WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Oxadiazole

Gandham Moses[1], Dr. M. Sunitha Reddy[2]

[1]Student, Department of Pharmaceutical Chemistry, Jawaharlal Nehru Technological University, Hyderabad.
[2]Proffessor, Department of Pharmaceutical Chemistry, Jawaharlal Nehru Technological University, Hyderabad.
Email ID: gandhammoses07@gmail.com

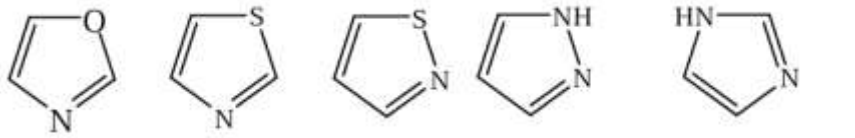
ABSTRACT

Oxadiazole constitutes a five-membered heterocyclic compound featuring two nitrogen atoms and one oxygen atom. The 1,3,4-oxadiazole and 1,2,4-oxadiazole manifest advantageous physical, chemical, and pharmacokinetic attributes, thereby significantly augmenting their pharmacological efficacy through hydrogen bond interactions with biomacromolecules. Recently, oxadiazole has proven to be the bioactive moiety in various compounds. Derivatives of oxadiazole showcase activities such as antibacterial, anti-inflammatory, anti-tuberculous, anti-fungal, anti-diabetic, and anticancer properties. This article presents a compilation of compounds incorporating oxadiazole rings, exclusively covering the last three years This compilation is intended to provide valuable insights for researchers in the domains of organic synthesis, medicinal chemistry, and pharmacology.

KEYWORDS: Oxadiazole, Synthesis, Antimicrobial, Anti-inflammatory, Applications

INTRODUCTION

The category of five-membered aromatic heterocycles surpasses the size of the six-membered heterocycle group[1]. This discrepancy arises from the fact that only one atom within the ring needs to be divalent, allowing for the incorporation of a greater number of heteroatoms into neutral five-membered rings[2].



Oxazole Thiazole Isothiazole 1H-Pyrazole 1H-Imidazole

Oxadiazole

Nitrogen heterocycles play a pivotal role in the landscape of drug discovery. These nitrogenated cores are prevalent as fragments in the structures of numerous drugs, exhibiting diverse ring sizes, including both aromatic and nonaromatic rings, as well as fused and bicyclic rings[3].

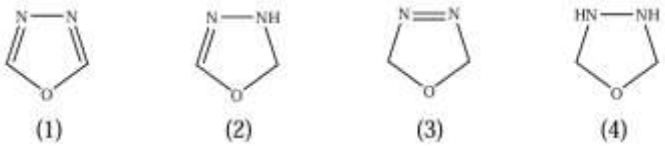
Oxadiazoles, a specific class of heterocyclic compounds, consist of two carbon atoms, two nitrogen atoms, and one oxygen atom. Discovered in 1884 by Tiemann and Krüger, they were initially designated as furo[ab]diazoles. Oxadiazoles can be isosterically compared to furan; however, the substitution of two methine groups (-CH=) with two sp2 nitrogen atoms (-N=) diminishes their aromaticity. As a result, some isomers exhibit electronic comparability to conjugated diene systems[4]. Oxadiazoles manifest in four distinct isomeric structures.

Properties of oxadiazole:

Molecular weight	:	$C_2H_2N_2O$
Molecular formula	:	70.05
Physical State	:	Liquid
Boling point	:	150˚C

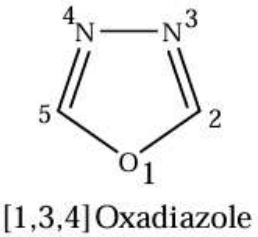
Structure

1,3,4-oxadiazole (1) stands out as a thermally stable neutral aromatic molecule[5]. It is the sole isomer devoid of an oxygen-nitrogen bond and exists in two partially reduced forms: 2,3-dihydro-1,3,4-oxadiazole (2) and 2,5-dihydro-1,3,4-oxadiazole (3), contingent upon the position of the double bond. The fully reduced version of 1,3,4-oxadiazole is denoted as 2,3,4,5-tetrahydro-1,3,4-oxadiazole.



