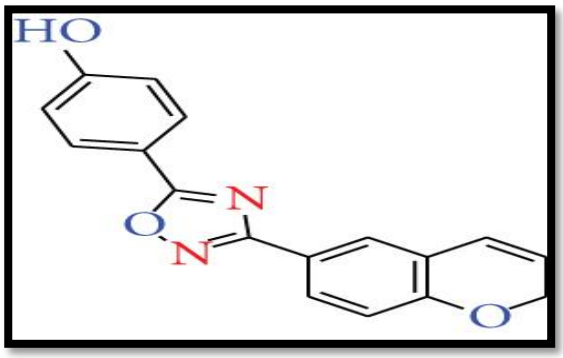


Figure Number 01- The Structure of 1,2,4-Oxadiazole

Methods of 1, 2, 4-Oxadiazole Synthesis-

To date, several methods have been developed to synthesize 1,2,4-oxadiazole derivatives. Most of them are based on the heterocyclization of amidoximes and carboxylic acid derivatives or the 1,3-dipolar cycloaddition of nitriles and nitrile oxides. The first approach proposed by Tiemann and Krüger uses an amidoxime and an acyl chloride to form two products. The use of TBAF or pyridine as a catalyst in the above reaction improves synthetic efficiency [6].

Reactions between amidoximes and carboxylic acid esters, especially methyl and ethyl esters, activated carboxylic acids (using coupling reagents such as EDC, DCC, CDI, TBTU or T3P) or carboxylic acid anhydrides have also been used. Despite the simplicity of the above methods, poor yields, purification difficulties, and infeasibility due to harsh conditions were usually observed. It is worth noting that microwave irradiation (MWI) has also been applied to the heterocyclization of amidoximes and acyl chlorides/carboxylic acid esters in the presence of NH4F/Al2O3 or K2CO3 [7].

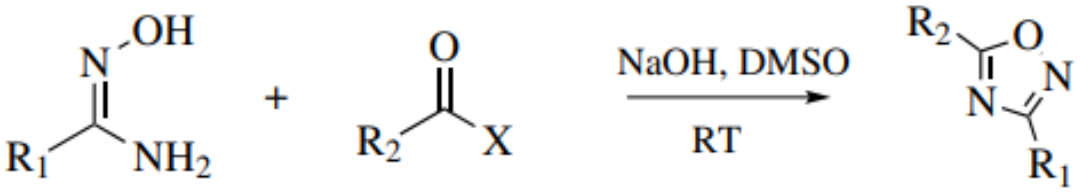
This synthetic approach provided 3,5-disubstituted-1,2,4-oxadiazoles in good yields within a very short reaction time. Furthermore, the formation of aryl amidoximes by microwave-assisted reaction of aryl nitriles with hydroxylamine hydrochloride in the presence of catalysts (MgO or CHCOOH or KF) has also been reported. This procedure provided 1,2,4-oxadiazoles in a simple two-step process. Interestingly, the application of MWI showed several advantages compared to conventional synthetic strategies [8, 9].

Remarkably short reaction times, high yields, and easy purification. Additionally, the amount of volatile organic solvents was significantly reduced. This is the currently preferred green synthetic approach. A second method to form 1,2,4-oxadiazoles involves the 1,3-dipolar cycloaddition of nitrile oxides and nitriles [10].

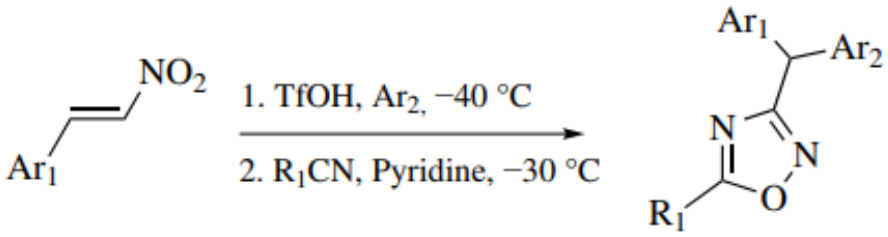
Despite the availability of starting materials and reagents, this synthetic method is not suitable for 1,2,5-oxadiazole-2-oxide and 1,2,4- It is difficult because it can form oxadiazole. -4-oxide by dimerization of nitrile oxide. However, in 2003 Bokach N. and others. published a study on the 1,3-dipolar cycloaddition of nitrile oxides with nitriles in the presence of platinum(IV) catalysts, resulting in the formation of 1,2,4-oxadiazoles under mild conditions.

