RESEARCH PAPER

Synthesis and Characterization of Some Novel Thiadiazole Derivatives from 5-Substituted-2-Amino-1,3,4-Thiadiazole

Nidhi Arpit Raichura[1], Dr. Neelam Khan[2], Dr. Aher Bhaskar Onkar[3], Avika Joshi[4], Pravin Gomase[5], Sanjay Giri[4], Dr. Bartakke K.V.[6], Dr. Rahil Salim Meman[7*], Dr. Amol Mohan Shirode[8]

[1] Assistant Professor, Department of Pharmaceutical Chemistry, School of Pharmacy, Parul University, Limbda, Waghodia, G.J., India.

[2] Professor & Principal, Amaltas Institute of Pharmacy, Amaltas University, Dewas, M.P., India.

[3] Department of Pharmaceutical Chemistry, K.B.H.S.S. Trust Institute of Pharmacy, Malegaon - 423105, M.S., India.

[4] Assistant Professor, Amaltas Institute of Pharmacy, Amaltas University, Dewas, M.P., India.

[5] Department of Pharmacognosy, Jijamata Education Society's College of Pharmacy, Nandurbar - 425412, M.S., India.

[6] Associate Professor, Department of Microbiology, Swa. Sawarkar Mahavidyalaya, Beed - 431122, M.S., India.

[7*] Associate Professor, Ismail Mehta College of Pharmacy, Ambad, Dist Jalna - 431204, M.S., India. (Corresponding Author) Email: memon.rahil99@gmail.com

[8] Assistant Professor, Pharmaceutical Chemistry, K.B.H.S.S. Trust Institute of Pharmacy, Malegaon - 423105, M.S., India.

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ABSTRACT

The present study focuses on the synthesis and characterization of novel thiadiazole derivatives derived from 5-substituted-2-amino-1,3,4-thiadiazole. Heterocyclic compounds, particularly thiadiazole derivatives, are of significant interest due to their wide range of biological and pharmacological activities. The synthesized compounds were prepared through a multi-step synthetic route involving the formation of substituted thiadiazole intermediates followed by nucleophilic substitution reactions. The purity and identity of the synthesized compounds were confirmed using various analytical techniques such as Thin Layer Chromatography (TLC), melting point determination, Infrared (IR) spectroscopy, UV-Visible spectroscopy, and Mass spectrometry. Spectral data confirmed the presence of characteristic functional groups and structural features of the synthesized derivatives. The study highlights the successful synthesis of thiadiazole-based compounds, which may serve as potential candidates for further pharmacological evaluation.

Keywords: 1,3,4-Thiadiazole, Schiff bases, nucleophilic substitution, Streptomycin, Spectral characterization, IR spectroscopy.

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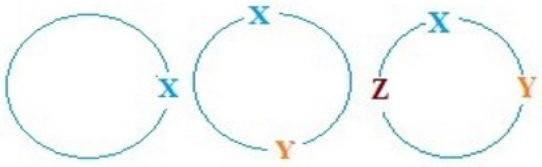
Introduction

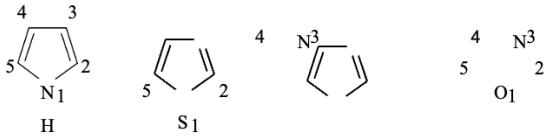
The study of organic substances and the reactions between them has a much longer history than the field of organic chemistry, which dates back fewer than two hundred years. Indeed, we have been mostly made of organic substances due to our reliance on them for both nutrition and survival. The correlation between organic chemistry's practical uses and rising living standards is strong, which is why we are privileged to live in the age of organic chemistry.Biology, biochemistry, medicine, pharmacology, polymer technology, agriculture, petroleum engineering, and countless more fields are all impacted by organic chemistry. In organic chemistry, a carbocyclic compound is one in which the ring structure is formed entirely of carbon atoms. An organic compound is considered heterocyclic if its ring structure contains an element other than carbon [1]. If you want to know what another classic reference book says about heterocyclic compounds, you can look it up in the Encyclopaedia Britannica. This element is typically sulphur, nitrogen, or oxygen, and it indicates that these compounds are organic and contain at least one atomic ring. The heteroatom is an element other than carbon [2].