1,3,4-oxadiazole ring is symmetrical and planer with the following structural parameters.

1,3,4-Oxadiazole is an aromatic molecule characterized by a resonance energy of 167.4 kJ/mol. The bond lengths within the 1,3,4-oxadiazole molecule illustrate the delocalization of π-electrons[6]. Nevertheless, the C=N bond lengths closely resemble those in acyclic compounds (1.27 Å), suggesting the presence of some dienic character in 1,3,4-oxadiazole.

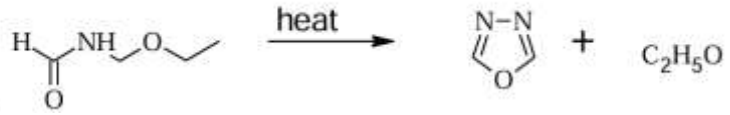


IMPORTANCE OF HETEROCYLCLLIC COMPOUNDS

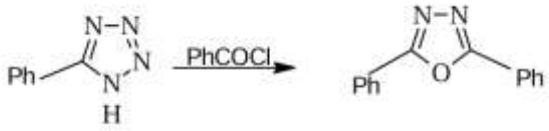
- Heterocyclic compounds exhibit a diverse range of pharmacological activities, continually yielding novel therapeutic agents. The biological effects attributed to heterocycles stem from their ability to interact with various enzymes, binding either to active sites or enzyme pocket structures through a spectrum of intra-molecular interactions, including van der Waals and hydrophobic forces, hydrogen bonding, and metallic coordination bonds. This property positions them as vital scaffolds in medicinal chemistry (Pearce 2007)[7]. A myriad of naturally occurring substances, such as haemoglobin, chlorophyll, pyrimidines, purine bases, and enzyme co-factors, fall under the umbrella of heterocycles, playing integral roles in cellular processes (Arunachalapandi and Roopan 2021; Sompalle and Roopan 2016)[8]. Their significance spans almost every step of essential biochemical processes crucial to life.
- Heterocyclic compounds, particularly those incorporating nitrogen, sulfur, and oxygen heteroatoms, represent a pivotal class in pharmaceutical and agrochemical industries, constituting approximately 60% of drug substances. Five-membered nitrogen- and oxygen- or sulfur-containing heterocycles, such as oxazolidine, isoxazolidine, oxazole, isoxazole, thiazolidine, isothiazolidine, thiazole, isothiazole, oxadiazole, and thiadiazole, serve as crucial structural motifs found in numerous biologically active compounds. These heterocycles form the foundational structure of various drugs, making them of paramount interest in the pharmaceutical sector (Manjupriya and Roopan 2021; Li et al. 2013).
- The subsequent sections delve into the review of 5-membered oxadiazole and thiadiazole heterocycles, as their derivatives attract ongoing interest among researchers. These derivatives serve as bio-isosteric replacements in drug design and are extensively studied for their applications in agrochemicals and material science (Sauer et al. 2019; Kumari et al. 2020)[9]. The primary objective of this review is not to encompass a wide range of topics but rather to focus specifically on recent advancements in the anti-tubercular and anticancer pharmacological activities of isomers 1,2,4-oxadiazole and 1,3,4-thiadiazole. Due to their robust chemical and thermal properties, these isomers hold potential significance in the pharmacological sector[10]. The literature review aims to comprehensively cover a substantial number of related research articles, incorporating the most recent findings for currency. The detailed technical discussion and accompanying figures in this review article aim to facilitate an in-depth analysis and serve as a valuable starting point for future research in this field.

GENERAL SYNTHESIS:

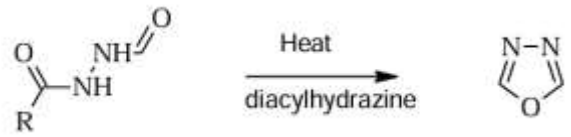
1. 1,3,4-Oxadiazole is a liquid with a boiling point of 150˚C. It was initially synthesized by Ainsworth in 1965 through the thermolysis of ethylformate formally hydrazone under atmospheric pressure.