I was, however, problems such as low solubility of starting materials, low yields, and expensive catalysts still make this synthetic route intractable. Recently, a new synthetic approach to the formation of 1,2,4-oxadiazoles was reported, Bykov et al. First one-pot synthesis for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from the corresponding amidoximes and carboxylic acid methyl or ethyl esters in the superbasic medium NaOH/DMSO at room temperature (RT). Published research on law [11].

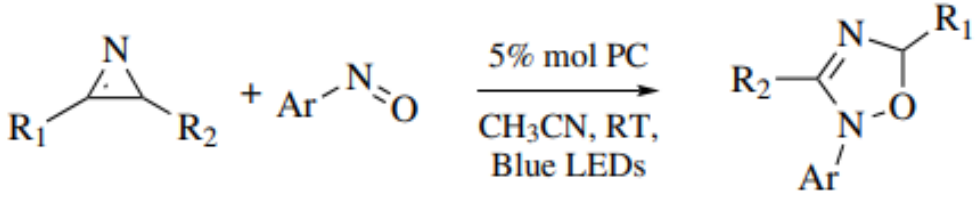
This synthetic approach yields a wide variety of oxadiazole analogues that can be isolated via a simple purification protocol despite moderate to long reaction times (4–24 h) and low yields (11–90%). Got it. Furthermore, the presence of -OH or -NH2 groups in the carboxylic acid ester structure limited the formation of the desired compounds. Synthesis of 1,2, 4-oxadiazole analogs in the superbase medium (R1 = 4-methylphenyl, R2 = methyl or phenyl, X = methoxy or ethoxy) [12].



Synthesis of 3,5-substituted-1,2,4-oxadiazoles using gem-dibromomethylarenes (R1 = phenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 2-chloro-4-fluorophenyl, 4-cyanophenyl or 4-methoxyphenyl, R2 = H, methyl or methoxy). Recently, Golushko A. et al. developed a novel synthetic method of 1,2,4-oxadiazoles based on tandem reaction of nitroalkenes with arenes and nitriles in the presence of TfOH. Despite the excellent yields (~90% in most cases) and short reaction time (10 min), the usage of a superacid requires resistant starting materials, which can be a serious limitation [13].



Reaction of nitrostyrene with arenes and nitriles in the presence of TfOH gives 1,2,4-oxadiazoles (R1 = methyl, ethyl, chloromethyl, phenyl or cyclopropyl, Ar1 = phenyl, 4-methylphenyl, 4 -fluorophenyl, 4-chlorophenyl, 4-bromophenyl, Ar2 = phenyl, p-xylene, o-xylene). In 2019, we investigated the [3+ 2] Studies have been carried out on cycloaddition reactions. Presented. As a result, 2,3,5-trisubstituted 1,2,4-oxadiazoles are formed. This synthetic strategy provided an efficient synthetic route for the synthesis of 1,2,4-oxadiazoles with green chemistry. Moderate yields (35–50%) limit the widespread application of this type of transformation, despite promising and environmentally benign conditions. However, further research is still underway to improve this rational method [14, 15].



Biological Activity of oxadiazole-

Anticancer Agents-

Each year, cancer affects approximately 20 million people worldwide and causes millions of deaths. Unfortunately, the number of new cancer cases is still rising, and by 2040, about 30 million people in developed countries will be diagnosed with cancer. The search for new cancer treatments and effective drugs is therefore one of the greatest needs of today's communities and a challenge for modern medicine [16].

