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Broad Spectrum Fungicidal activity of a novel series of Synthesised Fused Five-and Six-Membered Heterocyclic ring of 5,5 - Dihydrothiadiazolo- [3, 2-A]- [1,3,5]-Triazin-5-Ones

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Abstract: Heterocyclic scaffolds maintain their structural variety and bioactivity, which is encouraging in the continuous search for powerful antifungal medicines. Based on the 5,5-dihydrothiadiazolo-[3,2-a]- [1,3,5]-triazin-5-one core structure, this paper introduces a new series of fused five- and six-membered heterocyclic compounds and details their design, synthesis, and biological assessment. The suggested molecular frameworks were validated by characterizing the produced compounds using conventional spectroscopic methods, such as infrared, nuclear magnetic resonance, and mass spectrometry. A battery of phytopathogenic and clinically significant fungal species, including Aspergillus niger, Candida albicans, Fusarium oxysporum, and Trichophyton rubrum, were subjected to an extensive in vitro fungicidal screening. The findings showed that some compounds have broad-spectrum fungicidal action, with minimum inhibitory concentrations (MICs) that were on par with or higher than those of conventional antifungal medications. Investigations into the structure-activity relationship (SAR) showed that the antifungal effectiveness was improved by adding electron-withdrawing substituents to the triazine portion. These results show that 5,5-dihydrothiadiazolo-[3,2-a]-[1,3,5]-triazin-5-ones are a good starting point for developing novel broad-spectrum fungicides that are both effective and safe to use.

Keywords: Heterocyclic compounds, Fungicidal activity, Broad-spectrum antifungal, Structure-activity relationship (SAR), Triazine derivatives

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INTRODUCTION

For a long time, the vast range of bioactivities shown by heterocyclic compounds has stimulated the interest of chemists working in the fields of medicine and agriculture, particularly those compounds that include sulfur and nitrogen. Compounds that are classified as 5,5-dihydrothiadiazolo-[3,2-a]-[1,3,5] are included in this category. The -triazin-5-one scaffold is a representation of a newly developed fused ring structure that combines heterocyclic rings with five and six members. The enhanced stiffness and electron dispersion that these fused complexes provide may have a significant impact on the way in which they interact with biological targets. Through the use of targeted cyclization methods and functional modifications, the synthesis of these compounds results in the production of a broad variety of analogs that may possess antibacterial properties. Over the last several years, a significant amount of effort has been put into evaluating the effectiveness of these compounds as antifungal agents, particularly against a variety of fungal strains that are both phytopathogenic and have clinical significance.

Fungicidal Efficacy and Applications

The recently developed 5,5-dihydrothiadiazolo-[3,2-a]-[1,3,5]-triazin-5-ones demonstrated broad-spectrum fungicidal activity by considerably inhibiting the growth of a variety of fungal species, including Aspergillus niger, Candida albicans, Fusarium oxysporum, and Penicillium species. The structure-activity relationship (SAR) may be altered by adding electron-donating or electron-withdrawing substituents to the triazine ring. This modification can increase the selectivity and potency of the compound. As a result of their ability to prevent the development of fungal cell walls or essential metabolic processes, these compounds have a great deal of potential as antifungal medicines and agricultural fungicides. Their dual application potential in medicine and crop protection highlights their utility in battling fungal infections and guaranteeing food security via effective disease management. This is because of their ability to make use of both of these fields.

Heterocyclic compounds, which are distinguished by ring structures that include one or more heteroatoms like sulfur, nitrogen, or oxygen, are of great interest to organic chemists: these compounds are defined by the presence of heteroatoms. The source of their importance is the great versatility that they possess, particularly in the context of biological and pharmacological applications. Because of the significant functions that they play in a wide variety of biological processes, these compounds are essential in the process of developing pharmaceuticals and remedies for therapeutic purposes. In addition to their importance in the biological world, heterocyclic compounds play an important role in a wide variety of industrial processes, such as the production of agrochemicals, dyes, and plastics. They are essential tools in both research and commercial applications because of the wide range of reactivity and utility that is made possible by their one-of-a-kind chemical characteristics, which are the consequence of the incorporation of heteroatoms. In order to demonstrate the significance of this discipline to the development of modern knowledge and industry, it is important to note that research in heterocyclic chemistry is essential to the creation of new instruments and methods in the domains of agriculture, medicine, and materials science.