2. 1,3,4 oxadiazoles are also obtained on heating tetrazoles with acid chlorides (in C6H5N at 50°C)



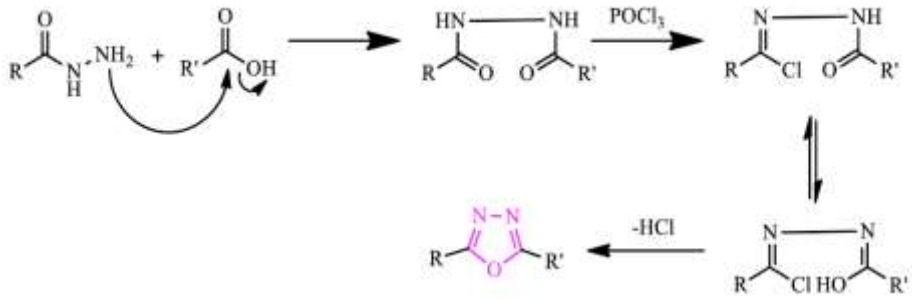
3. The application of heat to diacyl hydrazines in the presence of thionyl chloride (SOCl2) results in the formation of an oxadiazole.



DRUGS CONTANING OXADIAZOLE MOIETY

The 1,3,4-oxadiazole moiety is recognized for inducing various pharmacological activities, including anticancer, antiviral, antibacterial, antifungal, antidiabetic, antioxidant, antimalarial, analgesic, and anti-inflammatory effects. This structural motif is frequently encountered in numerous drug molecules, as depicted in Fig. Notable examples include Raltegravir, an antiretroviral drug featuring the 1,3,4-oxadiazole moiety, and the antibacterial agent furamizole, which incorporates 1,3,4-oxadiazole. Additionally, drugs such as nedsapidil and tiodazosin, both containing the 1,3,4-oxadiazole moiety, exert their actions as antihypertensive agents[11]. Zibotentan is another noteworthy example belonging to the category of anticancer agents, underscoring the diverse pharmacological roles associated with the 1,3,4-oxadiazole motif[12].

The predominant synthetic method for the laboratory preparation of 1,3,4-oxadiazole-based compounds involves the cyclodehydration of an acid and hydrazide[13]. This process is typically conducted in the presence of dehydrating agents like phosphorus oxychloride, trifluoroacetic anhydride, thionyl chloride, or polyphosphoric acid. These dehydrants facilitate the elimination of water molecules during the cyclization reaction, leading to the formation of the 1,3,4-oxadiazole structure[14].

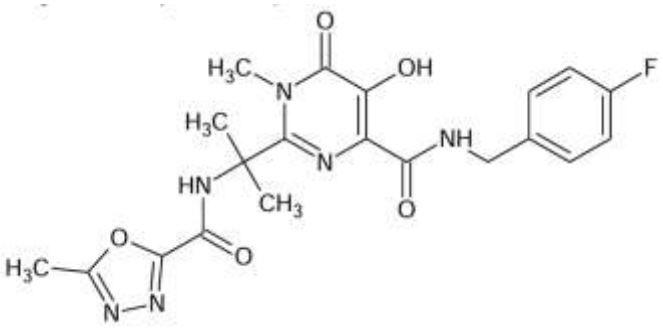


Mechanism of Synthesis

BIOLOGICAL ACTIVITIES OF OXADIAZOLE MOIETY CONTAINING DRUGS

Raltegravir

A chemical compound approved for therapy contains a 1,3,4-oxadiazole moiety. This substance exhibits a potent **antiviral effect** and serves as the primary drug for treating **HIV infection**. Its mechanism of action involves inhibiting **integrase**, an enzyme responsible for integrating viral genetic material with human chromosomes—a critical step in AIDS pathogenesis[15]. Clinical studies have demonstrated that Raltegravir significantly reduces viral dynamics and accelerates viral decomposition in the human body. Notably, the viral load in one millilitre of blood drops below 50 copies after Raltegravir administration, surpassing the efficacy of other drugs that block reverse transcriptase reservoirs.