Biological evaluations of 1,2,4-oxadiazoles have revealed that some of their derivatives are potent anticancer agents. A major breakthrough was the discovery of his 3,5-diaryl-substituted derivatives of 1,2,4-oxadiazoles as a new series of apoptosis-inducing agents. Since then, research into the anticancer activity of 1,2,4-oxadiazole derivatives has been initiated and a broad compound library has been created. Recently, Maftei C.V. et al. reported the synthesis of 4-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl)aniline [17].

This aniline has moderate activity with an average IC50 value of approximately 92.4 μM against a group of 11 cancer cell lines. Display (human colon adenocarcinoma - CXF HT-29, human gastric cancer - GXF 251, human lung adenocarcinoma - LXFA 629, human non-small cell lung cancer - LXFL 529, breast cancer - derived from mouse athymic lung metastasis - MAXF 401, human melanoma - MEXF 462, human ovarian adenocarcinoma - OVXF 899, human pancreatic cancer - PAXF 1657, human pleural mesothelioma carcinoma - PXF 1752, human renal carcinoma - RXF 486, human uterine carcinoma - UXF 1138). Importantly, compound 1 became a precursor for the synthesis of new compounds with greater antiproliferative activity [18].

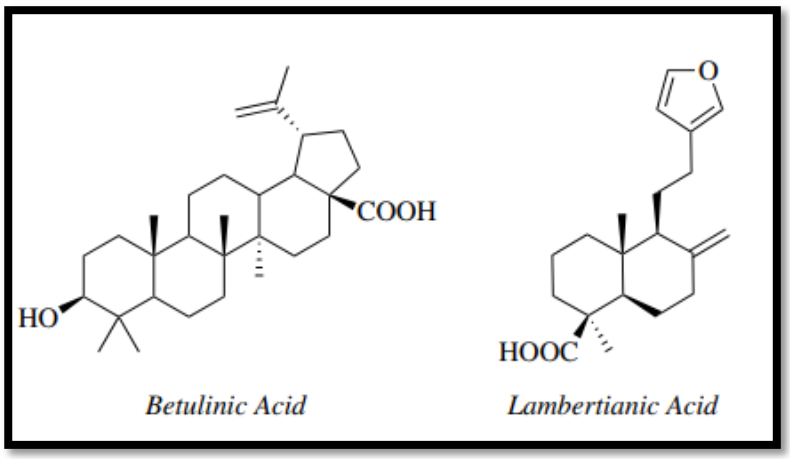


Figure Number 02- the examples of anticancer agent.

Antimicrobial Agents-

So far, the literature has identified more than 1400 species of microorganisms (including bacteria, viruses, protozoa, fungi, and helminths) that can cause disease and, very often, death in humans. Surprisingly, only 20 of them (mostly bacteria) account for about two-thirds of deaths. Estimates of deaths from infection are steadily declining, from 16 million in 1990 to about 15 million, and in developed countries, he is projected to reach 13 million in 2050. However, people still suffer a huge burden from pneumonia, HIV/AIDS, tuberculosis, malaria, diarrhea and many other diseases.

The threat of multiple pandemics in European countries and around the world, including the recent infection by the SARS-CoV-2 virus that causes COVID-19, has driven the discovery of new and effective antibacterial/antiviral drugs and up-to-date treatments. development presents two major challenges [19, 20].

2014, O'Daniel P.I., Mobashery S., Chang M. et al. Doctors from the University of Notre Dame in the United States, as a new antibiotic, he put a lot of effort into developing 1,2,4-oxadiazoles, a new class of non-β-lactam drugs that can convert PBP2a from methicillin resistance. discovered. Inhibits Staphylococcus aureus (MRSA). A detailed computational screen allowed us to select 29 compounds from the 1.2 million compounds tested (ZINC database) for antimicrobial activity against the ESKAPE pathogen and found compound 23 to be the most promising [21].

