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A REVIEW OF RECENT DEVELOPMENTS IN THE BIOLOGICAL ACTIVITY OF 1,3,4 THIADIAZOLES

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ABSTRACT

The 1,3,4 thiadiazole ring's exceptional flexibility and wide range of therapeutic activity have made it an intriguing pharmacophore. This study clarifies the inherent characteristics of this five-membered heterocycle, emphasizing its polar and aromatic nature as well as its adaptability to changes that optimize its biological effect. We discuss the broad spectrum of pharmacological action that 1,3,4 thiadiazole compounds display, including antimicrobial, antifungal, antiviral, anticancer, and anti-inflammatory effects. Additionally, this study highlights the enormous potential for developing targeted medicines with improved effectiveness and selectivity and examines the intriguing possibilities of this flexible framework in the next drug discovery and development. Overall, this analysis highlights how important 1,3,4 thiadiazole is as a flexible pharmacophore that has the potential to completely change the field of medicine.

Keywords: 1,3,4 thiadiazole, Pharmacological Activities, Anti-Cancer, Anti-Viral, Anti-Bacterial, Anti-Convulsant, Anti-Inflammatory.

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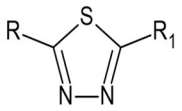
INTRODUCTION

Medical scientists are drawn to heterocyclic substances because of their diverse biological activity and unusual chemical characteristics. Identifying new heterocyclic compounds with strong bioactivities is still a priority, even with the substantial advancements in the science of the heterocyclic ring systems. Imidazole, oxazole, thiazole, oxadiazole, and thiadiazole are examples of five-membered heterocycles that are often encountered and usually exhibit biological properties. In earlier times, the thiadiazole ring was used to bind substances like antibacterial and antiparasitic medications, a few of which continue to be in use in medicine today. The thiadiazole circle serves as a crucial structural element with a wide spectrum of biological activities, as recent research has shown.[1] Sulfur and nitrogen atoms are two of the five elements of the chemical known as thiadiazole. The thiadiazole moiety functions as a "two-electron donating system" and a "hydrogen binding region." It is established that 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4 thiadiazole have four isomeric forms.[2] Thiadiazole comes in four different forms: 1,3,4-, 1,2,4-, 1,2,5-, and 1,2,3-thiadiazole. The 1,2,4- and 1,3,4-thiadiazoles have been the subject of the most investigation. Numerous studies have demonstrated the anticancer, anti-inflammatory, antifungal, antiviral, antibacterial, anticonvulsant, and antiparasitic properties of molecules having thiadiazole rings.[3]

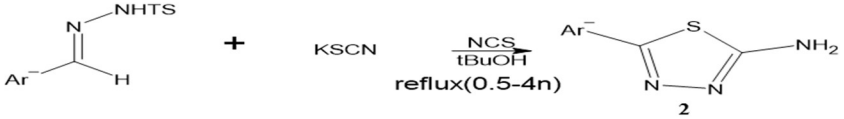


1

Synthesis of 1,3,4-Thiadiazole Nucleus

Scheme-I

The diversity-oriented synthetic procedure for 1,3,4 thiadiazole using N-Tosylhydrazones in the presence of NCS was carried out by Zeyang Wei *et al.*[4]

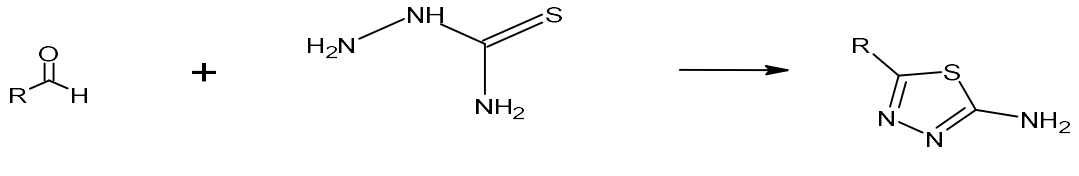


2

http://doi.org/10.31788/RJC.2024.1738857

Scheme II

By condensing with semicarbazide or thiosemicarbazide using aldehyde and I2-mediated oxidative bond formation, P. Niu *et al.* produced 1,3,4 amino thiadiazole in two steps.[5]