IUPAC Name: N-(2-(4-(4-fluorobenzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan 2-yl)

Nesapidil

Nesapidil drug classified as an **IV class antiarrhythmic drug**. Nesapidil operates by **blocking calcium channels**, directly inhibiting calcium ion influx into heart muscle cells and smooth muscle cells of blood vessels[16]. This action enhances blood flow, relieves coronary vasoconstriction, and contributes to slowing atrioventricular (AV) conduction and maintaining sinus rhythm

Zibotentan:

Zibotentan, also known by its development code ZD4054, is an experimental anti-cancer drug candidate being investigated by AstraZeneca.It functions as an endothelin receptor antagonist, specifically targeting the ETA receptor.

Mechanism of Action: Zibotentan inhibits apoptosis (programmed cell death) and cell proliferation. At higher concentrations, it also suppresses blood vessel growth within neoplastic (cancerous) tissue. Synergistic Effect: When combined with Paclitaxel, Zibotentan exhibits a synergistic effect, particularly enhancing apoptosis. Ongoing research explores its effectiveness against ovarian and breast cancer.

Tiodazosion:

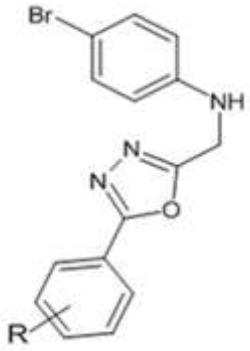
Tiodazosion is a medicinal preparation used for cardiovascular diseases.

Structure: It includes a quinazoline structure and a 1,3,4-oxadiazole core.

Antihypertensive Activity: Tiodazosion works by blocking adrenergic receptors, leading to the relaxation of vascular smooth muscles. It also inhibits the secretion of norepinephrine from the adrenal glands.

First-Line Treatment: Tiodazosin is a preferred choice for treating cardiovascular disease related to hypertension[17].

Prolonged Half-Life: Compared to a similar drug (Prazosin), Tiodiazosin has a longer half-life in blood plasma, extending its therapeutic action.



Furamizole

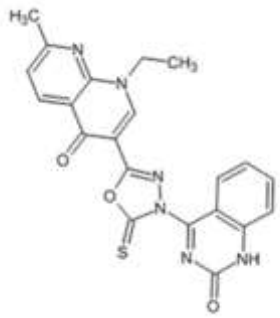
Furamizole, chemically known as 2-amino-5-[2-(5-nitro-2-furyl)-1-(2-furyl)-vinyl]-1,3,4-oxadiazole, is a derivative of nitrofuran.

Antibacterial Activity: Furamizole exhibits strong antibacterial activity.It's an intriguing compound with potential applications in medicine[18].

Antimicrobial Activity

Ramalingam Peraman, Reghu Veer Varma, and Y. Padmanabha Reddy have developed newer variants of nalidixic acid, as depicted in Figure. In their pursuit of designing novel compounds with anti-bacterial and anti-tubercular activity, they utilized the COOH group of nalidixic acid as a starting point. The evaluation of these compounds involved agar plate disk diffusion and microdilution methods against various bacterial species for anti-bacterial screening[19].

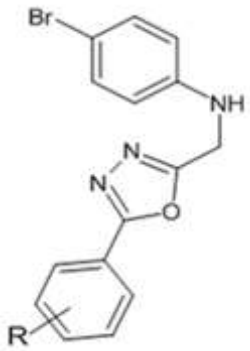
Among the compounds synthesized, 1-ethyl-7-methyl-3-(4-(3-oxo-3,4-dihydroquinoxaline-2-yl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1,8-naphthyridin-4(1H)-one (6) exhibited potent activity, with a concentration less than 6.25 µg/mL, surpassing the reference drug ciprofloxacin against S. aureus. Statistical analysis using the Student t-test indicated a 5% critical difference, demonstrating the significant activity of the compound[20].