Its further evaluation yielded a large number of derivatives and discovered 24 derivatives with good antibacterial activity against vancomycin-resistant Staphylococcus aureus (VRSA), vancomycin-resistant Enterococcus faecium (VRE), and MRSA. (Table 3). MIC values range from 1 to 2 μg/mL. Furthermore, a study on rapid killing kinetics showed that 24 was able to induce immediate cell death in VRE- and daptomycin-insensitive isolates at 4 mg/L in 1 hour, superior to the reference compound daptomycin. It became clear [22].

Twenty-four additional modifications and very detailed SAR analysis allowed us to obtain a broad library of its analogues (including hundreds of derivatives), 5-(1H-indol-5-yl)-3-(4-(4- (trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazole. ND-421 exhibited a longer half-life, greater mass distribution, lower clearance, better bioavailability, and a 3-fold longer post-antibiotic effect than linezolid, which had no inoculum effect, with no change in biological activity. I did. Furthermore, in vitro studies against 2- and 4-fold resistant Staphylococcus aureus revealed the first reported unique mechanism of MRSA resistance to 1,2,4-oxadiazole. Furthermore, these mutant pathogens did not show increased resistance to the antibiotics ampicillin, imipenem, linezolid, and vancomycin (the last line of defense against MRSA and VRSA), thus making ND-421 a complete killer of refractory organisms [23].

It has become a viable alternative. Also, unlike non-β-lactam antibiotics (vancomycin, linezolid, gentamicin, doxycycline, and azithromycin), ND-421 is highly synergistic with other β-lactams (oxacillin, piperacillin, imipenem, meropenem, and cefepime). It is also worth noting that . . Recently, the same research team performed additional in vitro studies with ND-421 against 210 different MRSA and VRE, showing MIC50 values of 4 μg/ml for all strains tested. Furthermore, MIC50 values were consistently reduced when the compounds under investigation were used in combination with oxacillin. In conclusion, 1,2,4-oxadiazoles 23, 24 and ND-421 are highly potent and highly promising non-β-lactam bactericidal antibiotics against Gram-positive multidrug-resistant bacteria with further in vivo Evaluation and clinical studies are awaited. The information has not been released to date, but it is pertinent [24].

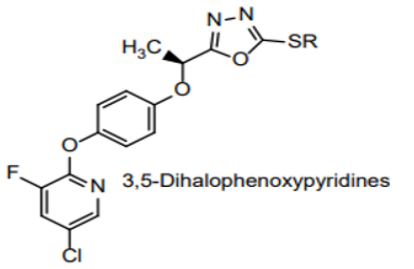
Anti-Allodynic Agents-

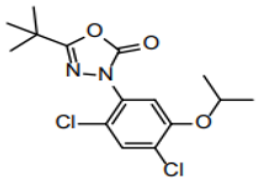
Neuropathic pain is a serious problem worldwide. Today, antidepressants, anticonvulsants, and opioids based on tricyclic structures are used to treat chronic pain. However, some of them are not effective in all cases and can cause serious unwanted side effects (even life-threatening addiction and abuse) during long-term treatment. and σ2), originally misidentified as opioid receptors (whose function is still not fully understood), have been identified as potential targets for central nervous system therapeutics. 40;CNS)disease and drug-resistant tumors [25].

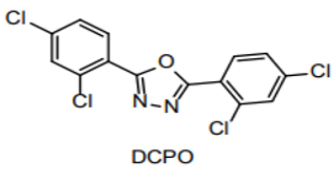
2018 Cao Pi X and others. A series of 3-phenyl-1,2,4-oxadiazole derivatives were synthesized and evaluated as potent antiallodynics with affinity for σ1 and σ1 receptors with low activity on other CNS receptors . Based on their previous work, the synthesis of hybrid compounds based on the 1,2,4-oxadiazole scaffold with six-membered heterocycles of pyrimidine and pyridazinone as pharmacophores led to improved activity [26].