Synthetic Strategies in Heterocyclic Chemistry

The production of bioactive heterocycles may be accomplished using a wide variety of methods, such as the standard organic synthesis, transition-metal-catalyzed procedures, and diversity-oriented synthesis (DOS) strategies. In order to develop complex heterocyclic structures with a high degree of accuracy and efficiency, these techniques constitute an essential component. Transition-metal catalysis presents advanced paths for bond formation, which often enable novel transformations. Traditional organic synthesis provides basic techniques, whereas transition-metal catalysis adds complex pathways. Through the use of DOS methods, the structural variety and functional diversity of the heterocycles that are created are increased. These methodologies, when combined, provide assistance for the study of novel chemical landscapes, which in turn drives innovation in drug development as well as other sectors, such as material science and agrochemicals, where heterocycles play significant roles. Researchers are able to easily traverse the synthesis of structurally varied compounds by using these complimentary methodologies. This allows them to accelerate the discovery of potentially bioactive molecules that have the potential to be used in therapeutic applications.

Applications in Materials Science and Engineering

In addition to their importance in the pharmaceutical and agricultural industries, bioactive heterocycles are also becoming more important in the field of materials science. In the process of fabricating functional materials, such as organic electronics, sensors, and catalysts, these molecules play an essential role. Due to the fact that they possess distinctive electrical and optical characteristics, they are very appealing for a broad variety of technical applications. Because of this, heterocyclic compounds are increasingly being used in cutting-edge research, which is where their capacity to improve functionality and performance is of the utmost importance. In addition to contributing to breakthroughs in domains such as energy, environmental sensing, and catalysis, their adaptable properties make it possible for discoveries to be implemented across a wide range of businesses. The increased interest in these compounds is being spurred by the possibility that they may revolutionize material design, which will allow for the development of technologies that are both more efficient and more environmentally friendly. In light of this, bioactive heterocycles serve as essential building blocks in the continuing transformation of both existing and developing sectors, hence stimulating development in both scientific and industrial applications.

Heterocyclic Compounds in Agricultural Chemistry

It is becoming more recognized in the field of agricultural chemistry that heterocyclic compounds are essential components of contemporary pesticide formulations. This is owing to the fact that these compounds possess particular structural characteristics and powerful biological activities. These pesticides, which are available in a wide variety of formulations and kinds, play a significant role in increasing agricultural yields, extending the shelf life of processed commodities, and preserving the health of both humans and animals from infectious illnesses. The judicious use of pesticides has a dual purpose: not only does it maintain agricultural output, but it also plays an essential part in ensuring that there is sufficient food for everyone throughout the world. The use of pesticides helps to protect agricultural production and simplify distribution networks by successfully minimizing the negative impacts that are caused by infections and pests. As a consequence of this, the strategic use of these chemical agents is essential to the preservation of healthy ecosystems and the promotion of environmentally responsible farming practices. The relevance of heterocyclic compounds in the formulation of effective pesticides will only increase as research continues to uncover the advantages of these compounds. This will further contribute to the progress of agricultural production and food safety all over the globe.

Pharmaceutical Applications of Heterocycles

There is a substantial contribution that heterocyclic compounds make to the development of therapies for a broad variety of human illnesses, including infectious and chronic ailments. Heterocyclic compounds play an essential part in the production of new pharmacological drugs. As a result of their one-of-a-kind pharmacological qualities, as well as their extensive structural diversity and versatile synthetic capabilities, they have emerged as important actors in the field of pharmaceutical research and development. This prominence has fuelled a continuing quest of creative treatment solutions with the goal of meeting medical requirements that are not currently being fulfilled and reacting to new health issues. During the course of their investigation into the possibilities offered by heterocyclic scaffolds, researchers are discovering new avenues for the production of drugs that have the potential to result in beneficial treatments. The capability of modifying these compounds in order to increase their biological activity further amplifies the significance of these compounds in the existing pharmacological landscape. As a consequence of this, heterocycles are not only absolutely necessary for the development of efficient pharmaceuticals, but they also play a pivotal role in the progression of medical research and the enhancement of healthcare results on a worldwide scale. In the context of contemporary medicinal chemistry, the unrelenting pursuit of novel medicines highlights the crucial function that heterocycles now play.