Oxadiazole with Nalidixic acid

KI Bhat et al. synthesized and reported 4-bromo [(N-5-substituted [1,3,4-oxadiazole-2yl)methyl] aniline derivatives, as illustrated[20]. These compounds were explored for their potential as anti-inflammatory and anti-microbial agents. Among the screened compounds, the 4-methoxy-substituted derivative demonstrated superior antibacterial activity, with zones of inhibition measuring 18 mm in S. aureus and B. subtilis, 19 mm in E. coli, and 15 mm in P. aeruginosa, when compared to the standard amoxicillin.

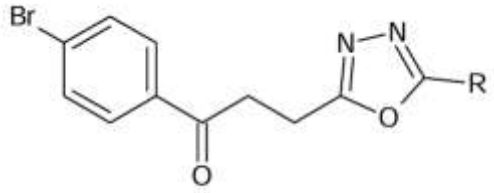
Moreover, the synthesized derivatives were tested against various organisms such as Candida albicans and Aspergillus niger for their anti-fungal activity, with ketoconazole serving as the standard for comparison.



Oxadiazole with aniline derivatives

Anti-Cancer Activity

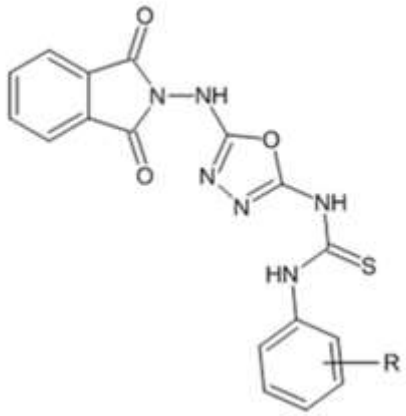
Gudipati R et al. reported the synthesis, characterization, and anticancer activity of specific 3-{4-(-mercapto-1,3,4-oxadiazole-2-yl)phenylimino}indolin-2-one derivatives. The anticancer activity of all the synthesized compounds was assessed against HeLa, IMR-32, and MCF-7 cancer cell lines using the MTT method. Among the series, a particular compound demonstrated notable anticancer activity.



Magda MF et al., reported synthesis and docking studies of novel benzopyran-2-ones as promising anticancer agents. Among the series following compound exhibited good anticancer activity[21].

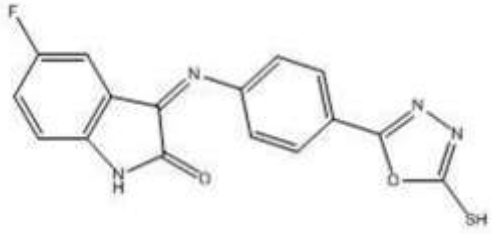
ANTI-INFLAMMATORY ACTIVITY

Asif Husain et al. reported the synthesis of a novel series of 2-[3-(4-bromophenyl)propan-3-one]-5 (substituted phenyl)-1,3,4-oxadiazoles. The objective was to develop improved anti-inflammatory and analgesic agents with minimal or no side effects, particularly in terms of ulcerogenicity. Two compounds, namely 2-[3-(4-bromophenyl)-propan-3-one]-5-(4-chlorophenyl)-1,3,4-oxadiazole and 2-[3-(4-bromophenyl)propan-3-one]-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole, exhibited anti-inflammatory activities of 59.5% and 61.9%, respectively. These results demonstrate comparable activity to that of indomethacin, which displayed 64.3% activity at the same dosage of 20 mg/kg.

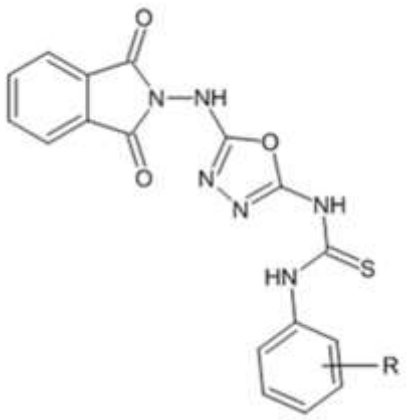


Anti-convulsant activity

In their investigation of anti-convulsant and neurotoxicity activity, Bhat et al. synthesized and evaluated several phthalimide derivatives of 1,3,4-oxadiazole. The maximal electric shock method was employed to assess the anti-convulsant properties of all compounds[22]. Neurotoxicity was examined using the rotarod method, revealing lower neurotoxicity compared to phenytoin. Behavioral tests using an actophotometer showed increased motor activity for all compounds except 13d.