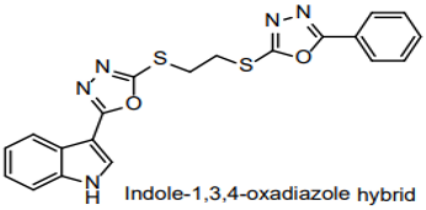
The synthesized compounds were evaluated in vitro in primary σ1 and σ2 binding assays using the radiolabeled ligands [3H] -pentazocine and [3H]-dio-o-tolylguanidine, respectively. rice field. 3-(2,4-Dichlorophenyl)-5-(4-(piperidin-1-yl)butyl)-1,2,4-oxadiazole has the highest affinity and selectivity for the σ1 receptor. The Ki value was 0.28 nM, with σ and σ of 164 nM, respectively. Surprisingly, the activity of 37 was higher than that of the S1RA σ1 and σ2 agonists of the reference compounds currently in phase II clinical trials (11 and >2000 nM for σ1 and σ2, respectively) [27, 28].

Furthermore, SAR studies have shown that the presence of a hydrophobic pharmacophore and halogen atoms in the phenyl ring structure is important for maintaining high biological activity and selectivity. Moreover, substituting the chlorine atom with other halogens or substituting the piperidine heterocycle significantly reduced the activity. Additionally, 37 in vivo studies in the rat formalin test and chronic contractile injury (CCI) pain model assay demonstrated a surprising potential as a drug for neuropathic pain [29, 30].









Anticonvulsant Agents-

Epilepsy is a neurological disorder characterized by frequent and unpredictable seizures that affects more than 50 million people of all ages worldwide. Unfortunately, we don't yet know what causes epilepsy, but it can be caused by stroke, brain injury, tumors, infections, or birth defects. Although there are many examples of drugs on the market today (carbamazepine, phenobarbital, phenytoin, diazepam, etc.), these drugs are ineffective in

approximately 30% of patients and have undesirable side effects such as dizziness, drowsiness, and gastrointestinal upset. There is also I have an observed experience [31].

Therefore, the development of new safe and effective antiepileptic drugs is needed. Most recently, Mohammadi Kanaposhtani M. and colleagues published a series of acridone- and coumarin-based 1,2, 4-oxadiazoles as potent anticonvulsants against pentylenetetrazole (PTZ)- and maximal electric shock (MES)-induced seizures in mice.

The investigated acridone-based compounds and coumarin derivatives showed promising antiepileptic properties in PTZ and MES assays (except coumarin derivatives in MES assay). Compounds 38 (ED50 values of 2.08 and 3.71 mg/kg in PTZ and MES, respectively) and 39 (100% protection from seizures in mice at a dose of 7 mg/kg in MES test) had the highest anti-epileptic activity. However, the anticonvulsant efficacy was lower than diazepam as a reference (0.68 and 0.98 mg/kg in PTZ and MES tests, respectively; 100% protection against seizures at doses of 2 mg/kg in MES test). For this reason, structural modifications (e.g., aromatic ring substitutions) in further development may reveal features of the as yet undisclosed acridone- and coumarin-fused 1,2,4-oxadiazoles [32].

Anti-Alzheimer Agents-

Alzheimer's disease (AD) is a chronic neurodegenerative disease that usually slowly and continuously worsens over time leading to dementia, language-disorders, disorientation, mood swings and behavioral issues, resulting usually in death within 3 to 9 years after diagnosis. Importantly, all over the world AD impacts more than 40 million people leading to death of approximately 2 million people every year. Although, over 100 years have passed since the first AD case has been described, to date the cause of this disease is still poorly understood.

Acetylcholinesterase (AChE) and butyryl-cholinoesteraze (BChE) are enzymes responsible for the hydrolysis of neurotransmitter in brain tissues—acetylcholine (ACh)—leading to a decrease of its concentration, which is characteristic feature of AD. Nowadays, AChE inhibitors such as galantamine, donepezil, and rivastigmine are used for treating AD, however, their application leads only to a slowdown in the disease development or reduction of AD symptoms, but the progress cannot be stopped or reversed. Therefore, the development of new, effective treatment methods is of special significance [33].