X, Y, Z are usually N, O, S

Heterocyclic compounds can be inorganic or organic, but in their ring structure, the majority of them have carbon and maybe sulphur, oxygen, or nitrogen as well. 3. Heteroatoms describe non-carbons since they are commonly thought of as having substituted carbon atoms.[3] Both aromatic and non-aromatic (aliphatic) rings are possible building blocks. Countless organo-sulfur compounds can be found in both living and nonliving things. Compounds with sulphur or nitrogen atoms in their structure can be classified as open chain, alicyclic, aromatic, or heterocyclic. Research, technology, and medicine can all benefit from the isolation, characterisation, and use of these organo-sulfur compounds. Over the past 30 years, organo-sulfur chemistry has outpaced all other areas of organic chemistry in terms of development rate (4, 5). There has been a lot of research on 1, 3, 4-thiadiazoles and other sulfur-containing heterocyclic compounds. In order to set the stage, this section provides a brief overview of 1, 3, 4-thiadiazoles, touching on their chemical reactivity, synthetic routes, and biological significance.[4].

Medicinal chemistry's understanding of the heterocyclic ring system tells us that many medications and physiologically significant compounds with this ring system are active in the body. [5] An increase in biological activity is noted when simple five or six membered aromatic heterocycles like pyrrole, furan, thiophene, pyridine, pyrimidine, etc., add one divalent hetero atom, such as sulphur, nitrogen, or oxygen. [6].



1*H*-pyrrole 1, 3-thiazole 1, 3-oxazole

1, 2, 4-thiadiazole 1, 2, 5-oxadiazole

Thiadiazole is a ring compound of five carbon atoms, two hydrogen atoms, two nitrogen atoms, and one sulphur atom. Its chemical formula is C2H2N2S. It smells like pyridine and is a transparent, yellowish liquid. It dissolves in ether and alcohol but only to a lesser extent in water. Sulphur is an accelerator of chemical reactions and the parent material for many other chemical compounds, such as biocides, fungicides, colours, and sulphur medicines. Extensive research is being conducted using state-of-the-art instrumental methods to understand the various tautomeric forms that thiadiazoles with mercapto, hydroxyl, and amino substituents can take on [7]. Thiadiazoles and their derivatives may undergo the N-quaternization reaction, similar to azoles, even though they are extremely weak bases caused by the inductive impact of an additional hetero atom. Compounds with heterocyclic structures including a ring of five members rose to prominence as a result

of the adaptive strategies.[8]. The thiadiazole ring system is one of the most valuable heterocycle intermediates and subunits for the synthesis of novel medicinal compounds, according to a number of studies. Many studies have focused on 1, 3, 4-thiadiazoles and other heterocyclic compounds with five-member ring systems because of their high chemical reactivity, potential chemotherapeutic and pharmacotherapeutic effects, and ease of accessibility.

$2(CH_3)_2N\text{-}CHCl.Cl^-$ + OCH-NH-NH-CHO → $(CH_3)_2N\text{-}CH\text{-}NH\text{-}NH\text{-}CH\text{-}$ N $(CHCH_3)_2Cl$
S

Fig.No.1: Synthetic protocol of 1, 3, 4-thiadiazole

The following canonical forms depict 1, 3, 4-thiadiazole, a pseudo heteroatom ring comprising three heteroatoms.