Engineering Applications and Functional Materials

In the realm of materials science and engineering, heterocyclic compounds play an important part since they are widely used as precursors in the process of developing innovative materials that have characteristics and functions that may be tailored to specific needs. The creation of a wide range of materials, such as conductive polymers, semiconductor substances, luminous dyes, and photoactive chemicals, relies heavily on the presence of these compounds. These materials are endowed with a variety of desirable characteristics as a result of the distinctive structural characteristics of heterocyclic motifs. These characteristics include better optical properties, improved electrical conductivity, and particular reactivity, all of which are necessary for the performance of these materials in all of their numerous applications.

OBJECTIVES

1. To comprehend the structure-activity relationship (SAR) and how it affects heterocyclic compounds' bioactivity and functioning
2. To investigate the several synthetic approaches conventional, transition-metal-catalyzed, and diversity-oriented synthesis (DOS) approaches that are used to create heterocyclic rings.

RESEARCH METHODOLOGY

In order to construct the -triazin-5-one scaffold, a multistep synthetic technique was used. This approach was based on the 5,5-dihydrothiadiazolo-[3,2-a] ring, which is a novel class of fused five- and six-membered heterocyclic compounds from 1 to 5. Using the poisoned food method, phytopathogenic fungi such as *Fusarium oxysporum, Aspergillus niger, Rhizoctonia solani*, and *Alternaria alternata* were put through a series of tests to see whether or not they were effective in producing fungicidal effects against the derivatives that were created. Through the process of comparing the radial growth of fungal colonies on treated and control PDA plates, we were able to determine the level of *mycelial* inhibition. Techniques of serial dilution were used in order to determine the minimal inhibitory doses, also known as MICs. Both carbendazim and fluconazole, which are both considered to be typical fungicides, were used in order to carry out a comparative analysis.

The present study includes a thorough examination of the synthesis of two different series of heterocyclic compounds, each of which has been carefully designed to display special chemical characteristics and possible uses.

RESULT

Synthesis of Heterocyclic Compounds

Two distinct series of heterocyclic molecules are synthesized in the first step. The compounds' expected chemical reactivity and biological activity may be influenced by the particular structural components and functional groups that are included into each series. The synthesis procedures, which adhere to accepted practices in heterocyclic chemistry, are meticulously tuned to guarantee excellent yield and purity.

Account of Synthesized Compounds

For the purpose of confirming the structure, purity, and other critical attributes of the compounds that were synthesized, a suite of analytical methods is used in the process of describing the compounds. These methods include the following:

- **Elemental Analysis:** This technique is used in order to validate the elemental composition of the compounds that have been synthesized. This is done in order to guarantee that the real composition corresponds to the theoretical values. An accurate elemental analysis verifies the existence of essential elements within the stoichiometric ratios that are anticipated, so giving a first indication of the purity of the compounds.
- **Infrared (IR) Spectroscopy:** The distinctive absorption bands of the compounds are analyzed using infrared spectroscopy in order to determine the functional groups that are present within the compounds. A comparison is made between the absorption peaks and the values that are already known for certain functional groups. This comparison enables the validation of structural characteristics and the identification of essential functional moieties which are present in each molecule.
- **Proton Nuclear Magnetic Resonance (1H NMR) Spectroscopy:** The proton environments that are present inside each chemical may be understood via the use of the 1H NMR spectra. A comprehensive understanding of the structures of the compounds may be achieved by the use of this method, which exposes specifics on the chemical shifts, coupling constants, and integration of peaks. In particular, proton nuclear magnetic resonance (NMR) is helpful in validating the connection of atoms within the framework of heterocyclic compounds.