Recently, Zhang J. et al. performed the synthesis and biological evaluation of coumarin-1,2,4-oxadiazole-fused hybrids as selective BChE and AChE antagonists with potent neuroprotective activity. The previous study of Phidianidine B modifications led to the discovery of neuro-protectants against Aβ25-35-induced neurotoxicity in human neuroblastoma (SH-SY5Y) cancer cell line. Obtained 1,2,4-oxadiazole-coumarin derivatives were evaluated against AChE and BChE. All tested compounds exhibited moderate activity toward AChE with the IC50 values ranging from 89.7 to 45.6 μM. Compound 40 turned out to be the most selective BChE inhibitor exhibiting the IC50 values of 8.2 and 77.6 μM against BChE and AChE, respectively [34].

Interestingly, the second enantiomer of 40 showed similar activity (IC50 = 9.6 and 72.5 μM against BChE and AChE, respectively). Moreover, compound 40 demonstrated significant neuroprotective activity against Aβ25-35-induced neurotoxicity in SH-SY5Y cell line (18.8% cell viability increases at 1 μM, compared with Aβ25-35

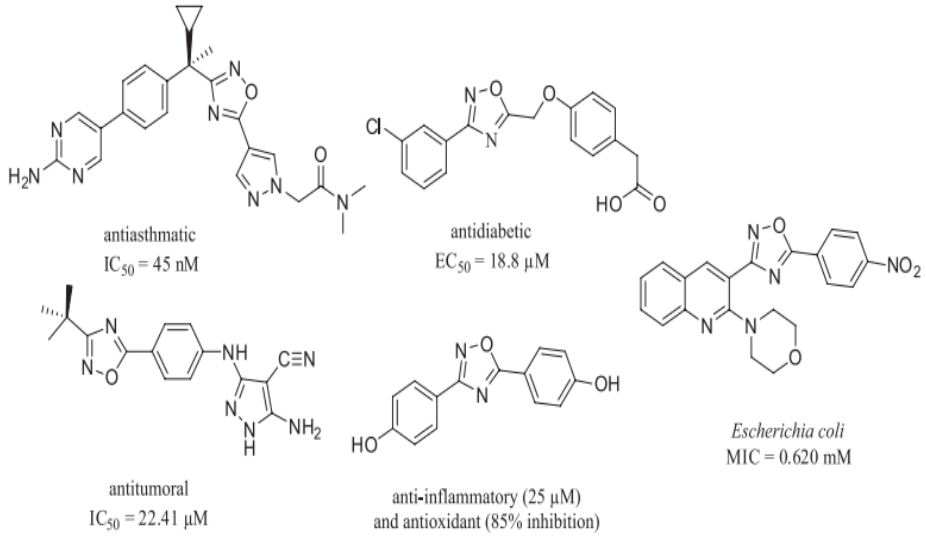
treated cells). Discovering the 1,2,4-oxadiazole/coumarin derivatives may lead to a new molecular framework for developing dual-AChE-BChE inhibitors as anti-Alzheimer agents [35].

Anti-Insomnia Agents –

Insomnia is a health disorder associated with unsatisfactory or inadequate sleep, usually resulting in poor rest, concentration and learning abilities, bad mood, irritability, as well as cardiovascular disease, high blood pressure, dementia, or depression. Insomnia is a serious public health problem, estimated to affect up to 70% of the general adult population. For many years, insomnia was primarily treated with GABA antagonists, but the high risk of addiction and decreased next-day mood prompted the further development of new drugs for insomnia.

The neuropeptides orexin A and orexin B were discovered in 1998 and their antagonists have been discovered since then. B. Almolexant, lemborexant achieved clinical trials. In 2014, the FDA approved suvorexant as the first dual orexin receptor antagonist (DORA) for the treatment of insomnia, marketed under the brand name Belsomra [36, 37].

However, morning drowsiness, muscle weakness, strange dreams and sleepwalking are common side effects, so there is still a need for more potent compounds with better pharmacological profiles and safety. Brotschi C. and Boss A recent study by C. led to the development of new 1,2,4-oxadiazole derivatives as DORA. This study is a continuation of extensive research aimed at finding effective drugs for the primary treatment of insomnia [38, 39].