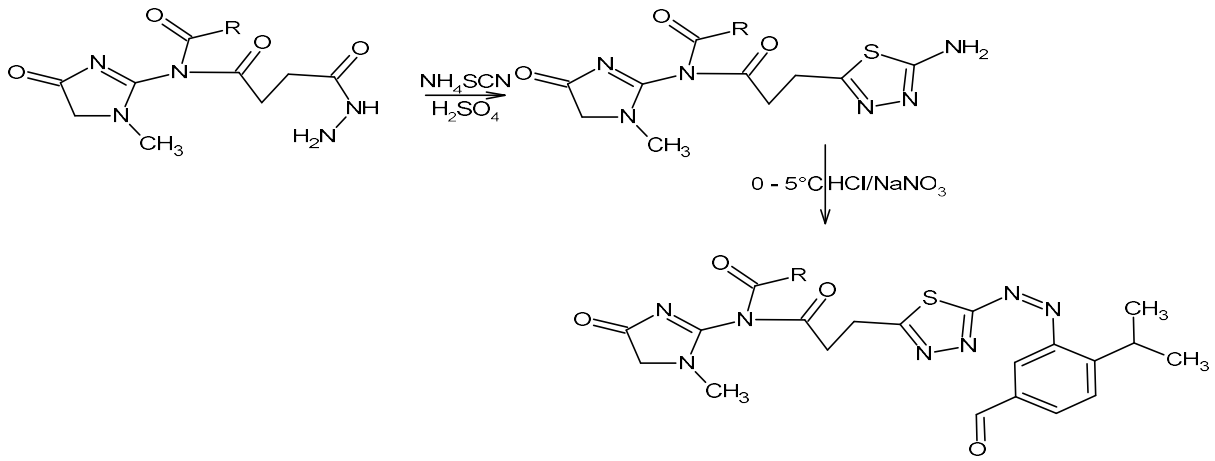


R- Ar,alkyl,vinyl

3

Scheme III

In 2022, Zainab Amer *et al.* synthesized a new 1,3,4 thiadiazole compound with an acidic hydrazide-derived azo category and then investigated the compound's antioxidant capabilities.[6]

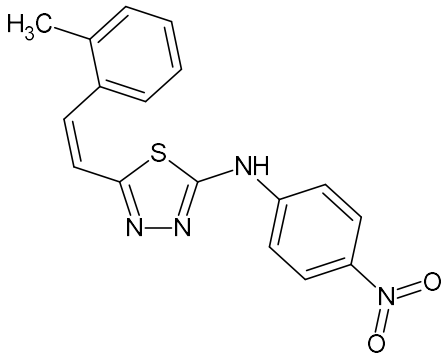


4

Pharmacological Activity

Antibacterial Activity

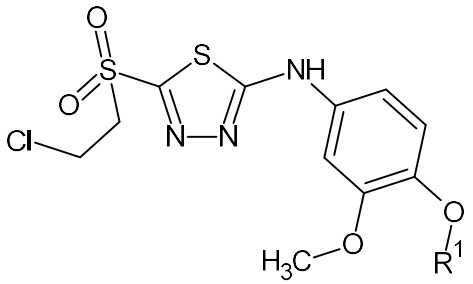
Hakan S. Sayiner *et al.* 2022 studied the creation and evaluation of many 1,3,4 thiadiazole compounds, together with an examination of their antibacterial efficacy.[7] A series of 1,3,4 thiadiazole were synthesized and characterized by UV, FTIR, 13C NMR 1H NMR. Among all compounds, compound 5 had an inhibitory effect on staphylococcus epidermidis and also all the compounds confirm the interaction with CT-DNA.