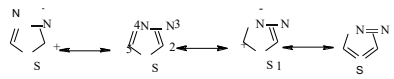


Fig.No. 2: Canonical forms of 1, 3, 4-thiadiazole

A protonated 1, 3, 4-thiadiazole becomes resistant to additional electrophilic assault, and ring nitrogen is easily protonated. The presence of three hetero atoms, each with an unpaired electron, makes the ring site an inhospitable target for nucleophilic attacks. Ring isomerisation and transformations involving 1, 3, 4-thiadiazole rings are commonplace due to the ring's characteristic electrical composition and the transfer of electronic charge to nearby atoms. Compared to their 2, 5-dialkyl counterparts, 2, 5-diaryl-1, 3, 4-thiadiazoles are more stable, although 2, 5-disubstituted-1, 3, 4-thiadiazoles in general are stable.[9]

Nomenclature of Thiadiazole ring

The thiadiazole series includes 1, 3, 4-thiadiazole as an isomer. Because of its wide range of uses as a medicinal, an oxidation inhibitor, a cyanide dye, and a metal complexing agent, 1, 3, 4-thiadiazole has been the subject of more research than any of its isomers, according to a review of the relevant literature. A nitrogen-containing ring structure with at least two heteroatoms is denoted by the ending -azole. The monocyclic azole system starts with the element with the lowest atomic weight in the group above it in the periodic table, followed by the heteroatom in the highest group. The following is the procedure for numbering 1, 3, 4-thiadiazole. This indicates that the ring has one sulphur group.

Fig.No. 3: Structure of thiadiazole moiety

Materials and methods

We used the open capillary tube method to find the melting points of all the synthesised substances. The data were presented without adjustment and in Celsius. All synthetic compounds were tested for purity on GF plates with a silica gel thickness of 0.2 mm using a thin layer chromatography method that used iodine as a visualising agent. The results were obtained by means of a UV-VIS spectrophotometer, more especially the UV-SPECORD® 50 PLUS-232H1004. A THERMO NICOLET iS10 FT-IR spectrometer was used to record infrared spectra in the 4000-400 cm-1 range, and a Euro EA (CHN) elemental analyser was used to estimate nitrogen, carbon, and hydrogen. The analysis was carried out at Andhra University, and the chemical shift was represented as δ (delta values). Chemical and FT-IR studies were carried out at Guwahati Biotech Park's Central Analytical Instrument Facility (CAIF). The 1H-NMR spectra were captured at 400 MHz using a BRUKER spectrometer. The solvent used was dimethylsulfoxide-d6, and the internal standard was tetramethylsilane (TMS).

Synthesis of the 1,3,4 thiadiazole derivatives

Synthesis of 5-(substituted phenyl)-2-amino - [1, 3, 4]-thiadiazole, (I)

The following was refluxed for two to three hours:

equimolar thiosemicarbazide and salicylic acid, 5 millilitres of concentrated sulphuric acid in 50 millilitres of ethanol. In order to track the reaction, a mobile phase of chloroform: methanol (4:1) was used in the TLC analysis. The fluid was then poured onto crushed ice once the reaction had finished. After filtering, washing with cold water, and recrystallisation from ethanol, the solid was obtained as crystals.

Synthesis of 2-chloro-*N*-substituted phenyl acetamide, (II)

A mixture of 25 ml of glacial acetic acid and 25 ml of saturated sodium acetate was used to dissolve various aromatic amines, including aniline, phenyl hydrazine hydrate, diphenyl amine, and 2, 4-dinitrophenyl hydrazine, each with a molecular weight of 0.05. To ensure full dissolution, the mixture was heated before being chilled in an ice bath while stirring. To mitigate the strong reaction, 0.06 moles of chloroacetyl chloride was added to the mixture dropwise. The substance, which had a white hue, was filtered and separated after 30 minutes. Half an equiv of water and half aqueous acetic acid were used to wash the product. Recrystallisation from aqueous alcohol resulted in a percentage yield of 85, 73, and 67%, respectively; melting points of 128–130, 143–145, and 126–128 0C were recorded.

A N-(substituted-phenyl)-2-[5-(3-substituted-phenyl)-1, 3, 4-thiadiazol-2yl amino] synthesised -anhydride, (III)

The following compounds were combined in 15 millilitres of 1, 4-dioxane: compounds I, II, and III (0.05 moles) and 2-chloro-N-substituted-phenyl-acetamide (0.05 moles). This was then combined with 0.005 ml of triethylamine (TEA) solution and refluxed for three hours to complete the reaction. After cooling, it was poured over a bed of crushed ice. It was filtered out when the solids separated. Water and 10% K_2CO_3 were used to wash the filtered material.