The compounds demonstrated all the necessary pharmacophoric structural requirements in their basic structure. Notably, the presence of constituents like -OCH3 at the para position of the phenyl ring and an alkyl group at the distant aryl ring exhibited potent activity. To enhance the lipophilicity of the molecule, a thioureido moiety was introduced into the structure. The study concluded by highlighting that the phthalimide derivatives exhibit anti-convulsant activity comparable to phenytoin.



Phthalimide-1,3,4-Oxadiazole derivative

Applications

1. The optical characteristics of oxadiazole moieties possess significant value.
2. The 1,2-diazole fragment within the molecule serves as an electron-withdrawing group, contributing to its broad utilization in various conducting systems.
3. This application facilitates an augmentation in the quantum yield of fluorescence and an improvement in the overall stability of the molecule[23].
4. As a result, derivatives of oxadiazole find extensive use in various applications, such as organic light-emitting diodes, laser dyes, optical brighteners, and scintillators.
5. It is noteworthy that these molecules are additionally found in materials like thermal insulation polymers.

CONCLUSION

This article deals with the introduction of oxadiazole, encompassing its fundamental chemistry, as well as its physical and chemical properties. The synthesis of oxadiazole and its derivatives is thoroughly explored. Additionally, the article investigates the common pharmacological properties associated with oxadiazole and highlights a few of the presently utilized drugs containing the oxadiazole moiety. Through this comprehensive exploration, it becomes evident that oxadiazole is a chemically potent entity with numerous beneficial properties, making it a focal point in various ongoing research projects.

REFERENCES

1. Praveen M and Tanya M authored the Textbook of Pathology, which was published by Jaypee Brothers Medical Publishers in New Delhi. The book is in its 4th edition, released in the year 2000.
2. Husain A, Ahmad A, Alam MM, Ajmal M, Ahuja P, investigated Fenbufen-based 3-[5-(substituted aryl)-1,3,4 oxadiazol-2-yl]-1-(biphenyl-4-yl)propan-1-ones as potentially safer anti-inflammatory and analgesic agents. This research was published in the European Journal of Medicinal Chemistry in 2009, with the citation 44, 3798-804.
3. Kujubu DA, Fletcher BS, Varnum BC, Lim RW, Herschman HR conducted a study on TIS10, an mRNA induced by the tumor promoter phorbol ester in Swiss 3T3 cells. This mRNA, identified in 1991, encodes a novel prostaglandin synthase/cyclooxygenase homologue. The findings were published in the Journal of Biological Chemistry, volume 266, pages 12866-72.
4. Marnett LJ explored the mechanisms of cyclooxygenase in a paper titled "Cyclooxygenase mechanisms," published in Current Opinion in Chemical Biology in 2004 (volume 4, pages 545-52).
5. Talley JJ, Bertenshaw SR, Brown DL, Carter JS, Graneto MJ, Kellogg MS, et al., investigated N-[[(5-methyl-3-phenylisoxazol-4-yl)-phenyl]sulfonyl]propanamide, sodium salt, parecoxib sodium. This compound, described as a potent and selective inhibitor of COX-2 for parenteral administration, was discussed in the Journal of Medicinal Chemistry in 2000 (volume 43, pages 1661-3).
6. Prakash O, Kumar M, Kumar R, Sharma C, Aneja KR conducted a study on the hypervalent iodine(III)-mediated synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4 oxadiazoles with potential antibacterial and antifungal properties. The research was published in the European Journal of Medicinal Chemistry in 2010 (volume 45, pages 4252-7).
7. Pearce 2007,Fuloria NK, Singh V, Mohammad S, Mohammad A synthesized and evaluated the antimicrobial properties of new oxadiazoles derived from phenylpropionohydrazides. The findings were presented in the journal Molecules in 2009 (volume 14, pages 1898-903).
8. Sompalle and Roopan 2016, Desai NC, Bhavsar AM, Shah MD, Saxena AK conducted synthesis and QSAR studies of thiosemicarbazides, 1,2,4-triazoles, 1,3,4-thiadiazoles, and 1,3,4-oxadiazoles derivatives as potential antibacterial agents. The research was published in the Indian Journal of Chemistry in 2008 (volume 47B, pages 579-89).