5

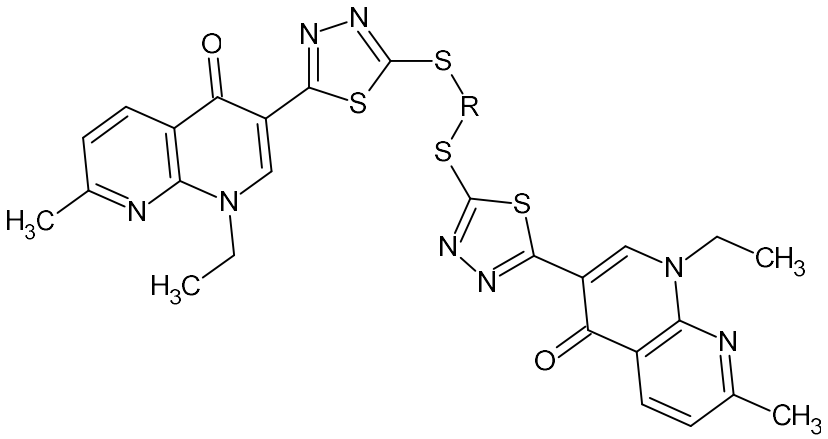
Qiong Wu *et al.* 2020 studied the new compounds of vanillin with the 1,3,4 thiadiazole group as possible antibacterial agents.[8] Thirty-four new compounds of vanillin derivatives were synthesized and their antibacterial activities were evaluated. Out of all compounds, compound 6 shows excellent antibacterial

activity with 3.14 and 8.83 µg/ml as EC50 values and also it reduces the production of exopolysaccharides and increases the cell permeability and cell damage.



6

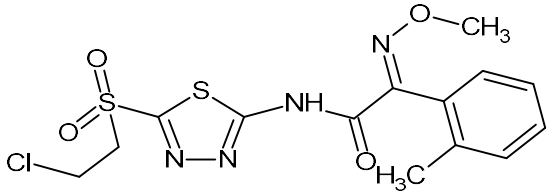
Nisha Agarwal *et al.* 2012 synthesized an innovation based on nalidixic acid 1,3,4 thiadiazole derivatives as potent antibacterial agents.[9] 1,3,4 thiadiazole was synthesized and characterized. The synthesized substance's antibacterial efficacy was assessed. Out of all compounds, compound 7 has the highest level of antibacterial activity and the lowest inhibitory concentration between 6.25 and 125 µg/ml.



7

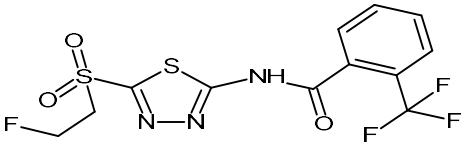
R--$CH_2C_6H_4CH_2$-

Zhibing *et al.* 2021 studied the creation, synthesis, antimicrobial efficacy, and underlying processes of new 1,3,4 thiadiazole compounds with an amide moiety.[10] New 1,3,4 thiadiazole compounds were synthesized and their antibacterial efficacy was assessed. Among these synthesized compounds, compound 8 shows higher antibacterial activity versus 1.8 and 2.1 µg/ml for the EC50 readings towards the pathogen PV.oryzicola.



8

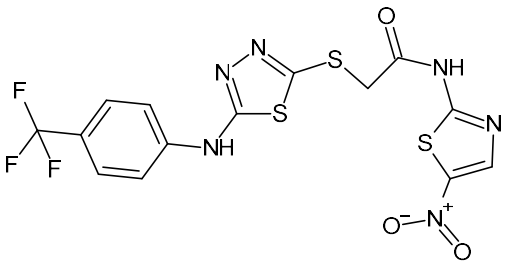
Jixiang *et al.* 2019 studied the new amide compounds with thiadiazole moiety. 1, 3, 4 an amide moiety containing thiadiazole moiety was created.[11] An assessment was made for the antibacterial activity using Xanthomonas oryzae with EC50 values of 0.4 and LC50 6.5 µg/ml. Out of all the synthesized compounds, compound 9 shows better antibacterial activity.