Result and Discussion

Melting point determination

The melting point is a useful metric for describing the point at which a substance changes state from solid to liquid. For pure crystalline substances, the melting point is clearly defined and easy to see. During melting, a substance uses up all the energy that was applied to it as heat of fusion, maintaining a constant temperature. Finding a chemical's melting point is the most essential and direct way to differentiate this physical constant across different chemicals. The melting points of all the synthetic substances were determined using Thiele's tube method in open capillaries.

Infra-red spectroscopy (IR) of synthesized derivatives

Light in the infrared spectrum, which has a longer wavelength and lower frequency than visible light, is the focus of infrared spectroscopy, or IR spectroscopy. Various methods are covered, with absorption spectroscopy being the most common. Chemicals can be identified and studied using this method, as with any spectroscopic technique. The Fourier transform infrared (FTIR) spectrometer is a typical piece of laboratory equipment that employs this method. One of the most useful methods for identifying functional groups and potential chemical structures is infrared spectroscopy. The method relies on the compound's molecular vibrations, which cause each bond to vibrate at a particular frequency, which in turn corresponds to the infrared frequency. As a result, spectra of every single bond will be generated. One major benefit of infrared spectroscopy over other methods is the ease with which it provides fingerprint-like information on a molecule's structure, including its functional groups and intermolecular bonds, at a wavelength range of 1300 to 650 cm-1. The fingerprint region of any two compounds will be unique. We used a THERMO NICOLET iS10 FT-IR spectrophotometer and the KBr disc approach to record the infrared spectra of all the chemicals that were synthesised.

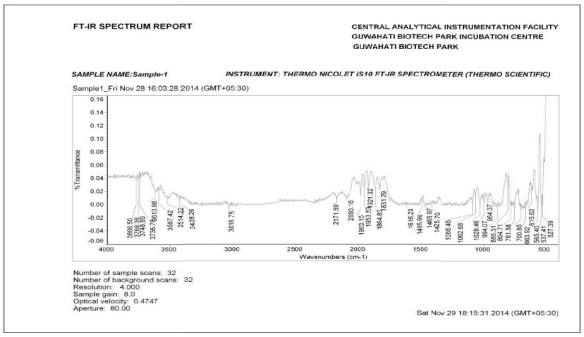


Fig.No.4 . IR spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.I)

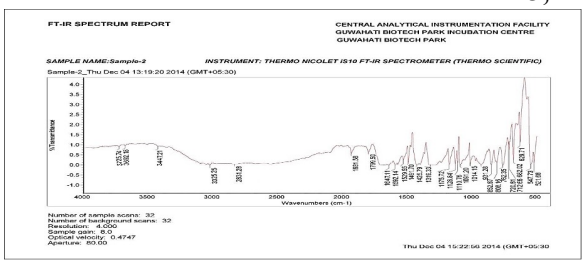


Fig.No.5 . IR spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.II)

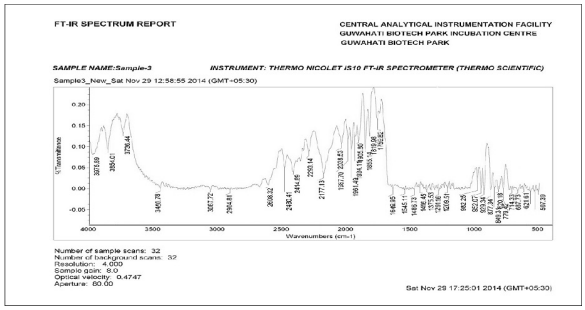


Fig.No.6 . IR spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.III)