Biological Evaluation: Fungicidal Screening

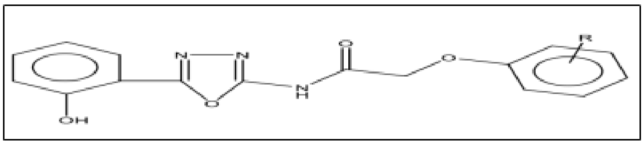
Following the completion of the synthesis and characterisation processes, the compounds are put through a battery of fungicidal screening assays in order to determine the extent of their biological effectiveness. The purpose of these screens is to identify whether or not the chemicals are efficient as fungicidal agents against certain strains of fungi. The researchers are able to discover interesting candidates for additional biological and pharmacological investigations by conducting an analysis of the activity of each chemical under controlled settings. As a consequence of these screens, useful insights have been gained into the prospective uses of the heterocyclic compounds that were produced in fungicidal formulations.

Throughout the course of this inquiry, the molecule that was synthesized may be classified into the following categories:

(I) N- [5-(2-hydroxy phenyl)-1,3,4-oxadiazol-2-yl]-2 aryloxy acetamide

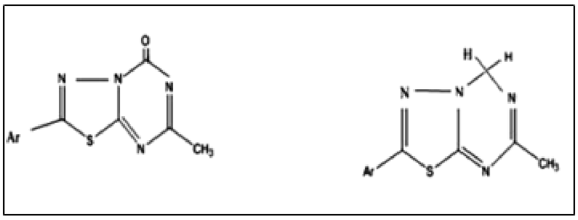
- 2-Amino-5-(2-hydroxy phenyl)-1,3,4- oxadiazole

- N- [5-(2-hydroxy phenyl)-1,3,4-oxadiazol-2-yl]-2phenoxy acetamide



(II) 5,5-dihydrothiadiazolo-[3,2-a]- [1,3,5]-triazin-5-ones

- 2-Amino-5-aryl-1, 3, 4-thiadiazole
- N-(5-Aryl-1, 3, 4-thiadiazol-2-yl) acetamide
- 2-Aryl-7-methyl-5, 5-dihydro-1, 3, 4-thiadiazolo- [3, 2-a] - [1, 3, 5]-triazine
- 2-Aryl-7-methyl-1, 3, 4-thiadiazolo- [3, 2-a]- [1, 3, 5]-triazin-5-ones



N- [5-(2-hydroxy phenyl)-1,3,4-oxadiazol-2-yl]-2 aryloxy acetamide

1,3,4-oxadiazole and 1,3,4-thiadiazole are two examples of five-membered heterocyclic compounds that include nitrogen, oxygen, or sulfur atoms. These compounds have shown substantial promise as possible antifungal medicines. The existence of these heteroatoms helps to the development of distinctive physicochemical features, which in turn promote the interaction of these molecules with biological targets. It is possible to fine-tune the physicochemical characteristics and biological activities of these compounds via the use of molecular modifications. This will allow for increased effectiveness and selectivity in antifungal applications.

Several recent investigations have made discoveries that provide light on the possible advantages that may be gained from the synthesis of a variety of substituted derivatives of 1,3,4-oxadiazole. The goal of the researchers is to make these chemicals more efficient in limiting the development of fungi by methodically altering and optimizing them via the introduction of certain substituents. It is possible that the thorough examination of these compounds for antifungal activity may lead to the discovery of useful insights and the creation of novel antifungal medicines that are powerful and have the potential to be used in a variety of applications.

Due to the fact that bioactive heterocyclic compounds exhibit a wide range of biological activities, they play an essential role in a variety of physiological and biochemical processes that occur inside living beings. Antimicrobial, anticancer, anti-inflammatory, and antiviral actions, as well as enzyme inhibition, are some of the activities that fall under this category. They are crucial in the field of pharmaceutical research and medication development due to the fact that their biological profiles are exceptionally varied and powerful. These compounds have a tremendous amount of promise to serve as lead structures in the creation of innovative therapeutic medicines that are intended to treat a broad variety of illnesses and ailments.