9

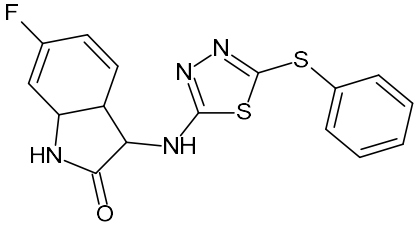
Anticancer Agents

The design, synthesis, and biological assessment of new 1,3,4 thiadiazole compounds were explored by Mehlika Dilek Altintop *et al.* 2018 as effective anti-tumor medicines against persistent myelogenous leukemia. The study focused on the remarkable impact of the nitrothiazole molecule.[12] 1,3,4 thiadiazole series were synthesized according to the docking studies. The synthesized compounds were evaluated against different cell lines for the treatment of cancer. Out of all compounds, compound 10 shows good anticancer activity.



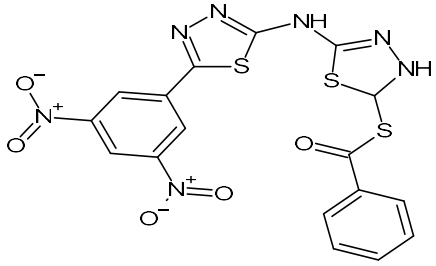
10

Through insilico designing and supramolecular green synthesis, Prashant J. Chaudhari *et al.* 2022 investigated the issue of anticancer discovery and synthesis of new 1,3,4 thiadiazole and aziridine-based indolin.[13] Depending upon the docking investigation, several unique 1,3,4 thiadiazole nuclei containing indolin were synthesized in this case. Using the aid of the protein known as C-KIT kinase, docking research was conducted; the results showed a docking score of -10.915 and -9.662. These chemicals are synthesized and then tested utilizing multiple types of cancer cells for anticancer efficacy. Compound 11 is one of them that has strong anti-colon tumor cell line action.



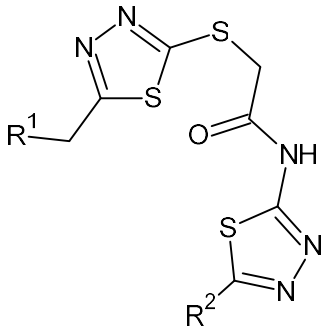
11

The development, synthesis, and molecular docking investigation of new heterocycles integrating 1,3,4 thiadiazole derivatives as possible antibacterial and cancer-fighting agents were the subjects of a 2019 study by Mohammed EL-nagar *et al.*[14] Several 1,3,4 thiadiazole compounds with heterocycles were created and synthesized in this investigation. Component 12 has the strongest anti-tumor activity of all the compounds, with the lowest IC50 values. Using the DHFR enzyme, docking research was conducted to determine its binding energy.



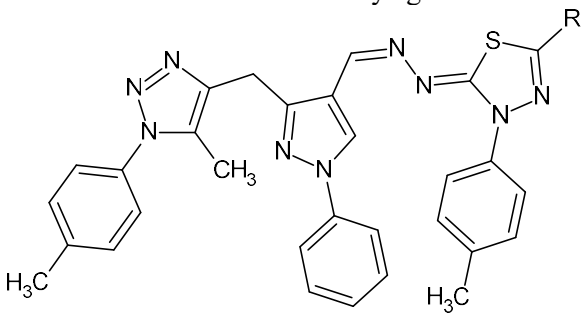
12

Ulviye Acarcevik *et al.,* 2020 produced a number of unique 1,3,4 thiadiazole compounds. Characterization of all the synthesized compounds was carried out utilizing IR, 1H NMR, 13C NMR, and MS.[15] Two distinct cell lines were utilized to assess the antitumor activity of the drugs (MCF and A549). Among these compounds, compound 13 showed better anticancer activity with IC50 values of 0.084 ± 0.020 and 0.034 ±0.008mmol L-1.