Mass spectroscopy of synthesized derivatives

Mass spectroscopy is a method for characterising molecules based on how they fragment when bombarded with high-energy electrons. Mass spectra are helpful for deducing molecular weight in addition to elucidating or interpreting molecular structure. Mass spectrometry is based on the physical principle that charged particles will be redirected along a circular path with a radius proportionate to the mass to charge ratio, m/z, as they pass through a magnetic field. An electron impact mass spectrometer creates molecular ions—radical cations—by displacing an electron from an organic molecule with a high-energy electron beam. When a molecular ion becomes too unstable, it splits into smaller ions. The ions are gathered, focussed into a beam, and accelerated into a magnetic field, where they are redirected along circular pathways based on their masses (m/e r 2). Using a collecting slit and a magnetic field adjustment, the ions are collected. The detector caught the various pieces, and a mass spectra was taken. All of the synthetic chemicals had their mass spectra recorded using a SHIMADZU 2010A LC-MS spectrometer. Complements I, II, and III were identified by mass spectra that showed molecular ion peaks at 354 [M -1]+, 370 [M+] and 431 [M+] and base peaks at 142, 136 and 221 corresponding to $C_{16}H_{13}N_5O_3S$, $C_{16}H_{14}N_6O_3S$, and $C_{22}H_{17}N_5O_3S$, respectively.

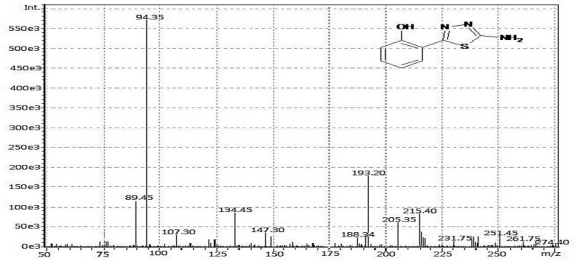


Fig.No.7 Mass spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.I)

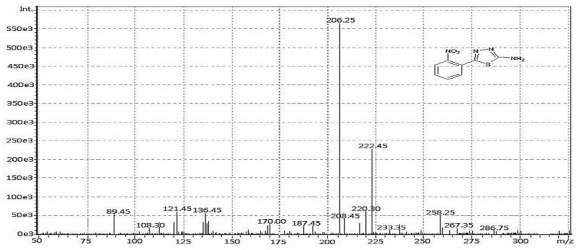


Fig.No.8 Mass spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.II)

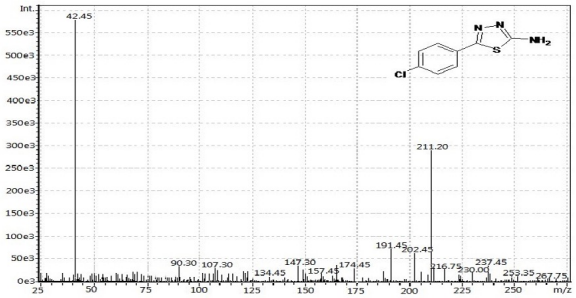


Fig.No.9 Mass spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.III)

Ultraviolet/Visible Spectroscopy

Analysis of electromagnetic energy between 160 and 780 nanometres in wavelength is the foundation of ultraviolet/visible molecular absorption spectroscopy. For your convenience, this specific range is roughly separated into two parts: the visible light spectrum (380 nm to 780 nm) and the ultraviolet spectrum (160 nm to 380 nm). The presence of certain groups, bonds, and functional groups inside the molecule causes the activation of bonding electronic transitions, which in turn cause the absorption of

UV/visible radiation in this region. The sorts of bonds in a species can be related to the wavelengths of its absorption peaks. Both the transition probability and the excited state's polarity determine the absorption intensity. Molecules whose electric dipole moment is fixed exhibit pure rotation spectra, whereas molecules whose dipole moment varies as a result of various types of motion in the radiation's electric field exhibit vibrational spectra. This method can be applied to identify hetero atoms such as S, N, O, and halogens, as well as to determine if unsaturation's are present or not by analysing the peak shapes.