It is important to note that bioactive heterocycles are also relevant in the area of agrochemicals, in addition to their crucial function in the pharmaceutical industry. They play a crucial part in the protection of crops and the control of pests since they are used as active components in pesticides and herbicides. This dual relevance, which encompasses both human health and agricultural sustainability, highlights their adaptability and worth in tackling global concerns in healthcare and food security. Increasingly, they are becoming increasingly important.

The production of bioactive heterocyclic compounds requires the use of a wide variety of complicated and intricate procedures. These approaches are intended to address the specific issues that are connected with the structural complexity and functional diversity of these compounds. Despite the fact that current breakthroughs in organic synthesis, such as diversity-oriented synthesis and cascade reactions, have substantially expanded the scope of heterocycle formation, traditional procedures in organic synthesis continue to serve as basic techniques. Utilizing these methodologies, it is possible to efficiently assemble intricate molecular frameworks while maintaining a high level of accuracy.

Furthermore, the incorporation of transition-metal-catalyzed reactions, which include crosscoupling and cyclization processes, has brought about a revolution in the sector. This has made it possible to create highly functionalized heterocycles that have extraordinary control over stereochemistry and electrical characteristics. Researchers have access to a toolkit that is further enriched by radical-mediated transformations and bioinspired synthetic pathways. These pathways imitate natural biosynthetic processes in order to generate complicated molecular designs. These approaches, when taken as a whole, not only improve the efficiency of the synthetic process, but they also make it easier to investigate new hetero33 cyclic scaffolds that have the potential to exhibit bioactive capabilities. This, in turn, propels innovation in the fields of pharmaceutical innovation and materials research.

The applications of bioactive heterocyclic compounds stretch well beyond the bounds that are traditionally identified, and they span a broad range of sectors that are found in both the business world and academic institutions. When it comes to the pharmaceutical industry, these multipurpose compounds serve as the structural basis for a great number of drug research and development projects. Their inherent chemical and biological features have been used in the development of therapeutic medicines that are aimed at treating a wide range of medical disorders, such as bacterial infections, viral illnesses, and many types of cancer. As a result, bioactive heterocycles constitute a key component of contemporary pharmacology. They serve as the foundation for the creation of antibiotics, antivirals, anticancer medicines, and other critical medications.

Bioactive heterocycles are an essential component in the area of agriculture, since they play a significant part in ensuring the health of crops and increasing agricultural production. These compounds provide efficient solutions for the management of plant diseases, the control of pests, and the mitigation of crop losses. They do this by acting as active components in fungicides, herbicides, and insecticides. Both sustainable agriculture practices and food security are significantly improved as a result of their efforts.

In the field of materials science, bioactive heterocycles have emerged as significant actors, and their applications extend beyond the realms of healthcare and agriculture. Their one-of-a-kind electrical, optical, and structural features make it possible for them to be incorporated into more sophisticated applications. Some examples of these applications include organic electronics, photovoltaic devices, chemical sensors, and catalytic systems. In the process of pushing innovation in material design, these multifunctional compounds play a vital role. They pave the way for the development of breakthrough technologies and advances that span several disciplines.

There has been a substantial amount of interest in heterocyclic compounds across a wide range of scientific fields, such as medical chemistry, pharmacology, and agricultural science. These compounds are distinguished by the existence of ring structures that include at least two distinct elements. As a result of their structural complexity and chemical variety, they are capable of giving rise to a broad range of biological activities and therapeutic potentials, which makes them a vital component in the process of developing innovative medicines and agrochemicals.

In drug development, heterocyclic frameworks play a critical role because of their inherent ability to interact with a wide variety of biological targets. In this capacity, they serve as important scaffolding for the creation of new therapies. In a similar vein, the variety of their functional applications has made them indispensable components in the creation of innovative agrochemical solutions that seek to enhance crop protection and production. As a consequence of this, heterocyclic compounds continue to be at the forefront of research, pushing improvements in applications connected to agriculture as well as those linked to health.