13

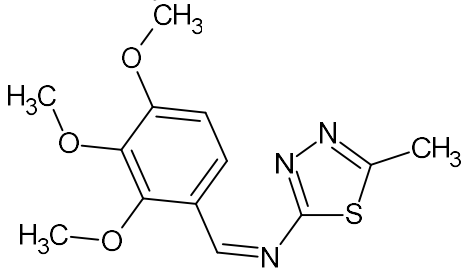
Huda R H Rashdan *et al.* 2019 studied the topic of 1, 3, and 4 thiadiazole compounds serve as an example of the rational design of new anticancer medicines according to targeting, solubility, and bioavailability in solvent-free environments.[16] Sequence of different 1,3,4 thiadiazole compounds was synthesized using solvent-free conditions. The characterization was done with the help of ^{1}H IR, NMR, and MS. All the synthesized were evaluated for lung cancer and breast cancer, compound 14 showed more activity against lung cancer and compounds 9b and 9h showed better activity against breast cancer.



14

Anticonvulsant Activity

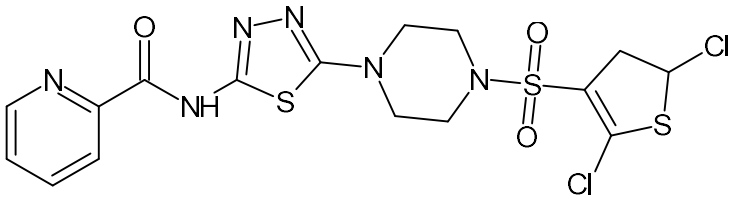
Aliyu *et al.* 2021 studied the design, synthesis, and in vivo anticonvulsant evaluation of 1,3,4 thiadiazole derivatives. According to ADME parameters and the pharmacophore model a series of 1,3,4 thiadiazole were synthesised.[17] The *chemical* composition was confirmed by UV, ^{1}H NMR, ^{13}C NMR, and MS. The synthesized molecules underwent assessment against the MES and PTS test models for anticonvulsant activity. Among all compounds compound 15 5-[(E)-(3,4,5 trimethoxybenzylidiene) amino]-1,3,4 thiadiazole shows better anticonvulsant activity.



15

The manufacturing of 1,3,4 thiadiazole compounds replaced with pyrazine and its anticonvulsant efficacy are studied by Kikkeri P. Harish *et al.* 2013.[18] 1,3,4 thiadiazole compounds having pyrazine were

synthesized. ^{1}H NMR, ^{13}C NMR, and MS were employed to characterize the compounds that were generated. Following this, the MES model was used to assess the drugs' anticonvulsant potential. When compared to the common medication phenytoin, molecule 16 and 17 had superior anticonvulsant properties.



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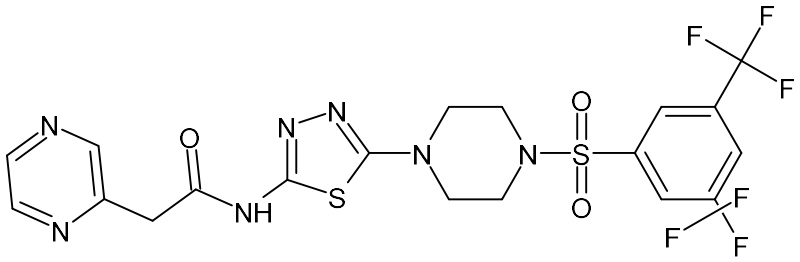
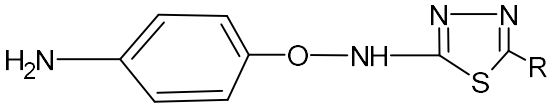


17

A study conducted in 2012 by Arvind K. Singn *et al.* examined the preparation, design, and anticonvulsant activity of several 1, 3, and 4 thiadiazole derivatives.[19] Novel 1,3,4 thiadiazole analogs (a1–a9) were synthesized in a sequence. ^{1}H NMR, ^{13}C NMR, and MS have been employed to characterize each chemical. MES was used to test the anticonvulsant potential of each of these substances in albino mice. compound 18 has the highest level of activity compared to the conventional medicine phenytoin, whereas molecules a2 and a5 have medium activity.