Anticonvulsant activities-

Preparation of sequences of novel 2-substituted-5-[2-(2-fluorophenoxy)-phenyl]-1,3,4-oxadiazoles 50 and evaluation of their anticonvulsant properties. In both the PTZ model and the maximal electroshock seizure (MES) model, compounds containing the -NH2 substituent at the 2-position of the oxadiazole ring show the highest anticonvulsant activity. PTZ testing showed that the effect was blocked by the benzodiazepine antagonist flumazenil, suggesting that the benzodiazepine receptors are involved in this effect [40].

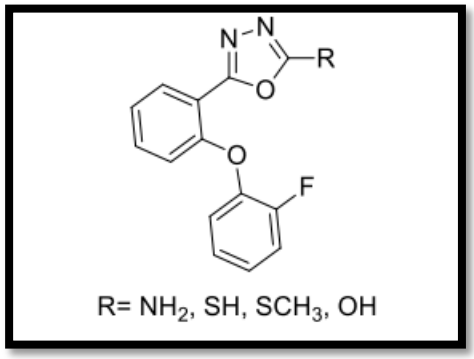


Figure Number 03- Family of 1, 3, 4-oxadiazoles exhibiting anti-convulsant activity.

Anti-protozoal activities-

New 5-(3,5-disubstituted -1H-indol-2-yl)-1,3,4- oxadiazole-2(3H)-thione and 2-[5-(3,5- disubstituted-1H-indol-2-yl) -2-thioxo-1,3,4- oxadiazol-3(2H)-yl] acetohydrazides were synthesized and evaluated for the potential antihelmintic property on Pheratimaposthuma using piperazine citrate 2 mg ml-1 as standard. 3- Ethyl-5-(5-methyl-3-phenyl-1H-indol-2-yl)- 1,3,4-oxadiazole-2(3H)-thione 55 and 3-benzyl5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4- oxadiazole-2(3H)-thione 56 were two tested molecules with better activity among the most common compounds in this series [41, 42].

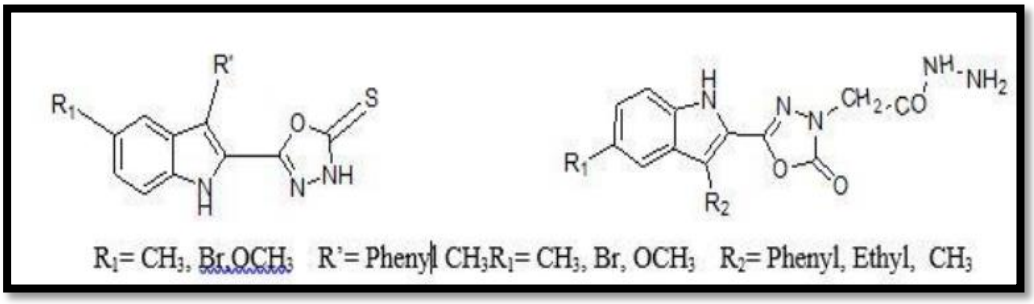


Figure Number 04- Family of 1, 3, 4-oxadiazoles exhibiting anti-protozoal activity.

Conclusion-

Five-membered 1,2,4-oxadiazole heterocycles have attracted considerable interest due to their remarkable bioisosteric properties and very broad range of biological activities. Therefore, it is an ideal structure for new drug development. One hundred years later, following the discovery of 1,2,4-oxadiazole, medicinal chemists were drawn to its extraordinary potential and investigated the few currently available compounds containing the 1,2,4-oxadiazole moiety. drugs have been identified. In particular, interest in biological applications of 1,2,4-oxadiazoles has doubled over the past 15 years. Oxydiazole is a five-membered heterocyclic compound containing one oxygen atom and two nitrogen atoms (historically also known as furadiazole). Depending on where the nitrogen atom is placed, oxadiazoles can take one of four different forms.

Conflicts of interest-

There are no conflicts of interest or disclosures regarding the manuscript.

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