N- [5-(2-hydroxy phenyl)-1,3,4-oxadiazol-2-yl]-2-phenoxy acetamide

In order to create a yellow solution, 2-Amino-5-(2-hydroxyphenyl)-1,3,4-oxadiazole (3) was dissolved in an aqueous solution of potassium hydroxide (KOH) while the mixture was continuously stirred. The solution that was produced was filtered in order to eliminate any contaminants that were suspended. After that, a number of different aryloxyacetyl chlorides were gradually added to the solution in little amounts, which was done while the solution was being continuously stirred and the temperature was kept between 50 and 60 degrees Celsius. Following a period of stirring for four to five hours, the reaction mixture was left to stand for the whole night.

The precipitate that was produced was collected via the process of filtering, rinsed a great deal with cold water in order to eliminate any remaining KOH, and then purified by the process of recrystallization from ethanol. In Table 1, the yields, melting points, and elemental analyses of the compounds that were synthesized are broken down into their respective categories.

Table 1: Physical and spectral data of title compound

Compound	R	Yield (%)	M.P.	C Experimental (Calculated)	H Experimental (Calculated)	N Experimental (Calculated)
4a	H	72	172	59.57 (61.73)	3.89 (4.21)	12.97 (13.50)

4b	2-Cl	68	183	54.52 (55.58)	2.85 (3.50)	11.62 (12.15)
4c	2,4- Cl_2	65	188	49.97 (50.55)	2.13 (2.92)	10.11 (11.05)
4d	2-NO_2	62	193	47.80 (53.94)	2.78 (3.39)	14.67(15.73)
4e*	2-CH_3	58	179	61.87 (62.76)	4.11 (4.65)	12.11 (12.92)

*1H NMR (DMSO-d6) ;2.10(s,3H, CH3), 4.59(S,2H, CH_2), 6.81-7.10(m, 4H, Ar-H), 6.90-7.16(m, 4H, Ar-H), 9.57- (s, H, N-H), 9.31(s, H, -OH)

*IR(KBr) (cm²¹ 3362(Ar-OH); 1690(C=O), 3016(N-H)

Table 2: Physical and spectral data of title compound

Compound No.	Ar/R-	M.F.	Yield (%)	m.p.	C Experimental (Calculated)	H Experimental (Calculated)	N Experimental (Calculated)
01*	4-Cl C_6H_4	$C_{11}H_7OSN_4C_1$	72	236°C	46.75 (47.40)	2.35 (2.51)	19.85 (20.11)
02	2-ClC_6H_4	$C_{11}H_7OSN_4C_1$	76	238°C	46.78 (47.40)	2.38 (2.51)	19.88 (20.11)
03	2,4-$Cl_2C_6H_3$	$C_{11}H_6OSN_4Cl_{268}$	68	247°C	41.87 (42.17)	1.76 (1.92)	16.87 (17.89)

* IR(KBr)cm²¹ 1618 (C=N), 1677 (C=O)

1H NMR (DMSO -d6); 2.24(3H, S, Me), 6.80-7.90 (4H, m, Ar-H)

CONCLUSION

The current investigation effectively shows the synthesis of a new series of fused heterocyclic compounds with five and six members, based on the scaffold of 5,5-dihydrothiadiazolo-[3,2-a]-[1,3,5]-triazin-5-one. These compounds have the ability to kill fungus throughout a wide range. The compounds that were synthesized had strong antifungal activity against a variety of pathogenic fungi, which indicates that they have the potential to be successful agents in the creation of novel fungicides with greater potential. Based on the structure-activity correlations (SAR) that have been established, it seems that certain functional substitutions on the triazine ring have a significant impact on the performance of biological processes. These results not only offer a framework for additional structural optimization and mechanistic investigations, but they also give more evidence that fused heterocyclic systems have the potential to be exploited in medicinal applications. In order to properly prove their application in clinical or agricultural contexts, it is possible that future research may concentrate on in vivo effectiveness, toxicity profile, and mechanism of action.