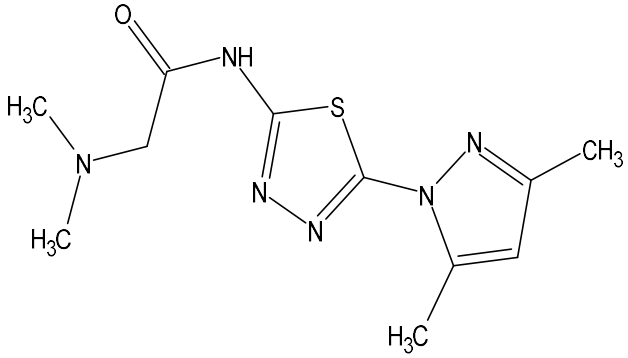


$a_1 - C_6H_5$

$a_4 - Cl\ C_6H_5$

18

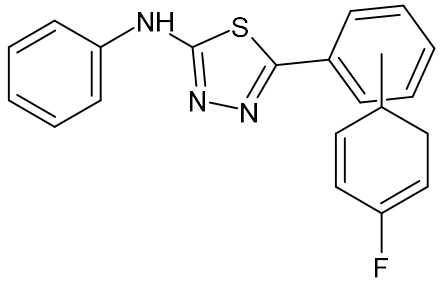
The production of many novel thiadiazole compounds and their anticonvulsant properties were investigated by M.A. Rahman *et al.* 2014. A new class of 1,3,4 thiadiazole analogs was created. ^{1}H NMR, ^{13}C NMR, and MS all validated the compounds' structures. Albino mice were employed to test all of the compounds' anticonvulsant potential utilizing a method called the MES technique. The most active chemical out of all of them is number 19.[20]



AR -5

19

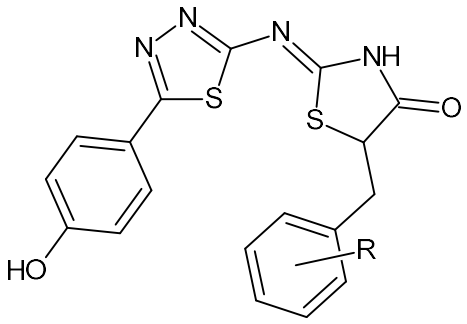
s epileptic drugs, Krishna Kumar *et al.* 2019 investigated the preparation and pharmacologic assessment of substituted 1,3,4 thiadiazole derivatives.[21] Using ^{1}H NMR, ^{13}C NMR, and MS, a number of unique 1,3,4 thiadiazoles were synthesized and evaluated. The phenylentetetrazole-induced technique (PTZ) was used to assess the anticonvulsant activity of the synthetic substances in mice. Drug 20 outperformed the others in terms of protecting mice against PTZ.



20

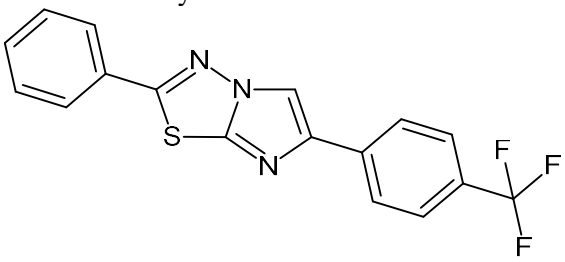
Anti-Inflammatory

The synthesis as well, biological assessment, and docking investigation of 1,3,4 thiadiazole compounds were investigated by Yasser M. Omar *et al.* 2018 as anti-inflammatory medications with dual inhibition of COX-2 and 15-LOX22. The thiadiazole equivalents were all synthesized. Characterization of the compounds produced from scratch was carried out using ^{1}H NMR, ^{13}C NMR, and MS. The invivo and invitro anti-inflammatory activity were performed. Out of all compounds, compounds 21 show higher activity compared to a standard drug celecoxib.[22]