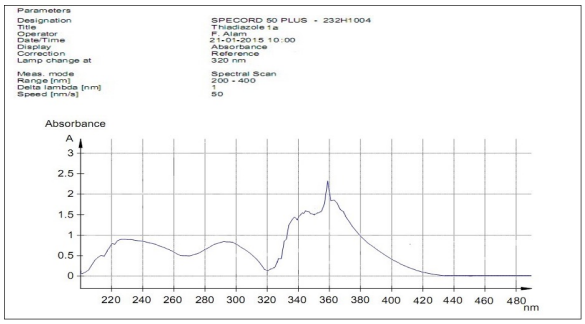


Fig.No.10 :UV/visible-spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.I)

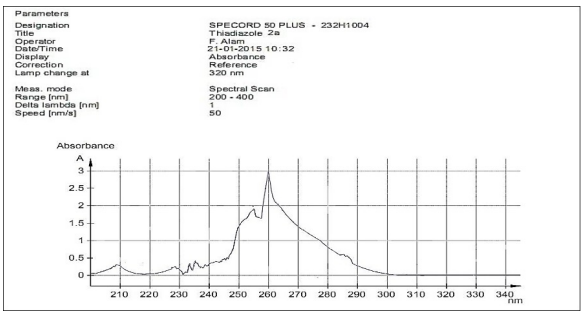


Fig.No.11 UV/visible-spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.II)

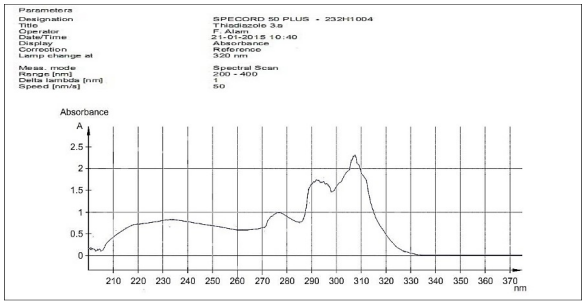


Fig.No.12 UV/visible-spectrum of 5-substituted-2-amino-1, 3, 4- thiadiazole derivative (Comp.III)

Discussion

The synthesis of thiadiazole derivatives was carried out using a systematic and efficient multi-step procedure. The initial formation of 5-substituted-2-amino-1,3,4-thiadiazole was achieved through the reaction of thiosemicarbazide with salicylic acid under acidic conditions. This step plays a crucial role in constructing the thiadiazole ring, which serves as the core structure for further modifications. Subsequent reactions involved the preparation of substituted acetamide derivatives and their coupling with thiadiazole intermediates via nucleophilic substitution. The use of triethylamine facilitated the reaction by acting as a base, promoting the formation of the final derivatives.

The synthesized compounds were characterized using various physicochemical and spectroscopic techniques. Melting point determination confirmed the purity and stability of the compounds. Thin Layer Chromatography (TLC) further validated the completion of reactions and homogeneity of the products. Infrared (IR) spectroscopy provided evidence of functional groups such as –NH, C=N, C–S, and aromatic rings, confirming the successful formation of thiadiazole derivatives. UV-Visible spectroscopy indicated electronic transitions associated with conjugated systems and heteroatoms present in the molecules. Mass spectrometry analysis revealed molecular ion peaks corresponding to the expected molecular weights, thereby confirming the structural integrity of the synthesized compounds.

Overall, the results demonstrate that the adopted synthetic strategy is reliable and effective for producing thiadiazole derivatives with well-defined structures. These compounds possess significant potential for biological applications due to the presence of heterocyclic moieties and functional groups known for pharmacological activity.

Conclusion

In conclusion, a series of novel thiadiazole derivatives were successfully synthesized from 5-substituted-2-amino-1,3,4-thiadiazole using a stepwise synthetic approach. The structures of the synthesized compounds were confirmed through various analytical techniques, including IR, UV-Visible spectroscopy, and mass spectrometry. The

results validate the effectiveness of the synthetic methodology and confirm the formation of the desired compounds with good purity. Given the well-known biological significance of thiadiazole derivatives, the synthesized compounds hold promising potential for further investigation in medicinal chemistry, particularly for antimicrobial, anticancer, and anti-inflammatory activities. Future studies may focus on evaluating their biological activity and optimizing their pharmacological properties.

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