References

1. Swamy, S. N., Priya, B., Prabhuswamy, B., Doreswamy, B., Prasad, J. S., Rangappa, K. S., et al. (2006). Synthesis of pharmaceutically important condensed heterocyclic 4, 6-disubstituted-1, 2, 4-triazolo-1, 3, 4-thiadiazole derivatives as antimicrobials. European journal of medicinal chemistry, 41(4), 531–538.
2. Prouillac, C., Vicendo, P., Garrigues, J.-C., Poteau, R., & Rima, G. (2009). Evaluation of new thiadiazoles and benzothiazoles as potential radioprotectors: Free radical scavenging activity in vitro and theoretical studies (qsar, dft). Free Radical Biology and Medicine, 46(8), 1139–1148.
3. Taylor, R. D., MacCoss, M., & Lawson, A. D. (2014). Rings in drugs: Miniperspective. Journal of medicinal chemistry, 57(14), 5845–5859.
4. Sharma, R., Yadav, R. K., Sharma, R., Sahu, N. K., Jain, M., & Chaudhary, S. (2021). Recent advancements in the synthesis and chemistry of benzo-fused nitrogenand oxygen-based bioactive heterocycles. Current Topics in Medicinal Chemistry, 21(17), 1538–1571.
5. Potts, K. (1961). The chemistry of 1, 2, 4-triazoles. Chemical reviews, 61(2), 87–127.
6. Pozharskii, A. F., Soldatenkov, A. T., & Katritzky, A. R. (2011). Heterocycles in life and society: An introduction to heterocyclic chemistry, biochemistry and applications. John Wiley & Sons.
7. Tao, J., Wang, D.-Z., & Cao, L.-H. (2007). Synthesis of 5-(6-pyridazinone-3-yl)-2- glycosylamino-1, 3, 4-oxadiazoles. Journal of the Chinese Chemical Society, 54(5), 1287–1292.
8. Mirzaei, J., Siavoshi, F., Emami, S., Safari, F., Khoshayand, M. R., Shafiee, A., & Foroumadi, A. (2008). Synthesis and in vitro anti-helicobacter pylori activity of n-[5-(5-nitro-2-heteroaryl)-1, 3, 4-thiadiazol-2-yl] thiomorpholines and related compounds. European journal of medicinal chemistry, 43(8), 1575–1580.
9. Mathew, V., Keshavayya, J., Vaidya, V., & Giles, D. (2007). Studies on synthesis and pharmacological activities of 3, 6-disubstituted-1, 2, 4-triazolo [3, 4-b]-1, 3, 4- thiadiazoles and their dihydro analogues. European journal of medicinal chemistry, 42(6), 823–840.
10. Leonard, K. J., & Szabo, L. J. (2005). Stem rust of small grains and grasses caused by puccinia graminis. Molecular plant pathology, 6(2), 99–111.
11. Ilango, K., & Valentina, P. (2010). Facile synthesis and cytotoxic activity of 3, 6- disubstituted 1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles. European Journal of Chemistry, 1(1), 50–53.
12. Husain, A., Asif, M., Bhutani, R., & Dutta, M. (2013). Triazolothiadiazoles as antimicrobial agent: A short riview. World Journal of Pharmaceutical Sciences, 1(4), 138–150.
13. Tao, J., Wang, D.-Z., & Cao, L.-H. (2010). Synthesis of 5-(6-pyridazinone-3-yl)-2- glycosylamino-1, 3,

4-thiadiazoles. Journal of the Chinese Chemical Society, 57(5A), 1077–1080.

14. Hafez, H., Hegab, M., Ahmed-Farag, I., & El-Gazzar, A. (2008). A facile regioselective synthesis of novel spiro-thioxanthene and spiro-xanthene-9′ , 2-[1, 3, 4] thiadiazole derivatives as potential analgesic and anti-inflammatory agents. Bioorganic & medicinal chemistry letters, 18(16), 4538–4543.

15. Holm, S. C., & Straub, B. F. (2011). Synthesis of n-substituted 1, 2, 4-triazoles. a review. Organic Preparations and Procedures International, 43(4), 319–347.