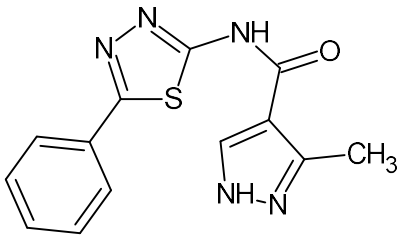
21

Gaurav M Doshi *et al.* 2021 evaluated the biological activity of 1,3,4 thiadiazole. A sequence of 1,3,4 thiadiazole was synthesized and characterized.[23] All the compounds are evaluated for invitro and invivo anti-inflammatory. The in vitro activity was carried out using membrane stabilization (48.89%) and proteinase enzyme inhibitory activity (66.78%). The invivo activity has been done by cotton pellet granuloma methods. The compound A shows better anti-inflammatory activity both in vitro and invivo. Anamaria Cristina *et al.* 2018 synthesized, characterized, and biologically evaluated the compounds of thiadiazole (medications that reduce inflammation).[24] A series of 1,3,4 thiadiazole derivatives were synthesized and characterized. They are assessed for invivo anti-inflammatory and analgesic activity. The compound 22 shows better anti-inflammatory than diclofenac.



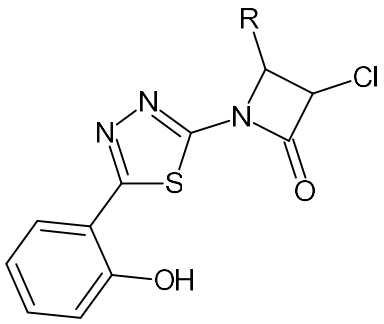
22

Maddilda *et al.* 2012 manufacturing of a series of 1,3,4 thiadiazole derivatives.[25] The elemental analysis and characterization were done using ^{1}H NMR, ^{13}C NMR, and MS. Among all the compounds, compounds 23 show potent activity.



23

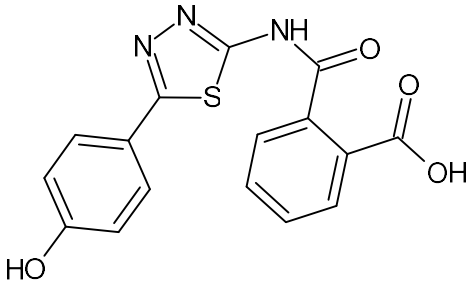
Shiv. K. Gupta *et al. 2*011 synthesized and studied the anti-inflammatory activity of disubstituted 1,3,4 thiadiazole derivatives.[26] A sequence of 1,3,4 thiadiazole was synthesized and characterized. The anti-inflammatory activity was checked. Out of all compounds, compound 24 shows maximum activity against inflammation.



24

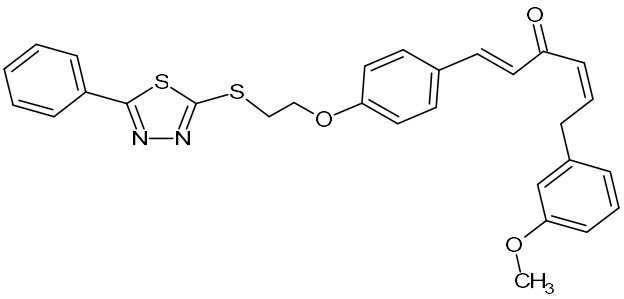
Antiviral Activity

Annalaura Brai *et al.* 2019 have done synthesis and antiviral activity of novel 1,3,4 thiadiazole derivatives.[27] Here a series of 15 novel 1,3,4 thiadiazole were designed and synthesised. The synthesized compounds are biologically characterized. All the compounds were evaluated for antiviral activity using HIV-I-infected H9 cells. Compound 25 shows a more promising effect against HIV I activity.