9. Sompalle and Roopan .; Elzaawely, A.A.; Fukuta, M.; Tawata, S. Herbicidal and fungicidal activities of lactones in Kava (Piper methysticum). J. Agric. Food Chem. 2016, 54, 720–725
10. Yajima, W.; Rahman, M.H.; Das, D.; Suresh, M.R.; Kav, N.N.V. Detection of Sclerotinia sclerotiorum Using a Monomeric and Dimeric Single-Chain Fragment Variable (scFv) Antibody. J. Agric. Food Chem. 2008, 56, 9455–9463.
11. Fisher, M.C.; Henk, D.; Briggs, C.J.; Brownstein, J.S.; Madoff, L.C.; McCraw, S.L.; Gurr, S.J. Emerging fungal threats to animal, plant and ecosystem health. Nature 2012, 484, 186–194. [CrossRef] [PubMed]
12. MacLean, D.E.; Lobo, J.M.; Coles, K.; Harding, M.W.; May, W.E.; Peng, G.; Turkington, T.K.; Kutcher, H.R. Fungicide application at anthesis of wheat provides effective control of leaf spotting diseases in western Canada. Crop Prot. 2018, 112, 343–349.
13. Obydennov, K.L.; Khamidullina, L.A.; Galushchinskiy, A.N.; Shatunova, S.A.; Kosterina, M.F.; Kalinina, T.A.; Fan, Z.; Glukhareva, T.V.; Morzherin, Y.Y. Discovery of Methyl (5 Z)-[2-(2,4,5-Trioxopyrrolidin-3-ylidene)-4-oxo-1,3-thiazolidin-5 ylidene]acetates as Antifungal Agents against Potato Diseases. J. Agric. Food Chem. 2018, 66, 6239–6245.
14. Fungal Disease Frequency. Available online: https://gaffi.org/why/fungal-disease-frequency/ (accessed on 4 April 2022)
15. Gadaginamath G S, shyadligeri A S, Kavali R R, Indian J Chem, (1999), 38B , 156.
16. Renukadevi P, Birada J S, Indian J Hetrocyclic Chem, (1999), 9, 107.
17. Abadi AH, Eissa AA and Hassan GS. Chem. Pharm. Bull., (2003), 51,838–844.
18. M.O. Losinskii, P.S. Pelkis, zh. Obshch. Khim. 32, 526 (1962); M.O. Losinskii, P.S. Pelkis, S.N. Sanova, idib., (1963), 33, 2231.
19. Ramalingam Peraman, M. Milone, E. Borello, Gazz. Chem. Ital., (1951), 81,, 677.
20. KI Bhat et al, J. Barrans, compt. Rent., (1959),249,,1096.
21. Magda MF et al, Toliwal S.D., Jadav K., Gupte A. and Banu A., Synthesis and biological evaluation of phenyl hydrazides and their derivatives from Rice bran oil, Der Pharma Chemica. 1, 2009, 185.
22. Chawla R., Arora, Parameswaran M.K., Sharma P.C., Michael S. and Ravi T.K., Synthesis of novel 1,3,4-oxadiazole derivatives as potential antimicrobial agents, Acta Poloniae Pharm. Drug Res., 67, 2010, 247.
23. Fuloria N.K., Singh V., Shaharyar M. and Ali M., Synthesis and antimicrobial evaluation of some new oxadiazoles derived from phenylpropionohydrazides, Molecules. 14, 2009, 1898.