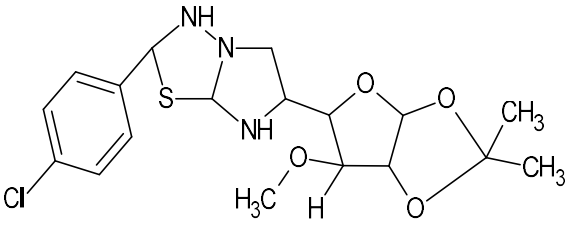
25

Lu Yu *et al.* 2017 studied the biological assessment and preparation of new bis(1,3,4-thiadiazole) derivatives with potential cytotoxic effects and antiviral effects against cucumber mosaic virus (CMV) and tobacco mosaic virus (TMV). Certain molecules had noteworthy antiviral activity, some of which outperformed ribavirin in terms of effectiveness. Investigations into the links between structure and action revealed how crucial groups that withdraw electrons on the aromatic circle are to antiviral properties.[28] Among these compounds, compound 26 shows better protection activity against TMV with EC50 values of 105.01, and 254.77 respectively.



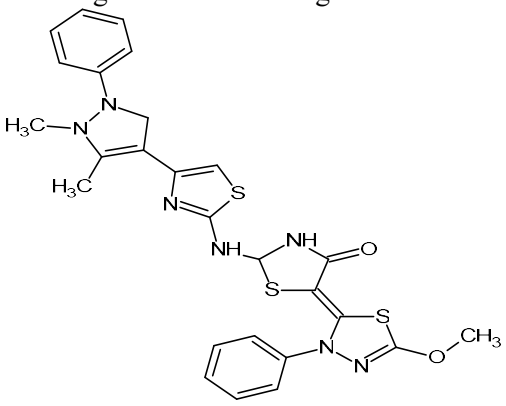
26

Mirta L. Fascio *et al.* studied the production and effectiveness of some antivirals imidazo thiadiazole carbohydrate derivatives.[29] Through the use of 1H NMR, 13C NMR, and MS, a new imidazo thiadiazole was synthesized from carbohydrates. A review of synthetic chemicals' antiviral efficacy towards JUNV strain IV4454 was conducted. Among all the compounds, compounds 8 and 27 show moderate and selective antiviral activity.



27

The preparation and characterization of novel substances with potential antiviral action, specifically compared to the Hepatitis C virus, were examined by Kamal M. Dawood *et al.* 2015. A variety of molecules with scaffolds made of thiazole and thiadiazole were created, described, and evaluated for their ability to inhibit various viruses. Compound 28 had the most encouraging results against HCV, underscoring the significance of creating new antiviral drugs.[30]



28

Xu Tang *et al.* 2018 examined the biological activity and synthesis of benzothiazole compounds with thiadiazole molecules.[31] A sequence of 1,3,4 thiadiazole-containing benzothiazole analogs was designed and synthesized. All the compounds were screened against "antiviral activity", antifungal and antibacterial activity. The "antiviral activity" was carried out using TMV (Tobacco mosaic virus). Results showed that compound 27 has better protective inactivation activities (79.5% and 88.3%) against TMV.

CONCLUSION

The renowned heterocyclic 1,3,4 thiadiazole has a variety of pharmacological and bioactive properties. The preparation and identification of novel 1,3,4 thiadiazole constituents is one of the most important fields in medicinal chemistry. Consequently, scientists focused on and created biological agents inspired

by 1,3,4 thiadiazole. Strong activity potency 1,3,4 thiadiazole compounds were analyzed in the present review, along with cytotoxic results from a range of in-vitro studies. In summary, pharmacophores featuring these heterocyclic rings can spread, and the identification of compounds with a 1,3,4 thiadiazole atom is interesting. All things considered, 1,3,4 thiadiazole is a special chemical with a wide range of biological uses. Promising characteristics include anti-inflammatory, antimicrobial, anticancer, and antibacterial effects. The 1,3,4 thiadiazole and its many pharmacological and biological actions are the main topics of this review.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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